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Editorial / Editorial

Understanding Suffering: Euthanasia, Palliative Sedation, and End-of-Life Decisions

Comprender el sufrimiento: eutanasia, sedación paliativa y decisiones al final de la vida

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"I can't take it anymore", a phrase commonly repeated by patients in the context of a terminal illness, when accompanying symptoms or situations such as pain, dyspnea, bleeding, delirium, loneliness are decisive factors to ask healthcare personnel for options. Faced with this scenario, the interest in anticipating death (euthanasia) has gained social and medical prominence. This editorial presents a reflection on patient's suffering at the end of their lives, the ethical obligation to provide options to alleviate that suffering, and the importance of clearly distinguishing between euthanasia and palliative sedation as a compassionate, ethical, and legal alternative [1].

It is important to remember that, in palliative care, we understand that pain is not only physical. The concept of total suffering, introduced by Dame Cicely Saunders, a pioneer in this branch of medicine, explains that it encompasses the physical, emotional, social, and spiritual components [2]. The individual process and the way in which each person experiences these components or spheres condition the overall well-being of the terminally ill patient. The problem arises when symptoms do not improve and the person loses autonomy, control over his/her body, ability to make decisions and, in many cases, there is also a feeling of losing dignity.

Pain so intense that makes blurs the mind; dyspnea that prevents speaking or resting; bleeding that frightens and, at times, stains tranquility with red; delirium that hurts and hinders reality. Last but not least, emotional and social isolation, feelings of fear and loss of meaning in the face of life finiteness do not always find space to be expressed or adequately accompanied. All this can turn suffering into an impossible burden to bear [3].

In this context, many patients see death as a liberation; however, palliative care guarantees an individualized assessment that brings us closer to comprehensive and respectful relief, recognizing the complexity of suffering in each of its dimensions. It neither advances nor delays death, as indicated by one of its fundamental principles, defined by the World Health Organization (WHO) [4].

Palliative sedation is a compassionate and ethical alternative in palliative care. It is reserved for patients whose symptoms do not respond to conventional therapy and who suffer intolerable physical or psychological illnesses. It is applied with respect for the patient's dignity and only seeks to reduce suffering, with no intention of hastening

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death. It is essential to clearly distinguish palliative sedation, which seeks to alleviate symptoms and ensure a peaceful death, from euthanasia [5] [6].

The European Association for Palliative Care (EAPC) recognizes palliative sedation as a relevant, widely accepted mediation for patients with life-limiting illness with refractory symptoms [7].

Unlike euthanasia, which aims to deliberately provoke the death of the patient [8], palliative sedation is considered within the principles of proper medical practice and respect for the rights of the patient, who is informed at all times when opting for this procedure. It is important to understand the principle of double effect, which states that alleviating symptoms may decrease the level of consciousness or, in rare cases, shorten life. The key will always be the goal: to relieve suffering [5]. Its application requires interdisciplinary assessment, informed consent, and continuous monitoring; thus ensuring compassionate care and humanity in one of the most delicate moments of life.

Hearing the word euthanasia is an invitation to listen deeply to what lies behind this request; it implies looking beyond the words, recognizing that, often, what is being asked is not to die, but to stop suffering.

As health care professionals, we have an ethical responsibility to provide relief. This care can be provided by any specialty. Of course, when indicated, we can offer palliative sedation within an ethical, legal, and compassionate framework that allows the patient to be accompanied with dignity without hastening or postponing the patient's outcome [1].

It is vital to work and strengthen end-of-life education, both for the medical community and for society. In this way, we will be able to promote informed decision-making, avoid misjudgments and, above all, provide humane responses to suffering.

True medicine not only cures, but also accompanies with respect and presence, prioritizing the individuality that goes hand in hand with the dignity of each patients and their families.

1. Abbreviations

WHO: World Health Organization.

EAPC: European Association for Palliative Care.

2. Administrative Information

2.1 Authors' contribution

Dr. Mariana Vallejo: Conceptualization, formal analysis, research and writing of the original draft, and approval of the manuscript.

Dr. Ericka Parra: Conceptualization, formal analysis, research, and writing of the original draft.

2.2 Conflict of interest

The authors declare no conflict of interest.

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Case report / Caso clínico

Primary breast follicular lymphoma: Case report

Linfoma folicular primario de mama: reporte de caso

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ABSTRACT
Introduction: Primary follicular lymphoma of the breast is a rare entity with unique clinical and pathological features. This report highlights the diagnostic challenges and management of this condition. **Case presentation:** A 63-year-old patient presented with an irregular nodule in the left breast, which was classified as BIRADS IV/C on core needle biopsy. Suspecting an intramammary tumor, she was referred for surgical excision. Histopathological and immunohistochemical studies confirmed a grade 1/2 follicular lymphoma. **Conclusion:** This case highlights the importance of integrating imaging, histology and immunohistochemistry for accurate diagnosis of primary mammary follicular lymphoma. Early multidisciplinary management is crucial for a favorable outcome.

Keywords: Breast neoplasms; Follicular Lymphoma; Immunohistochemistry; Mastectomy.

RESUMEN
Introducción: El linfoma folicular primario de mama es una entidad poco frecuente con características clínicas y patológicas únicas. Este informe destaca los retos diagnósticos y el tratamiento de esta enfermedad. **Caso clínico:** Una paciente de 63 años presentó un nódulo irregular en la mama izquierda, clasificado como BIRADS IV/C en la biopsia con aguja gruesa. Ante la sospecha de un tumor intramamario, fue remitida para extirpación quirúrgica. Los estudios histopatológicos e inmunohistoquímicos confirmaron un linfoma folicular de grado 1/2. **Conclusión:** Este caso enfatiza la importancia de integrar imágenes, histología e inmunohistoquímica para el diagnóstico preciso del linfoma folicular mamario primario. El tratamiento multidisciplinar precoz es fundamental para obtener resultados favorables.

Palabras Clave: Neoplasias de la mama; Linfoma folicular; Inmunohistoquímica; Mastectomía.

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1. Introduction

Primary breast lymphoma (PML) is a rare neoplasm of the lymphoid tissue of the breast [1-2] that occurs almost exclusively in women, with a median age of 60-65 years [3-4]. It is defined as a malignant neoplasm occurring primarily in the breast in the absence of previously identified sites of lymphoma.[5] This pathology is identified by the presence of neoplastic B or T cells, which classifies it as non-Hodgkin's lymphoma (NHL) [6] according to the World Health Organization (WHO) diagnostic criteria. There are several types of NHL: the follicular lymphoma (FL) subtype accounts for 22% of cases [7]. Primary follicular breast lymphoma (PFBL) is a rare disease without extramammary involvement; its pathogenesis is not yet understood. In general, primary breast lymphoma presents clinically as a painless palpable mass and is nonspecific on imaging. It may have a differential diagnosis with breast carcinoma, and a definitive diagnosis should be made by tumor biopsy [1,6,8]. The aim of this article is to report a rare case of primary follicular breast lymphoma in a 63-year-old woman, focusing on the diagnostic challenges and the clinical, pathologic, and imaging features of this unusual presentation. Our goal is to highlight the importance of integrating radiologic, histopathologic, and immunohistochemical findings in the accurate diagnosis and management of breast lymphoma. In addition, we emphasize the role of a multidisciplinary approach in obtaining favorable outcomes. The report was written in accordance with CARE guidelines to ensure a comprehensive presentation of cases.

2. Case report

A 63-year-old patient with no pathologic or family history of cancer presented to a mastologist fourteen months ago for the presence of a nodule in her breast. An ultrasound was requested and revealed an irregular solid nodule (BIRADS IV/B) in the left breast, and she was referred for core needle biopsy. This biopsy revealed follicular lymphoid hyperplasia, consistent with a probable intramammary tumor. The lesion was not consistent with radiologic imaging and, therefore, was reclassified as BIRADS IV/C.

Three months after diagnosis, the patient underwent surgical resection with intraoperative frozen pathology. A left breast quadrantectomy and excision of the sentinel node with intraoperative margin extension was performed with a frozen section diagnosis of undifferentiated malignant small cell neoplasm, and the material was sent for anatomic pathology and immunohistochemistry. Macroscopic examination revealed a firm, elastic, whitish nodular tumor measuring 5.2x3x3 cm along the superior and anterior margins (Figure 1). In addition, a 1.2 cm left axillary sentinel lymph node, and the surgical margins of the breast tissue were examined.

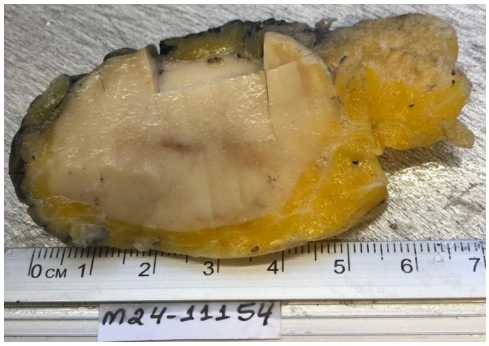

Figure 1. Macroscopic examination revealed a firm elastic whitish nodular tumor measuring 5.2x3x3cm along the upper and anterior margins.

Microscopic examination of the nodule revealed an undifferentiated small round cell neoplasm compatible with a follicular lymphoproliferative process (Figure 2), as well as adjacent mammary parenchyma with discrete ductal ectasia. Immunohistochemistry was requested for definitive diagnosis. Microscopy of the lymph node showed no evidence of neoplastic involvement. Surgical margins were free of neoplastic involvement.

Immunohistochemistry (Figure 3) was positive for CD3, CD20, CD5, CD10, BCL2, BCL6, and PAX5 in the perifollicular region. The CICLINAD1 marker was negative. The final diagnosis was primary follicular breast lymphoma grade 1/2. The patient was referred to by a hematologist who ordered a positron emission tomography scan (PET-Scan) for tumor control. The scan results were negative for evidence of abnormal metabolic activity in the examined body areas. As a result, ambulatory monitoring was without indicated the need for chemotherapy or radiotherapy.

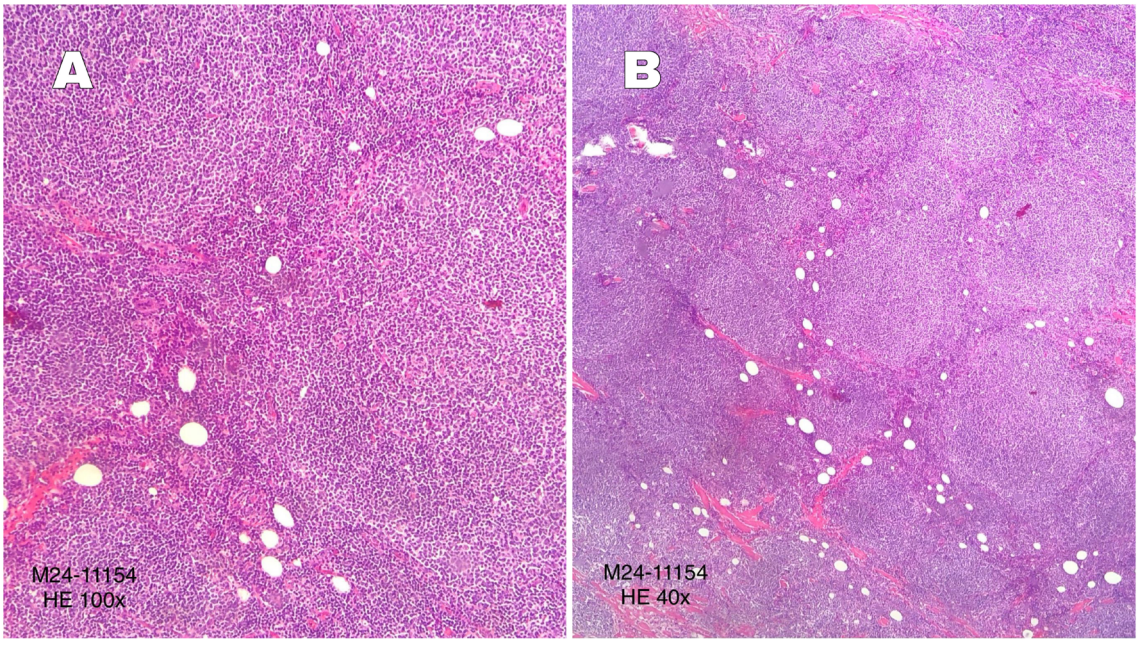

Figure 2A. Histopathology showing a follicular lymphoproliferative process consistent with follicular lymphoma (HE:100x). **Figure 2B.** Microscopic examination showing an undifferentiated small round cell neoplasm with a follicular lymphoproliferative process and adjacent breast parenchyma with discrete ductal ectasia (HE:40x).

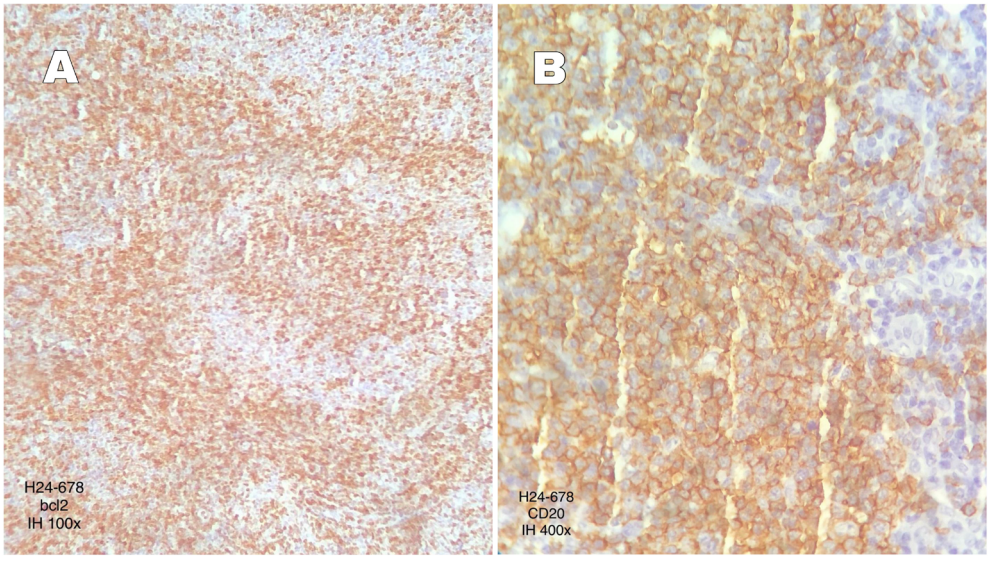

Figure 3A. Immunohistochemical image showing positive perifollicular Bcl-2 staining in the tumor (HE:100x). **Figure 3B.** Immunohistochemical image showing positive perifollicular CD20 staining in the tumor (HE:100x).

3. Discussion

Primary lymphoma accounts for less than 1-2% of all non-Hodgkin lymphomas and less than 0.5% of all malignant breast neoplasms [4-9]. Diffuse large B-cell lymphoma is the most common subtype of primary breast lymphoma, accounting for 40% to 70% of cases. Other less common subtypes include marginal zone lymphoma, follicular lymphoma, and mucosa-associated lymphoid tissue (MALT) [10]. PBL is characterized as a potentially curable neoplasm with clinical features and prognostic factors that are not yet well established. Its pathophysiology is still unknown, but it is thought to be derived from MALT, lymphoid tissue adjacent to mammary ducts and lobules or even from intramammary lymph nodes. Its clinical and imaging presentation is not different from that of breast carcinoma, the most common manifestations being a palpable, painless nodule, and about 12% of cases are incidental findings on mammography, as the patient is asymptomatic [3]. The low incidence of primary follicular lymphoma in the breast makes it difficult to generalize therapeutic approaches and prognoses [1,5]. Although a suspicious lesion was observed on ultrasound, core needle biopsy yielded inconclusive results, which raised doubts and made a definitive diagnosis difficult.

Criteria defined for the diagnosis of PBL [11] are breast as the site of presentation, breast tissue in association with lymphomatous infiltration, absence of disseminated disease beyond the ipsilateral axillary lymph nodes, and no previous diagnosis of lymphoma [3,9]. It is worth noting that these criteria exclude secondary breast lymphomas, i.e., those arising at a primary site but disseminating and manifesting in the breast [6]. Diagnostic criteria include the presence of breast tissue and lymphomatous infiltrate in an adequate specimen and the absence of previous disseminated or extramammary lymphoma, except in ipsilateral axillary lymph nodes [3]. PFBL is thought to originate from follicular B cells in mammary lymphoid tissue and is histologically distinct from other variants of PBL due to the presence of small follicles with small atypical centrocytes with cleaved nuclei. The clinical behavior of primary follicular lymphoma in the breast is heterogeneous, with unpredictable recurrence rates [2,4].

On mammography, most lesions are hyperdense oval masses, whereas on ultrasound they are single oval, circumscribed, microlobulated lesions. They are usually hypoechoic and calcifications or spiculated margins are uncommon [3,12]. The diagnosis of PFBL is usually made by excisional biopsy or wide excision of the tumor, confirmed by anatomopathological examination [7]. Characteristically, tumor cells express CD19, CD20, CD10 and BCL64 proteins, as well as the anti-apoptotic protein BCL25. In the case presented by Urooj et al., 2022, the immunophenotypic analysis was positive for CD20, CD10, BCL2 and BCL6 markers, resulting in a histological diagnosis of follicular Non-Hodgkin's Lymphoma and corroborating the results found in the examinations of this article [13-14].

PFBL has an excellent prognosis after treatment, with an overall response rate of 97% according to one study [6]. There is still no consensus on the best therapeutic approach, which may include surgery, radiotherapy, chemotherapy, or immunotherapy [3]. Mastectomy has been a common component of therapy for primary breast lymphoma, but some studies show that there is no benefit to this type of approach, with radical surgery being an unnecessary option. In this case, surgery would be limited to a biopsy to establish the correct histologic diagnosis, leaving treatment with curative intent to radiotherapy and chemotherapy [2,5]. In the reported case, breast quadrantectomy at the site of the nodule was curative for the neoplasm, and no other affected areas were found by PET-Scan, thus excluding the indication for adjuvant radiotherapy or chemotherapy. One study revealed a reduced risk of recurrence in treatment with radiotherapy alone or in combination with surgery, and this has since been supported by others [6]. Therapeutic decisions, such as the choice between radiotherapy and chemotherapy, still lack consensus due to the rarity of the condition [6,9].

As for chemotherapy, the regimen of Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (CHOP) is the most widely accepted. However, there is still controversy about the selection criteria for combination therapy. Five-year survival varies from 89% in stage I cases to 50% in stage II and, in some reports, age is considered an independent factor for long-term survival [3]. One study showed successful treatment of high-grade PFBL with radiotherapy in combination with Rituximab-Cyclophosphamide, Hydroxyunorubicin, Oncovin, and Prednisone (R-CHOP) [7].

Primary breast lymphoma behaves differently from nodal lymphomas and its early diagnosis is of great relevance. Prognosis depends mainly on the type, grade, and stage of the lymphoma. Its clinical presentation and nonspecific imaging features require a review of the clinical history, a multimodality imaging approach and histopathology for diagnosis and treatment [6,12,13,15]. As noted by Picasso et al., the lack of specific data on this subtype contributes to uncertainties regarding survival [15]. Therefore, primary and secondary lymphomas, although rare, should be considered in the differential diagnosis of breast neoplasms [1,6,7].

4. Conclusion

Although primary follicular breast lymphoma is a rare entity, it should be considered in the differential diagnosis of breast neoplasms, especially in older women. Diagnosis by imaging tests is challenging, which makes anatomopathological and immunohistochemical analysis essential for a definitive diagnosis.

5. Abbreviations

PBL: Primary breast lymphoma

WHO: World Health Organization

NHL: Non-Hodgkin's lymphomas

FL: Follicular lymphoma

PFBL: Primary follicular breast lymphoma

PET-Scan: Positron Emission Tomography scan

MALT: mucosa-associated lymphoid tissue

CHOP: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone

R-CHOP: Rituximab-Cyclophosphamide, Hydroxide-Unorubicin, Uncovin, and Prednisone

6. Administrative information

6.1 Additional files

No

6.2 Acknowledgements

None

6.3 Author Contributions

Bruno Pelinson Fogaça Duarte: conceptualization, methodology, formal analysis, research, project administration, writing of the original draft.

Julia Saccaro Duzzi: visualization and writing.

José Gabriel Kiel Francisco Petillo: visualization and writing.

Geovanna Vieira Araújo: visualization and writing.

Angelo Sementilli: supervision, review, and editing.

All authors read and approved the final version of the manuscript

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6.5 Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

7. Disclosures

7.1 Consent to publication

The patient gave written informed consent for the present study.

7.2 Conflict of Interest

The authors declare no conflict of interest.

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Case report / Caso clínico

Diagnostic challenge in gastrointestinal bleeding due to GIST: Case report

Desafío diagnóstico en hemorragia digestiva debido a tumor GIST: Reporte de caso

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ABSTRACT
Introduction: Gastrointestinal stromal tumors (GISTs) are rare non-epithelial neoplasms, with an incidence of 10 to 20 cases per million people, typically occurring in individuals between 50 and 71 years of age. These tumors are primarily located in the stomach and are associated with mutations in the Kit gene. **Clinical Case:** A 45-year-old female patient, who developed an abdominal tumor, is presented. The tumor clinically manifested as hypovolemic shock secondary to gastrointestinal bleeding; in this case, it was located in the mesentery, which is an unusual site for this type of neoplasm. The patient was successfully treated surgically. **Conclusion:** This case highlights the importance of considering GISTs as a differential diagnosis in patients with acute gastrointestinal bleeding and hypovolemic shock. The mesenteric location of the tumor is an uncommon feature, underscoring the variability in the presentation of GISTs. Early detection and appropriate surgical treatment are essential for managing this pathology. Additionally, this case emphasizes the need for thorough evaluation in younger patients, despite GISTs being more common in older adults.

Keywords (MeSH): Clinical case, GIST (Gastrointestinal Stromal Tumors), Non-epithelial neoplasms, Kit gene mutations, Gastrointestinal bleeding, Hypovolemic shock, Mesentery.

RESUMEN
Introducción: Los tumores del estroma gastrointestinal (GIST) son neoplasias no epiteliales raras, con una incidencia de 10 a 20 casos por millón de personas, que suelen presentarse en individuos de entre 50 y 71 años. Estos tumores se localizan principalmente en el estómago y están asociados con mutaciones en el gen Kit. **Caso clínico:** Se presenta el caso de una paciente femenina de 45 años que desarrolló un tumor abdominal, el cual se manifestó clínicamente como un choque hipovolémico secundario a hemorragia digestiva. El tumor, en este caso, se localizó de manera novedosa en el mesenterio, lo que constituye una característica poco común para este tipo de neoplasia. La paciente fue tratada quirúrgicamente con éxito. **Conclusión:** Este caso resalta la importancia de considerar los GIST como diagnóstico diferencial en pacientes con hemorragia digestiva aguda y choque hipovolémico. La localización mesentérica del tumor es una característica poco frecuente que destaca la variabilidad de presentación de los GIST. La detección temprana y el tratamiento quirúrgico adecuado son fundamentales para el manejo de esta patología. Además, este caso pone de manifiesto la necesidad de una evaluación exhaustiva en pacientes jóvenes, a pesar de que los GIST suelen ser más comunes en adultos mayores.

Palabras Clave (DeCS): Caso clínico, GIST (Tumores del estroma gastrointestinal), Neoplasias no epiteliales, Mutaciones del gen Kit, Hemorragia digestiva, Choque hipovolémico, Mesenterio.

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1. Introduction

Gastrointestinal stromal tumors (GISTs) have a global incidence of 10 to 20 cases per million people each year [1]. The average age at diagnosis is around 60 years, with no clear difference between sexes, although some studies suggest a higher prevalence in men. These neoplasms can affect the entire gastrointestinal tract, and in less than 1% of cases, they can present as extra-intestinal [2,3].

Extra-intestinal gastrointestinal stromal tumors (EGISTs) are rare, representing less than 5% of all GISTs, around 80% are located in the omentum or mesentery [4]. Three theories have been proposed for their development: the first suggests they originate in the gastrointestinal tract, with an exophytic growth followed by the acquisition of autonomy; the second suggests that EGISTs are peritoneal metastases of an undetected GIST; and the third proposes a mesothelial origin with characteristics similar to those of the Cajal cells [5].

Ninety percent of primary GISTs may have mutations in the KIT gene (in 80% of cases), resulting in a positivity for the monoclonal antibody CD-117 in 94-95% of cases, or in the PDGFRA gene (in the remaining 10%). The remaining 10% do not have mutations in either of these genes, so they are classified as wild-type GISTs. The main treatment is surgical resection, which can be curative in most cases [6].

This article presents a case of a GIST located in the mesentery, a rare site, diagnosed from an episode of persistent gastrointestinal bleeding.

2. Clinical Case

A 46-year-old female patient with a history of uterine fibroids, unspecified anemia, radical hysterectomy, and two cesarean deliveries. Her family history includes hypertension in her mother and siblings, and neurofibromatosis type 1 in her father and one brother.

She was admitted with a condition of several days' duration, characterized by melena, without abdominal pain and exacerbation over the last 48 hours, reporting lower gastrointestinal bleeding of approximately 400 cc. Upon examination, she presents generalized pallor, café-au-lait spots on her skin, and nodules on her posterior chest (Image 1). Laboratory studies reveal hemoglobin of 3.3 g/dl, hematocrit of 10%, and platelet count of 67,000 IU, thus categorizing her as having grade III hypovolemic shock due to upper gastrointestinal bleeding. A transfusion of packed red blood cells is initiated, along with treatment with proton pump inhibitors. Due to the severity of her condition, it was decided to admit her to the intensive care unit for continuous monitoring and further studies.

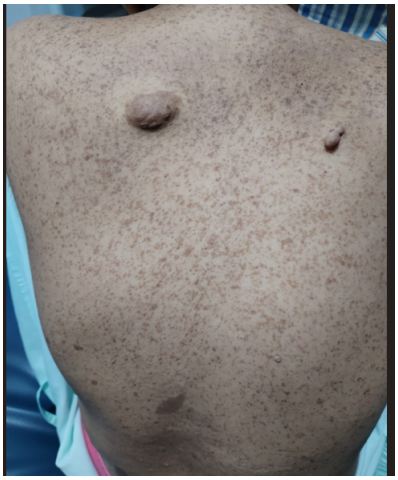


Image 1. Hyperpigmented and hypopigmented macules (café-au-lait color), with small tumors compatible with fibromas in the posterior thoracic region.

The patient is evaluated by the Gastroenterology service, which schedules an upper gastrointestinal endoscopy that showed normal mucosa without identifying the site of the bleeding. Subsequently, a colonoscopy is performed, revealing large clots and blood remnants that hinder the continuation of the study, so it is rescheduled for 48 hours later.

In the following days, the patient does not present new episodes of melena and maintains a stable hemoglobin level of 7.4 g/dl, without the need for transfusions. In the new colonoscopy, abundant blood remnants are observed throughout the colon. Due to the difficulty in locating the source of the bleeding, a capsule endoscopy study is scheduled.

On the fifth day of hospitalization, a slight decrease in hemoglobin levels is recorded (from 9.9 g/dl to 8.8 g/dl), and the diagnosis of gastrointestinal bleeding of uncertain origin is maintained. The capsule endoscopy study reveals normal villi in the duodenum, jejunum, and ileum, along with angiectasia in the proximal ileum (Image 2), without evidence of tumor lesions.

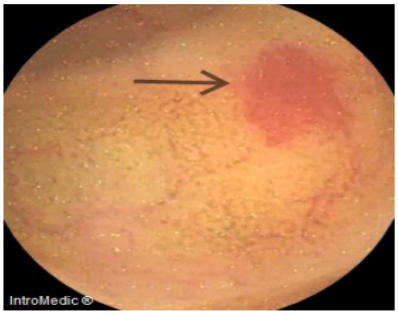


Image 2. Capsule endoscopy at the level of the ileum (proximal angiectasia).

A diagnostic angiography is performed, revealing a hypervascular solid lesion in the mesenteric branch of the proximal ileum (Image 3), which could correspond to a GIST tumor.

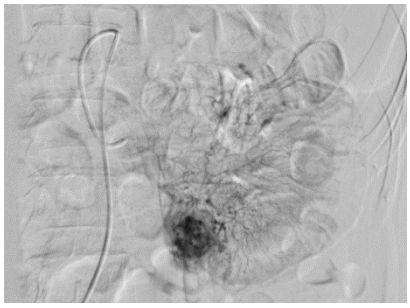


Image 3. Mesenteric angiography, showing an image compatible with a GIST tumor.

In reference to this finding and the family history of neurofibromatosis, imaging studies of the brain, chest, abdomen, and pelvis are requested, along with a thyroid ultrasound and tumor markers. Notably, the brain MRI, both simple and contrast-enhanced, shows enlargement of the optic chiasm and the intracranial segment of both optic nerves in the suprasellar region, isointense to gray matter on T1 and T2 sequences. After contrast administration, there is a slight heterogeneous enhancement, a finding suggestive of an optic pathway glioma (Image 4). Further tumor marker results are collected: carcinoembryonic antigen, alpha-fetoprotein, CA125, CA19-9, CA15-3, CA72-4, all negative, as well as additional imaging studies that rule out the presence of neoplasms in extra-intestinal organs.

On the 15th day of hospitalization, due to the persistence of melena episodes, the General Surgery service decided to perform a diagnostic and therapeutic laparoscopy. During the surgical intervention, a distended gallbladder with thickened and edematous walls and internal calculi is observed. Additionally, dense adhesions between the gallbladder and colon, as well as between the gallbladder and duodenum, are identified. In the proximal jejunum, between 4 and 20 small tumors are found on the antimesenteric

borders, located 30 and 40 cm from the Treitz angle. A rounded and irregular tumor of 4 cm is also observed on the antimesenteric border of the distal jejunum, 140 cm from the Treitz angle, vascularized and protruding into the abdominal cavity and the intestinal lumen (Image 5). Surgical resection of the intestinal tumor is performed, along with laterolateral isoperistaltic anastomosis, and samples are taken for histopathological study.

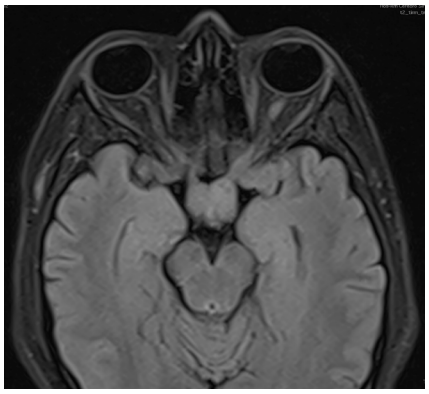
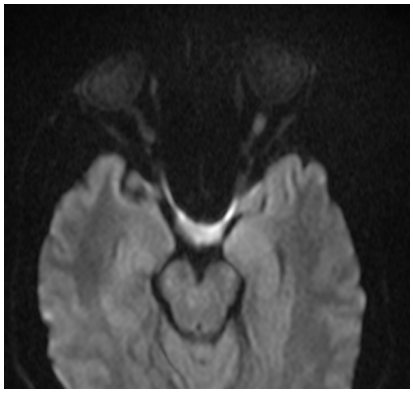
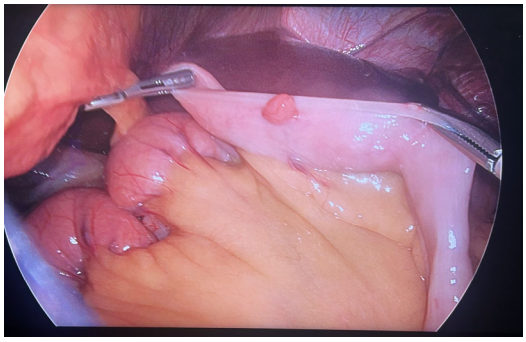
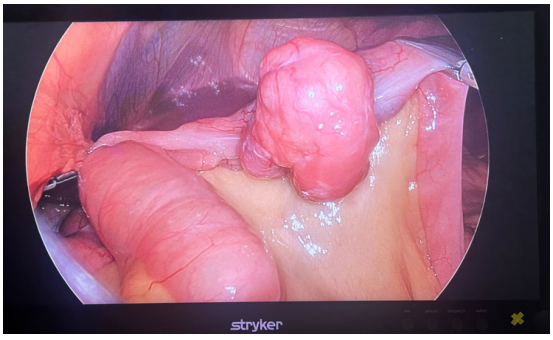
A  B 

Image 4. A: Simple brain MRI showing optic glioma and thickening of the optic nerve and optic chiasm. **B:** Diffusion MRI confirming the presence of optic glioma.

A  

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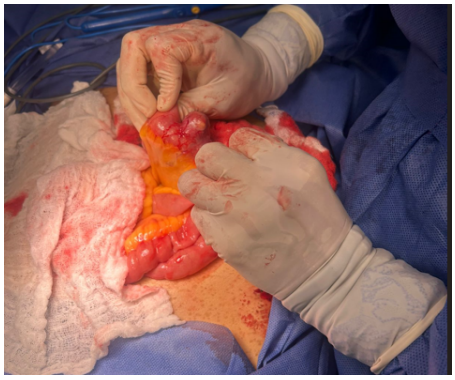

Image 5. A: Image obtained by laparoscopic surgery, showing small tumors on the antimesenteric border. **B:** 4 cm tumor located 140 cm from the Treitz angle. **C:** Larger tumors in the intestine.

The patient, after the surgical intervention, shows good oral tolerance and no new evidence of active gastrointestinal bleeding in the subsequent days.

During her recovery in the hospital, the biopsy result of the small intestine segment is obtained. The findings reveal a 5 cm biphasic mesenchymal neoplasm with slight atypia and low mitotic activity, consistent with a low-grade GIST. As a result, the patient was transferred in optimal health conditions to a third-level oncology center to continue her comprehensive oncological treatment (Image 6).

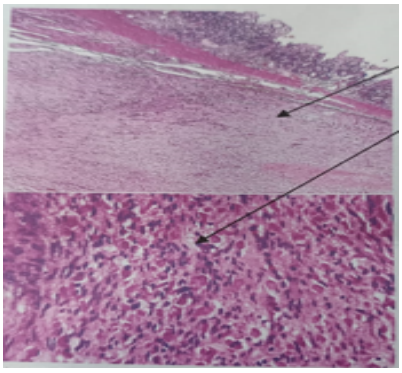

Image 6. Histopathological finding of intestinal tumor: with H&E staining, a moderately differentiated neoplasm is observed, composed of fusiform elements with slight atypia. At higher magnification, elongated nuclei arranged in loose fascicles are seen.

3. Discussion

Gastrointestinal stromal tumor (GIST) is a rare tumor of the small intestine, with an incidence of 10 to 20 cases per million inhabitants. Its early diagnosis is difficult due to nonspecific symptoms; gastrointestinal bleeding being the most common manifestation, which can be accompanied by anemia, melena, or hematemesis. Fifty percent of patients report bleeding, and 37.5% report pain, while only 5% are asymptomatic. Diagnosis is made through endoscopy, endoscopic ultrasound, and computed tomography [7,8,9]. In this case, the upper gastrointestinal endoscopy and colonoscopy were normal, so an abdominal angiography was performed, which located the vascular lesion at the mesenteric level, with a possible diagnostic of GIST based on imaging. What makes this case unique is its unusual location that makes it a diagnostic challenge during the approach.

Patients with neurofibromatosis type 1 have a higher risk of developing GIST, with a frequency of 5-25%. Gastrointestinal manifestations include submucosal hyperplasia, stromal tumors, carcinoids, and a greater predisposition to adenocarcinomas. GISTs in these patients may appear late, even after cutaneous symptoms, and are more common in women. They are often asymptomatic, especially if they are smaller than 3 cm, but they can cause gastrointestinal bleeding, anemia, abdominal pain, and intestinal obstruction [10,11]. It is important to note that the patient did not have an established diagnosis of neurofibromatosis, but due to her family history, specifically her brother, this condition should also be considered in her case, as it could be linked to GIST tumors. The main treatment is surgical, followed by adjuvant therapy with kinase inhibitors to reduce the growth of microscopic tumors after resection [12]. Imatinib is the drug of choice, showing improved recurrence-free survival. In cases where resection is not possible, neoadjuvant treatment with Imatinib for 4 to 6 months before surgery is considered, evaluated by computed tomography or PET scan [13,14]. Other therapeutic options within this family include Sunitinib and Regorafenib, which have been approved for patients who have previously received Imatinib, thus providing an additional option for subsequent treatment lines. Currently, the PEAK clinical trial is underway. This phase III study is evaluating the combination of Sunitinib with Bezuclastinib (formerly known as CGT-9486) in patients with progressive GIST after limited response to Imatinib treatment [15].

The prognosis after surgery depends on factors such as the mitotic rate, tumor size, location, surgical margins, and tumor rupture status. Studies show that most patients remain disease-free after surgical resection and adjuvant treatment, with success rates of 82% at 1 year, 89% at 3 years, and 92% at 5 years [16].

4. Conclusions

EGISTs are a rare and difficult-to-diagnose pathology that require a comprehensive approach managed by a multidisciplinary team. Although mesenteric GIST tumors are uncommon, imaging studies can be useful for early identification and assessing tumor resectability. Surgery is a crucial step and can offer a favorable prognosis when the diagnosis is made early. Neoadjuvant or adjuvant support will depend on the results of the pathological report. Additionally, it is recommended that patients with neurofibromatosis be screened for this type of tumor, given the higher likelihood of presenting GIST in this population.

5. Limitations of the study

The patient could not be approached from a genetic standpoint as the necessary studies were not available at the healthcare facility where she was located, despite having a family history of neurofibromatosis and physical exam findings compatible with it. Additionally, the patient was referred to an oncology center to continue her treatment, so follow-up could not be performed.

6. Abbreviations

GIST: Gastrointestinal Stromal Tumors

EGIST: Extra-gastrointestinal Stromal Tumors

dl: deciliter

PET: Positron Emission Tomography

ul: microliters

7. Administrative Information

7.1 Additional Files

No additional files declared by the authors.

7.2 Acknowledgments

We would like to express our gratitude to the patient and their family for agreeing to the publication of this scientific work.

7.3 Contributions of the Authors

All authors read and approved the final version of the manuscript.

7.4 Funding

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7.5 Data and Material Availability

Data is available upon request to the corresponding author. No other materials are reported.

8. Declarations

8.1 Informed Consent

The patient gave written informed consent for the publication of this case report and the accompanying images. The journal's chief editor holds a copy of the written consent for review.

8.2 Conflict of Interest

The authors declare no conflicts of interest related to this article. None of the authors have received funding from any organization or entity to conduct this study. There are also no personal, professional, or commercial relationships that could influence the results or interpretation of the data presented in this work.

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Review article / Artículo de revisión

Clinical and therapeutic aspects of Pancoast Tumor: A bibliographic review

Aspectos clínicos y terapéuticos del tumor de Pancoast: una revisión bibliográfica

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ABSTRACT
Introduction: Pancoast tumor (PT) is a rare and challenging form of lung cancer located at the pulmonary apex. Although it represents only 3 to 5% of all lung cancers, it poses significant diagnostic and therapeutic challenges. **Objective:** To identify and analyze the most recent clinical and therapeutic aspects of PT. **Materials and Methods:** We conducted a descriptive bibliographic review using databases such as PubMed and Google Scholar. We examined thirty-nine articles published between 2014 and 2024. **Results:** PT accounts for 3% to 5% of lung cancers, predominantly in male smokers. Clinically, it is associated with distinctive symptoms such as shoulder pain, Horner's syndrome, and muscle atrophy of the hand. Radiographic presentation and symptom similarity with other diseases complicate diagnosis. **Discussion:** Patients often confuse the clinical manifestation of pain from PT with other pathologies, underscoring the importance of a thorough differential diagnosis. The trimodal treatment combining surgery, chemotherapy, and radiotherapy remains the standard, although the development of less invasive techniques improves outcomes. The use of proton therapy and 3D-CRT optimizes the resectability of the tumor and enhances the postoperative quality of life. **Conclusion:** Despite advancements, early diagnosis of PT remains challenging due to its deceptive symptoms. The trimodal approach has significantly improved survival expectations, although the side effects of chemotherapy and radiotherapy persist. Future research could focus on biological agents and immunotherapy to offer more effective personalized treatments.

Keywords: Pancoast syndrome, lung cancer, combined modality therapy, chemoradiotherapy.

RESUMEN
Introducción: El tumor de Pancoast es una forma rara y desafiante de cáncer de pulmón ubicada en el ápice pulmonar. Aunque su porcentaje respecto a todos los cánceres de pulmón es bajo, conlleva importantes dificultades diagnósticas y terapéuticas. **Propósito:** Identificar y analizar los aspectos clínicos y terapéuticos más recientes de este tipo de tumor. **Materiales y métodos:** Se realizó una revisión bibliográfica descriptiva mediante bases de datos como PubMed y Google Scholar. Se examinaron 39 artículos publicados entre 2014 y 2024. **Resultados:** El tumor de Pancoast representa entre un 3 y un 5 % de los cánceres de pulmón, con predominio en varones fumadores. Clínicamente, se asocia con síntomas distintivos como dolor en el hombro, el síndrome de Horner y atrofia muscular de la mano. El diagnóstico se complica debido a su presentación radiográfica y a la similitud con síntomas de otras enfermedades. **Discusión:** La manifestación clínica del dolor en este tumor se confunde a menudo con otras patologías, lo que destaca la necesidad de un diagnóstico diferencial exhaustivo. El tratamiento trimodal que combina cirugía, quimioterapia y radioterapia se mantiene como el

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estándar, aunque el desarrollo de técnicas menos invasivas mejora los resultados. El uso de la terapia de protones y 3D-CRT está optimiza la resecabilidad del tumor y mejora la calidad de vida posoperatoria. **Conclusión:** A pesar de los avances, el diagnóstico temprano del tumor de Pancoast sigue siendo difícil debido a sus síntomas engañosos. El enfoque trimodal ha mejorado significativamente las expectativas de supervivencia, aunque los efectos secundarios de la quimioterapia y la radioterapia persisten. Futuras investigaciones podrían centrarse en agentes biológicos e inmunoterapia para ofrecer tratamientos personalizados más efectivos.

Palabras clave: tumor de Pancoast, cáncer de pulmón, terapia combinada, quimioradioterapia.

1 Introduction

Lung cancer (LC) ranks among the leading causes of cancer-related mortality worldwide, accounting for 12.8% of all oncological diagnoses [1]. Pancoast tumor (PT), which is also known as superior sulcus tumor, is a rare and difficult type of LC [2, 3]. It only makes up 3% to 5% of all lung carcinomas [4]. This kind of tumor is usually a subtype of non-small cell lung cancers (NSCLC), which make up more than 95% of cases [5–8]. Small cell lung carcinomas (SCLC) are not common in this area. The most common histological types are adenocarcinoma, which is currently predominant, and squamous cell carcinoma, which was historically the most frequent [7, 8].

The peculiarities of PT reside in its location at the pulmonary apex and its ability to invade adjacent structures of the thoracic inlet, such as the brachial plexus, ribs, and pleura [9]. These characteristics can lead to a clinical presentation known as Pancoast-Tobias Syndrome (PTS), characterized by shoulder and arm pain, Horner's syndrome (HS), and muscle atrophy of the hand [10].

Identifying relevant clinical and therapeutic factors is crucial for the development of effective treatment strategies; our review focuses on this aspect [11, 12]. In this analysis, we will explore recent advancements related to PT, focusing on diagnostic and therapeutic modalities such as trimodal treatment that integrates chemoradiotherapy with surgical intervention.

This study aims to address the research question: What are the most recently described clinical and therapeutic aspects of the Pancoast tumor?. We narrowed the focus to characteristic clinical signs, updated diagnostic modalities and innovative therapeutic strategies with the intention of enriching the shared body of knowledge and optimizing the clinical approach to this peculiar type of pulmonary neoplasm.

2. Materials and Methods

2.1 Study Design

A descriptive bibliographic review study was conducted, focusing on the identification, collection, and analysis of existing literature on the clinical and therapeutic aspects of PT.

2.2 Analyzed Databases

The electronic databases PubMed, Google Scholar, and SciELO were selected to carry out the search for scientific literature related to the topic. These databases were chosen due to their comprehensiveness and ease of access to various studies, including original investigations, systematic reviews, case reports, and clinical trials.

2.3 Search Terminology

To conduct the search of medical terms in both Spanish and English, Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) vocabulary was used. The searched terms were "*Síndrome de Pancoast*", "*Tumor de Pancoast-Tobias*", "*Cáncer de pulmón*", "*Terapia combinada*", along with their equivalents in English. Boolean operators such as AND ("Pancoast syndrome AND Lung cancer") and OR NOT were entered to optimize the results and to exclude non-pertinent terms.

2.4 Inclusion Criteria

Studies published between 2014 and 2024 in both English and Spanish were included, encompassing qualitative and quantitative ones, systematic reviews, and case studies that provide updated information on PT.

2.5 Exclusion Criteria

Duplicate articles, non-peer-reviewed works, and those not specifically addressing PT were excluded.

3. Results

Out of all the studies found, 39 articles were selected and examined to conduct this research.

3.1 Clinical Manifestations

PT, also known as a superior sulcus tumor, is a particularly complex type of LC, presenting various symptoms that often mimic other pathologies, thus complicating the diagnosis. One of the most predominant symptoms in its clinical presentation is severe shoulder pain, attributed to the invasion of the brachial plexus [2, 9]. This pain is present in up to 96% of patients and is generally described as burning or electric, which can lead to confusion with orthopedic ailments [2, 8, 9, 12, 13]. These findings support the observations by authors such as Al Shammari et al. (2020) and Calabek et al. (2015), who note that this pain can radiate to the arm and hand, thus confusing this condition with musculoskeletal diseases [6, 14].

HS is among the most characteristic manifestations of PT. This is a triad of symptoms consisting of ptosis, miosis, and anhidrosis, resulting from the involvement of the stellate sympathetic ganglion [1]. This syndrome reflects the more extensive compromise of adjacent structures and is also referred to by Sobash et al. (2021) and Calabek et al. (2015) as a classic manifestation in advanced stages, which, in conjunction with shoulder pain, arm pain, and hand muscle atrophy, corresponds to PTS [6, 15]. However, although HS is common, Rao et al. (2023) and Mohamud et al. (2022) report that its presence, along with symptoms such as dyspnea and muscle atrophy, increases the complexity of the clinical picture [1, 9].

The diagnostic challenge is compounded by the similarity of PT symptoms to other conditions, such as thoracic outlet syndrome and cervical radiculopathy [5, 16]. Studies by Berntheizel et al. (2023) and Bishnoi et al. (2023) highlight that this similarity underscores the need for high clinical suspicion, especially in patients with a smoking history [5, 16]. This is because, at times, the differential diagnosis is complicated due to endemic areas presenting other diseases like tuberculosis, as Nugroho et al. (2023) found frequently [11].

In more advanced stages, clinical manifestations can include respiratory difficulty and even metastasis to distant organs [1, 7, 9]. Mohamud et al. (2022) document cases where these atypical symptoms have challenged physicians to diagnose accurately [9]. Marulli et al. (2016) and Rao et al. (2023) point out that, although rare, metastasis to distant sites such as the heart adds up to clinical complexity [1, 7]. Additionally, authors like Forooghi et al. (2019) describe rare cases of atypical manifestations, including jaw and dental pain, which can mimic oral diseases and delay proper diagnosis [17].

Early and accurate diagnosis is essential to optimize treatment outcomes, although it is complicated due to the misleading clinical presentation of PT [5, 12, 16]. As studies by Bishnoi et al. (2023) and Berntheizel et al. (2023) indicate, the initial presentation of these tumors often lacks typical pulmonary symptoms and lead to misdiagnoses [5, 16]. Therefore, the use of advanced imaging techniques, as mentioned by Chu et al. (2022) and Mohamud et al. (2022), is crucial for clarifying the diagnosis and correctly differentiating between these conditions [9, 12].

Lastly, tobacco use has been observed to strongly correlate with the occurrence of these tumors, being a common etiological factor in the personal history of many patients [9, 17]. This etiological aspect, coupled with the clinically challenging presentation of this tumor, underscores the need for a thorough reevaluation when persistent shoulder pain is found in individuals with a history of smoking.

3.2 Diagnostic Evaluation

The diagnosis of PT can be complicated due to its misleading clinical presentation, frequently confused with other musculoskeletal or neurological conditions, which can delay the definitive diagnosis [8, 12, 17–19]. Suspicion of a PT typically arises in patients with shoulder pain and neurological symptoms in the distribution of C8, T1, and T2, or HS, combined with a mass in the pulmonary apex identified in imaging studies [11, 20, 21].

In the presence of persistent shoulder pain, advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are essential, as simple radiography often fails to identify masses in the apex. CT stands out as a useful tool for evaluating the tumor's invasion into bone and soft tissue structures, while MRI provides a more precise analysis of the involvement of the brachial plexus and spinal cord, necessary for surgical treatment planning [1, 11, 12, 21].

Histological confirmation of PT by CT-guided biopsy is standard practice, although case reports have demonstrated that in situations where percutaneous biopsy is not conclusive, alternative methods such as endobronchial ultrasound (EBUS) with a transesophageal approach or mediastinoscopy are effective for obtaining diagnostic samples [4, 10]. Foroughi et al. (2019) and Mohamud et al. (2022) describe these techniques as having become essential to ensure accurate identification and avoid inappropriate treatments that may result from a misdiagnosis [9, 17].

The differential diagnosis is complex due to symptomatic overlapping with various pathologies [2, 9, 22]. One of the main differential diagnoses is NSCLC, which represents most of PT cases TP [9]. Within this group, adenocarcinoma is currently the most common histological subtype, followed by squamous cell carcinoma. Although less frequent, large cell carcinoma may also be present. These subtypes should be considered when evaluating any mass at the pulmonary apex [7, 8].

SCLC constitutes another relevant differential diagnosis, though it is uncommon in this location. Its rapid progression and specific response to chemoradiotherapy make it a significant diagnostic challenge requiring histological confirmation [2, 8].

Pulmonary tuberculosis, particularly in endemic regions, can manifest as apical masses mimicking PT [11]. This differential diagnosis is crucial in patients with compatible epidemiological backgrounds and should be ruled out through specific microbiological and imaging studies [17].

Thoracic outlet syndrome is another condition that frequently shares symptoms with PT, such as shoulder pain and neurological disturbances. Precise differentiation requires a comprehensive clinical and radiological approach to avoid diagnostic errors. Pulmonary metastases originating from extrapulmonary tumors, such as those of the breast, colon, or kidney, should also be considered [1, 7, 10, 12]. These lesions can be located at the pulmonary apex and present clinical and radiological characteristics like PT, emphasizing the importance of thorough evaluation [11].

Other less frequent pathologies include pleural mesothelioma, which can involve the apical region of the lung in advanced cases, and musculoskeletal diseases like cervical spondylosis and disc hernias, which are often initially misdiagnosed due to overlapping symptoms [6, 21].

Finally, Jevremovic et al. (2017) highlight that rare diagnoses such as myxoid sarcoma and other neurogenic tumors like schwannomas or neurofibromas may be found in atypical presentations of PT. These conditions underscore the importance of maintaining a broazd and multidisciplinary diagnostic approach to ensure appropriate clinical management [23].

This highlights the significance of a multidisciplinary approach where imaging, histopathology, and clinical evaluation converge to ensure an accurate diagnosis. Collaboration among oncologists, radiologists, pathologists, and neurologists is essential to prevent treatment delays resulting from misdiagnoses [4, 7, 22]. Advanced imaging modalities, e.g., positron emission tomography (PET) with 18F-FDG, are increasingly used to identify occult metastases, complementing traditional diagnostic strategies [10].

3.3 Treatments

3.3.1 Surgery

Historically, the surgical treatment of PT was considered challenging due to the critical anatomical location at the lung apex, often involving complex thoracic structures such as brachial plexus nerves,

subclavian vessels, and spine. The surgical approach to this tumor must be multidisciplinary, combining the skills of thoracic surgery, oncology, and radiotherapy to improve patient outcomes [20].

Modern surgical techniques have evolved significantly from the anterior transcervical approach described in the 1980s, which provided innovative access to the thoracic inlet and subclavian vessels. Newer surgical techniques, such as Video-Assisted Thoracic Surgery (VATS) and the use of proton beam radiotherapy, have allowed for more precise and less invasive management of PTs, thereby reducing postoperative complications such as chylothorax and ulnar nerve paralysis [15, 23–26].

The trimodal approach, which combines neoadjuvant chemoradiotherapy and surgical resection, has become the standard in PT treatment due to improvements in survival rates, which can reach up to 55% if complete resection is achieved [1]. However, as noted by Gundepalli & Tadi (2024), there are clear contraindications for surgery in cases of extensive invasion of the brachial plexus or significant involvement of the soft tissues of the neck [2].

Various studies have shown that VATS techniques, when combined with advanced diagnostic methods like PET and MRI, are effective in assessing tumor extent and optimally planning surgery [12, 26]. The cases reported by Rosso et al. (2016) emphasize that VATS avoids muscle damage and facilitates a minimally invasive approach, promoting shorter recovery times without compromising oncological outcomes [26].

A multidisciplinary medical-surgical approach integrating proton beam radiation therapy with robotic surgery for complex cases is crucial. It allows patients with significant respiratory impairment to benefit from a quicker functional recovery [26, 27]. For example, the experiences of Kawai et al. (2017) demonstrate that the use of LigaSure in thoracic surgery can significantly reduce tissue damage and facilitate less invasive procedures [27].

The advancement of robotic surgery has provided a viable option to improve precision and control in difficult surgeries, also allowing for better visualization and maneuverability without the need for extensive thoracic incisions [28, 29]treated by induction concurrent chemoradiotherapy (CRT. This results in surgical management is not only more effective but also minimizes postoperative complication rates and enhances patient recovery.

3.3.2 Chemotherapy

Chemotherapy emerges as an essential component within a multimodal approach, frequently combined with radiotherapy to maximize the effectiveness of neoadjuvant treatment in patients with PT [1, 11, 30]. This type of treatment has been shown to improve tumor respectability and increase survival, although high recurrence rates still pose challenges [12, 17, 31]. Induction chemotherapy, often in combination with radiotherapy, is recommended for patients with locally advanced tumors, assisting them toward potential surgical resection with regimens of cisplatin combined with other agents like gemcitabine [10, 26, 27, 32].

Recent studies, such as that by Bansal et al. (2022), explore the addition of biological and immunotherapeutic agents as part of the therapeutic arsenal, although these practices are predominantly investigational at present [33]. The synergy between cisplatin and gemcitabine aims to optimize the elimination of tumor cells while preserving functional lung tissue, standing out for its effectiveness in reducing tumor volume before surgery [27, 32].

A clear limitation of using chemotherapy in PT is the severe side effects, including hematological toxicity and neurotoxicity [16, 28]. Authors such as Jeannin et al. (2015) and Bishnoi et al. (2023) assert that these factors not only affect patient quality of life but can also limit the administration of doses necessary for a complete therapeutic effect [16, 28]. However, Jevremovic et al. (2017) noted that by adjusting dosages and applying sequential regimens along with supportive treatments, more patients can tolerate the regimen to achieve maximum therapeutic benefits [23].

The prognosis for patients with PT undergoing trimodal treatment varies. Factors such as local tumor invasion and the presence of metastases require continuous adaptation to new therapeutic strategies based on emerging data from clinical trials [19, 24, 31].

Chemotherapy, as part of a multimodal treatment, continues to evolve. The inclusion of more modern approaches, which integrate molecular biology and potential personalized therapies could offer more adaptive and effective alternatives for managing PT in the future [17, 26, 29, 34, 35].

3.3.3 Radiation Therapy

Over time, radiation therapy has transitioned from its application as a primary treatment to being part of a multimodal therapeutic regimen, including chemotherapy and surgery, particularly for stage III non-small cell LC tumors [19, 30, 31].

Several studies have demonstrated that trimodal therapy, which incorporates neoadjuvant radiation therapy, significantly improves survival rates and locoregional control of the disease [2, 11].

The objective is to reduce the tumor size and minimize the impact on vital structures, allowing for a more effective and safer resection [4]. Beyond its neoadjuvant applications, radiotherapy has also been established in the palliative domain. In the context of advanced metastatic disease, its role focuses on alleviating pain and improving the quality of life for patients [1]. However, its effectiveness in palliative scenarios is limited due to disease progression; therefore, its value would lie in managing acute complications arising from metastases or nerve compression.

Advancements in radiation techniques such as three-dimensional conformal radiotherapy (3D-CRT) and proton therapy have allowed more precise dose delivery, minimizing damage to surrounding tissues [7, 23].

Reviews and case studies have also examined the impact of radiotherapy on resectability and surgical recovery. Different studies, like those by Kalagara et al. (2019) and Mariolo et al. (2018), have found that chemoradiotherapy regimen before surgery not only make the resection safer but also seem to lower the number of complications after surgery related to these aggressive procedures [32, 34]. This approach has proven effective for tumors traditionally considered inoperable or whose resection could be extraordinarily challenging.

3.3.4 Immunotherapy

Therapies based on immune checkpoint inhibitors, such as PD-1 (programmed death-1) and PD-L1 (programmed death-ligand 1) inhibitors, have shown promising results in patients with advanced NSCLC, extending overall survival and improving the quality of life [36–38].

Although specific experience with immunotherapy in PT is limited due to its low incidence, preliminary studies suggest that patients with high PD-L1 expression might benefit from these treatments, especially as a neoadjuvant in combination with chemoradiotherapy [30].

Tang et al. (2021) described the case of a patient with a Pancoast tumor treated with tislelizumab in combination with chemotherapy in a neoadjuvant approach, achieving a tumor reduction of 71%. Post-surgical intervention, pathological analyses confirmed a complete pathological response. Furthermore, circulating tumor cell tests were negative after the first adjuvant treatment [30].

Additionally, ongoing research is evaluating its role in the neoadjuvant setting and as part of trimodal approaches, aiming to optimize therapeutic outcomes in this complex tumor type [30, 36, 37].

4. Discussion

The in-depth analysis of the selected literature highlights the diagnostic and therapeutic complexity represented by PT; emphasizing both the persistence of classic challenges and the evolution toward more comprehensive and effective approaches. Therefore, what are the most recently described clinical and therapeutic aspects of Pancoast tumor?

Regarding the clinical manifestations of PT, most studies agree that shoulder pain, primarily derived from brachial plexus invasion, remains the most prevalent symptom [2, 9]. However, Al Shammari et al. (2020) and Calabek et al. (2015) emphasize the potential for this pain to be mistaken for orthopedic conditions, which poses a challenge in differential diagnosis [6, 14]. These difficulties underscore the importance of a thorough clinical evaluation to differentiate the cause of the pain, as other pathologies affecting the same area may present with similar symptoms, as indicated in the studies by Berntheizel et al. (2023) and Bishnoi et al. (2023) [5, 16].

HS, also common in this context, is a significant sign of the involvement of adjacent structures. Still, its presence does not always indicate a definitive diagnosis of PT due to clinical similarities with other diseases [1, 9]. The need for innovations in diagnosis is evident, as studies such as Nugroho et al.

(2023) highlight the possibility of endemic diseases, such as tuberculosis, complicating the differential diagnosis [11].

In the diagnostic field, the combination of CT and MRI remains the standard for detecting the extent of PT, especially in evaluating brachial plexus and bony structures invasion. However, Forooghi et al. (2019) and Mohamud et al. (2022) point out the growing importance of technologies such as EBUS and PET, which can provide additional details in cases where there are diagnostic uncertainties [17, 39]. The issue of differentiating between PT and similar conditions, such as sarcomas or other neoplasms, underscores the complexity of a correct diagnostic assessment, as discussed by Jevremovic et al. (2017) and Kazimirko et al. (2016) [22, 23].

From a therapeutic perspective, the trimodal treatment combining surgery, chemotherapy, and radiotherapy has significantly transformed survival expectations for patients with Pancoast tumor (PT). Although surgery remains a key component, the approach has evolved towards less invasive techniques, such as VATS, which offers better functional outcomes without sacrificing oncological effectiveness [26, 27]. However, as Gundepalli & Tadi (2024) indicate, the invasion of the brachial plexus continues to be a hurdle for surgery, requiring careful clinical consideration [2].

Chemotherapy and radiotherapy, as part of the trimodal approach, have been refined with the inclusion of techniques such as proton therapy and 3D-Conformal Radiation Therapy (3D-CRT), enhancing both tumor resectability and postoperative quality of life [23, 32]. Nevertheless, side effects remain a significant challenge, and as suggested by Jeannin et al. (2015) and Bishnoi et al. (2023), optimizing dosages and therapeutic regimens is crucial for improving outcomes without compromising patient tolerability [16, 28].

The use of biological agents and immunotherapy in PT management is promising, although it is currently more experimental. Bansal et al. (2022) indicate that these strategies may become more prevalent in the future, suggesting a move towards personalized treatments [33], while Cheng et al. (2024) and Huang et al. (2024) state that their use offers new hope in the fight against this complex type of cancer [36, 37].

5. Conclusion

PT represents a unique clinical entity within the context of LC, characterized by its specific anatomical location and distinctive symptoms that complicate both its diagnosis and clinical management. Our findings reinforce the need for a multimodal treatment approach that incorporates innovative surgical, chemotherapeutic, and radiotherapeutic strategies to significantly improve patient outcomes. Future research must continue to explore ways to reduce the adverse effects associated with current treatments and develop more personalized therapies. Existing literature highlights the importance of collaborative and multidisciplinary approaches to optimize clinical outcomes. Finally, additional studies that include novel agents and improved diagnostic techniques are needed to evolve and refine the treatment of this challenging type of cancer.

6. Abbreviations

LC: Lung Cancer

PT: Pancoast Tumor

NSCLC: Non-Small Cell Lung Cancer

SCLC: Small Cell Lung Carcinoma

PTS: Pancoast-Tobias Syndrome

HS: Horner's Syndrome

CT: Computed Tomography

MRI: Magnetic Resonance Imaging

EBUS: Endobronchial Ultrasound

PET: Positron Emission Tomography

VATS: Video-Assisted Thoracic Surgery

7. Administrative Information

7.1. Additional Files

None declared by the author.

7.2. Acknowledgments

Not applicable.

7.3. Author Contributions

Marlon Moreira Morán: Conceptualization, methodology, investigation, project administration, writing - draft/original, writing - review and editing.

Fiorella Castillo Cruz: Conceptualization, methodology, writing - draft/original, writing - review and editing.

Ana Noriega Cabrita: Conceptualization, project administration, supervision, writing - draft/original, writing - review and editing.

All authors read and approved the final version of the manuscript.

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7.5.2. Conflicts of Interest

The author declares no conflicts of interest.

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Article / Artículo

Efficacy and safety of PD-1/PD-L1 inhibitors as immunotherapy in advanced endometrial cancer: a systematic review

Eficacia y seguridad de la inmunoterapia anti-PD-1/PD-L1 en cáncer de endometrio avanzado: una revisión sistemática

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ABSTRACT
Introduction: Endometrial cancer is the most common malignant neoplasm of the female genital tract in developed countries. The standard first-line treatment in advanced stages is platinum-based chemotherapy. However, a standardized chemotherapy regimen is not available for second and subsequent lines after disease progression. Immune checkpoint inhibitors, which target PD-1 proteins (pembrolizumab, nivolumab, dostarlimab, and sintilimab) or PD-L1 (durvalumab and avelumab), have emerged as effective alternatives in the second-line treatment of advanced or recurrent endometrial cancer, either as monotherapy or in combination with other targeted therapies. **Materials and Methods:** We conducted a bibliographic search of articles published in the last 5 years. Databases such as PubMed, Web of Science and Cochrane have been used for this purpose. **Results:** Twelve articles were selected for review that collect efficacy and safety data on the use of immunotherapy in patients with advanced endometrial cancer who have previously received at least one line of platinum-based chemotherapy treatment. Four of the publications refer to the use of pembrolizumab, in monotherapy or associated with lenvatinib, two of them being carried out by the same research team. **Conclusions:** Immunotherapy presents a high response rate in advanced endometrial cancer that expresses alteration of the DNA base repair pathway and microsatellite instability. In comparison to conventional chemotherapy in patients with advanced endometrial cancer, immunotherapy has shown efficacy, either as monotherapy or in combination with other targeted therapies.

Keywords: Endometrial cancer, immunotherapy, targeted therapy, immune checkpoint inhibitors.

RESUMEN
Introducción: El cáncer de endometrio es la neoplasia maligna más frecuente del tracto genital femenino en países desarrollados. El tratamiento estándar de primera línea en estadios avanzados es la quimioterapia basada en platino. Sin embargo, no se dispone de un régimen estándar de segunda línea y sucesivas tras la progresión de la enfermedad. Los inhibidores de punto de control inmunológico, que actúan contra las proteínas PD-1 (pembrolizumab, nivolumab, dostarlimab y sintilimab) o PD-L1 (durvalumab y avelumab), en monoterapia o en combinación con otras terapias dirigidas, han surgido como alternativas eficaces en el tratamiento de segunda línea del cáncer de endometrio avanzado. **Material y métodos:** Se realizó una búsqueda bibliográfica de artículos publicados en los últimos cinco años en las bases de datos PubMed, Web of Science y Cochrane. **Resultados:** Se seleccionaron 12 artículos para su revisión; estos recogen datos de la eficacia y la seguridad del uso de inmunoterapia en pacientes con cáncer de endometrio avanzado que ya habían recibido al menos una línea de quimioterapia basada en platino. Cuatro de las publicaciones se refieren al empleo de

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pembrolizumab, en monoterapia o en combinación con lenvatinib, y dos de ellas fueron realizadas por el mismo equipo de investigación. **Conclusiones:** La inmunoterapia presenta una elevada tasa de respuesta en el cáncer de endometrio avanzado que expresa alteraciones de la vía reparadora del ADN e inestabilidad de microsatélites. Ha demostrado además eficacia respecto a la quimioterapia convencional, tanto en monoterapia como en combinación con otras terapias dirigidas, en pacientes con cáncer de endometrio avanzado.

Palabras Clave: neoplasias endometriales, inmunoterapia, terapia dirigida, inhibidores de puntos de control inmunitarios.

1. Introduction

Endometrial cancer (EC) is the most frequent malignant neoplasm of the female genital tract in developed countries [1], affecting mainly women over 50 years of age, with a median age at diagnosis of 63 years old [2,3]. Its incidence has increased due to population aging and obesity [1-5]. Although more than 90% of cases are sporadic, up to 10% are hereditary in origin, generally associated with Lynch syndrome [6].

Microsatellite instability (MSI) is a common genetic abnormality in EC caused by defects in proteins of the DNA repair mechanism (mismatch repair, MMR). Depending on the degree of alteration, MSI can be high (MSI-H) or low (MSI-L) [7]. About 30% of ECs are deficient in MMR (dMMR) and MSI-H proteins, while most of them are tumors with microsatellite stability (MSS) and presence of MMR (pMMR) [8,9].

Twenty percent of patients with SC are diagnosed with advanced or metastatic disease (stage III or IV). Between 10-15% of ECs recur and 80-90% of recurrences occur within the first three years after diagnosis [9]. The standard first-line treatment of advanced or recurrent unresectable SC is platinum-based chemotherapy (QT) using the combination of carboplatin and paclitaxel [10,11]. Considering that second-line treatment options are limited, and advanced or recurrent EC ends up being largely resistant to QT, it is crucial to develop more effective and safer novel therapies [12,13].

PD-1 and PD-L1 proteins negatively regulate T-cell activity, preventing tumor cell killing and favoring cancer progression [14]. Immune checkpoint inhibitors (ICIs) block this interaction and have demonstrated antitumor activity with a good safety profile in patients previously treated with QT [12,13].

Monoclonal antibodies directed against PD-1 or PD-L1 enhance the immune response to attack cancer cells [12]. Their efficacy can be enhanced when combined with targeted therapies, such as receptor tyrosine kinase (RTK) inhibitors (e.g., Lenvatinib) or poly (ADP-ribose) polymerase enzyme inhibitors (PARP, e.g., Olaparib).

2. Materials and Methods

2.1 Primary objective

To evaluate the efficacy and safety of PD-1/PD-L1 inhibitors therapy, in monotherapy or in combination, in advanced SC.

2.2 Secondary objectives

To study the efficacy of immunotherapy and targeted therapies in patients with advanced CE dMMR/MSI-H versus pMMR/MSS.

To analyze the efficacy and safety of immunotherapy and targeted therapies versus QT in second-line treatment in patients with advanced SC.

2.3 Study design

A descriptive, observational, systematic review with a qualitative approach was carried out.

2.4 Databases and Search Terminology

The bibliographic search was performed in the PubMed, Web of Science, and Cochrane databases.

The search strategy was conducted by combining the MeSH terms "immune checkpoint inhibitors", "Pembrolizumab", "dostarlimab", "Lenvatinib", "paclitaxel", "carboplatin", "doxorubicin" and "endometrial neoplasms" with the Boolean operators AND and OR, as follows: (((((((((Immune Checkpoint Inhibitors)) OR (Pembrolizumab)) OR (Dostarlimab)) OR (Lenvatinib)) OR (Paclitaxel)) OR (Carboplatin)) OR (Doxorubicin)) AND (Endometrial Neoplasms))).

2.5 Inclusion criteria

Randomized and non-randomized clinical trials published in the last 5 years, in English and in humans, with patients who received at least one line of platinum-based QT.

2.6 Exclusion criteria

Studies that addressed several solid tumors (e.g., EC and ovarian cancer), compared brachytherapy and/or radiotherapy versus pharmacological treatments, evaluated the efficacy of the combination of immunotherapy and QT versus QT in monotherapy, or were cost-effective studies.

2.7 Study variables

The clinical variables evaluated in the studies were objective response rate (ORR), overall survival (OS), progression-free survival (PFS), complete response (CR), partial response (PR), disease progression (DP), duration of response (DR), and disease control rate (DCR) [15]. RECIST 1.1 and iRECIST criteria were applied [15,16]. Safety and toxicity were evaluated according to CTCAE v4 criteria [17], including the most frequent and serious adverse events (AEs).

2.8 Selection of articles

Twelve studies evaluating the effectiveness and toxicity of PD-1/PD-L1 inhibitor agents and targeted therapies in advanced SC were selected. The selection from electronic databases was performed by title and abstract, followed by a full-text review, choosing those that met the inclusion criteria. Figure 1 presents the article selection process using a PRISMA flowchart [18].

3. Results and Discussions

Table 1 lists the characteristics of the 12 studies [19-30]. In all of them, patients presented advanced or recurrent SC.

Five studies evaluated PD-1/PD-L1 inhibitors agents in monotherapy, including Durvalumab [20], Pembrolizumab [23,26,27], and Dostarlimab [28], in addition to a study on Cabozantinib [19]. Six analyzed combinations of PD-1/PD-L1 inhibitors and targeted therapies, including Nivolumab-Cabozantinib [21], Sintilimab-Antolinib [22], Avelumab-Talazoparib [24], Durvalumab-Olaparib [25], and Pembrolizumab-Lenvatinib [29,30]. Except for the study by Wei et al [22], all were multicenter.

3.1 Efficacy of immunotherapy and targeted therapies in patients with advanced or recurrent dMMR/MSI-H vs. pMMR/MSSS SC.

Studies highlight the differential efficacy of immunotherapy according to the molecular profile of EC, especially between dMMR/MSI-H and pMMR/MSS subtypes. PD-1/PD-L1 inhibitor agents, such as

Pembrolizumab [23,26], Durvalumab [20] and Dostarlimab [27] show higher antitumor activity in dMMR/MSI-H ECs, with ORR between 43.5% and 58%, due to their high neoantigen load and higher PD-1/PD-L1 expression [31]. Factors such as tumor microenvironment and previous exposure to QT also influence the response, as QT can increase tumor antigen presentation and immune susceptibility [20].

The combination of immunotherapy with antiangiogenic agents has been shown to extend efficacy in molecular subtypes less sensitive to ICI monotherapy. In the KEYNOTE-146 study, Pembrolizumab and Lenvatinib achieved an ORR of 39.8% and a PFS of 7.4 months, even in pMMR ECs [29]. Sintilimab and Anlotinib achieved an ORR of 100% in dMMR/MSI-H and 85.7% in pMMR, although the sample size limits the generalizability of the results [22].

Combinations of ICIs with PARP inhibitors have also been investigated, especially in patients with pMMR CE, although the results are less conclusive [24,25].

In general, treatments were well tolerated, with mild AEs including fatigue, diarrhea, anemia, and hypothyroidism [20,26,27]. Less frequent severe AEs include hypertension, neutropenia, and elevated liver enzymes [29]. Combinations with antiangiogenic agents showed higher rates of grade ≥3 AEs, such as hypertension and lipase elevation, but were manageable [22,29].

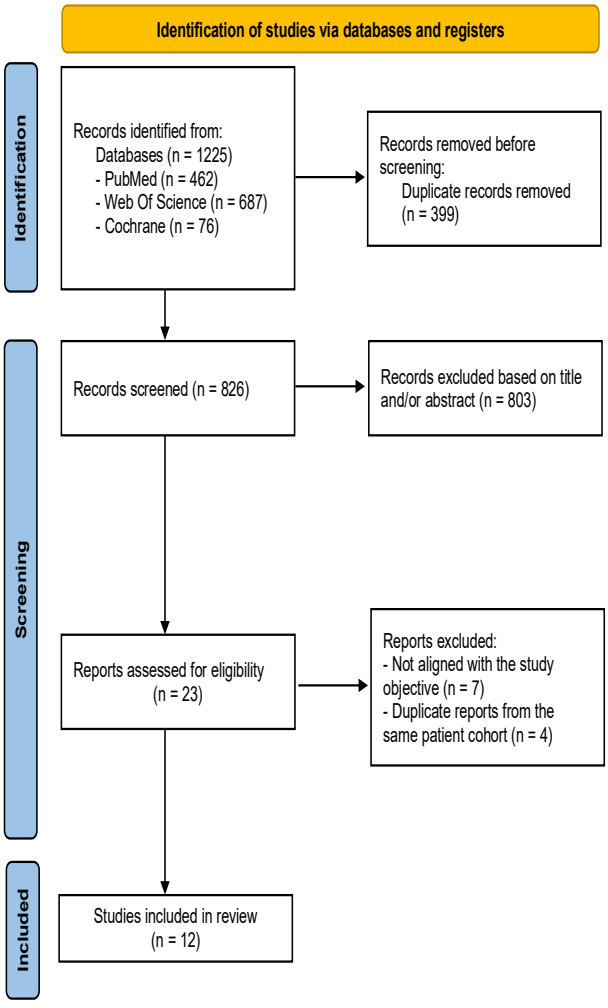

Figure 1 . Flow chart according to the PRISMA model of item selection. Source: Own elaboration based on the PRISMA 2020 flow chart.

Table 1. Description of the main characteristics and results of the studies.

Study data	n	Target	Conclusions
Dhani et al. (2020) [19]. United States.	102	Phase II trial on the efficacy of Cabozantinib in monotherapy in 2 cohorts of patients. Primary endpoint: PFS at 12 weeks and ORR.	Cabozantinib showed activity in the experimental cohort (endometrioid and serous histology), with a median PFS of 4.6 months and 6-month PFS of 37%. In the exploratory cohort (other histologies), PFS at 12 weeks was 47% and ORR 16%. Most common AEs: fatigue (61%), diarrhea (51%), palmar-plantar erythrodysesthesia (39%), and hypertension (25%).
Antill et al. (2021) [20]. Australia.	71	PHAEDRA phase II trial on the efficacy of Durvalumab in monotherapy: CE dMMR (n=35) and CE pMMR (n=36). Primary objective: TRO	Durvalumab showed ORR of 47% in dMMR EC compared with 3% in pMMR EC. OS at 12 months was 71% in dMMR and 51% in pMMR. The most frequent AEs were related to immunotherapy (20%).
Lheureux et al. (2022) [21]. United States.	54	Phase II trial on the efficacy of Cabozantinib and Nivolumab (n=36) versus Nivolumab monotherapy (n=18). Primary target: SLP.	The combination of Cabozantinib and Nivolumab significantly improved PFS compared to Nivolumab monotherapy (5.3 months vs. 1.9 months). Most frequent AEs: diarrhea (42%), AST elevation (42%), fatigue (36%) and anorexia (31%).
Wei et al. (2022) [22]. China.	23	Phase II trial on the efficacy of the combination of Sintilimab and Anlotinib in dMMR/MSI-H (n=9) and pMMR/MSS (n=14) ECs. Primary objective: TRO.	The combination obtained an ORR of 73.9%, reaching 100% in dMMR/MSI-H EC and 85.7% in pMMR/MSS EC. A total of 43.5% presented adverse effects, the most common being palmo-plantar erythrodysesthesia (100%), skin rash (69.6%), and hypothyroidism (69.6%).
Bellone et al. (2022) [23]. United States.	24	Phase II trial on the efficacy of Pembrolizumab in monotherapy in patients with CE dMMR/MSI-H (75% sporadic, 25% hereditary, associated with Lynch syndrome). Primary objective: TRO.	Pembrolizumab showed antitumor activity in recurrent dMMR/MSI-H SC. ORT, PFS and OS results were superior in patients with EC associated with Lynch syndrome. Most common AEs: diarrhea (12.4%), skin disorders (7.9%), fatigue (6.8%), and perfusion-related reactions (5.6%).
Konstantinopoulos et al. (2022) [24]. United States.	35	Phase II trial on the efficacy and safety of Avelumab and Talazoparib in pMMR SC. Primary objective: ORT and PFS at 6 months. .	The combination demonstrated a favorable AE profile and met the prespecified criteria for further evaluation in pMMR CE. ORR was 11.4% and PFS at 6 months was 22.9%. The most common grade 3-4 AEs: anemia (46%), thrombocytopenia (29%), and neutropenia (11%).
Post et al. (2022) [25]. Netherlands.	50	DOMEC trial (phase II) on the efficacy of the combination Durvalumab plus Olaparib. Primary endpoint: PFS at 6 months (effective treatment if PFS rate at 6 months at ≥ 50%).	The combination was well tolerated, but did not achieve the target PFS ≥ 50%, so it was not advanced to phase III. Median PFS was 3.4 months, and median OS was 8.4 months. In CE dMMR, median PFS was 5.7 months and ORR was 16%. Most frequent AE's: fatigue (44%), nausea (38%), anemia (32%), and diarrhea (26%).

O'Malley et al. (2022) [26]. United States.	90	KEYNOTE-158 trial (phase II) on the efficacy and safety of Pembrolizumab in monotherapy in dMMR/MSI-H SC. Primary objective: TRO	Pembrolizumab showed durable antitumor activity in previously treated dMMR/MSI-HSC. ORR was 48% and median PFS was 13.1 months. Median OS was not reached. Most AEs were grade 1-2 (76%), the most frequent being pruritus (24%), fatigue (21%), and diarrhea (16%).
Study data	**n**	**Target**	**Conclusions**
Oaknin et al. (2022) [27]. United States.	264	GARNET trial (phase I) on the efficacy and safety of dostarlimab: CE dMMR/MSI-H (n=108) and CE pMMR/MSS (n=156). Primary target: TRO and DR.	Dostarlimab showed antitumor activity in dMMR/MSI-HSCs, with an ORR of 43.5%, being less effective in pMMR/MSSSCs (ORR of 14.1%). Grade 1-2 AEs: fatigue (17.6%), diarrhea (13.8%), and nausea (13.8%).
Mathews et al. (2022) [28]. United States.	325	Indirect comparison of the efficacy and safety of Dostarlimab (GARNET trial) in CE dMMR/MSI-H (n=92) vs. Doxorubicin (ZoptEC trial; n=233). Primary objective: to compare OS.	Dostarlimab showed greater OS than Doxorubicin, with a 59% lower risk of death. PFS was 2.5 times longer (12.2 vs. 4.9 months), as was ORR (44% vs. 14%). AEs were similar in both treatments, with fewer serious AEs in Dostarlimab (34.1% vs. 30.1%).
Makker e t al. (2023) [29]*. United States.	108	Trial 111/KEYNOTE-146 (phase Ib/II), on the long-term efficacy and safety of Pembrolizumab and Lenvatinib. Primary objective: TRO.	The combination of Pembrolizumab and Lenvatinib showed ORR of 39.8% and median RD of 22.9 months. Median PFS was 7.4 months and OS was 17.7 months. Most frequent AEs: hypertension (33.3%), lipase elevation (9.3%), fatigue (8.3%) and diarrhea (7.4%).
Makker et al. (2023) [30]**. United States.	827	309/KEYNOTE-775 trial (phase III) on the efficacy and safety of Pembrolizumab and Lenvatinib (n=411) vs. QT (doxorubicin and paclitaxel; n=416). Primary target: SG and SLP.	Pembrolizumab plus Lenvatinib was more effective than QT, with an OS of 18.7 months vs. 11.9 months and a median PFS of 7.3 months vs. 3.8 months. ORR was higher in Pembrolizumab + Lenvatinib (32.4%) than in QT (15.1%), achieving CR in 5.8% vs. 2.6%. Most common AEs: hypertension (65%) in the Pembrolizumab and Lenvatinib arm; and anemia (48.7%) in the QT arm.

*This article is an update of Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *J Clin Oncol*(.) (2020;38(26):2981-92. **This article is an update of:) Makker V, Colombo N, Casado Herráez A, Santin AD, Colomba E, Miller DS, et al. (Lenvatinib Plus Pembrolizumab for Advanced Endometrial Cancer.) *N Engl J Med*(. 2022;386(5):437-48. (ORR: objective response rate; PFS: progression-free survival; AE: adverse events; EC: endometrial cancer; DR: duration of response; OS: overall survival; QT: chemotherapy; CR: complete response).

3.2 Efficacy and safety of immunotherapy and targeted therapies against QT in second line of treatment in patients with advanced or recurrent SC.

The reviewed studies show that immunotherapy and targeted combinations have shown greater efficacy than conventional QT in patients with advanced or recurrent SC, especially in terms of survival and disease control in both pMMR and dMMR tumors.

In the study by Dhani et al [19], Cabozantinib showed improved disease control rates and manageable toxicity, although AEs such as gastrointestinal fistulas were reported, especially in patients with carcinosarcomas. Pseudoprogression, a phenomenon of ICIs, involves an initial increase in tumor burden followed by regression [32]. According to Lheureux et al [21], the combination of Cabozantinib and Nivolumab showed promising synergy between both mechanisms of action, outperforming monotherapy with ICIs and standing out as a potential strategy in immunotherapy-resistant EC.

Dostarlimab showed superiority over QT (Doxorubicin), with lower toxicity and better safety profile [28]. However, its indirect comparison with Doxorubicin implies possible methodological biases as it was not performed in a randomized controlled trial. The KEYNOTE-775 trial highlighted the significant benefit of Pembrolizumab and Lenvatinib in terms of OS and PFS. Although toxicity was high, proper management of AEs optimizes their therapeutic benefit [30].

4. Conclusions

Immunotherapy, both in monotherapy and in combination, has shown greater efficacy in patients with dMMR/MSI-H SC than in pMMR/MSS SC. PD-1/PD-L1 inhibitor agents have achieved superior response rates in dMMR/MSI-H tumors due to their high neoantigen load, increased lymphocyte infiltration and PD-1/PD-L1 overexpression, making DNA repair deficiency a key predictive marker. However, the resistance observed in some dMMR/MSI-H tumors suggests the need for future research to identify responsible mechanisms, such as alterations in the tumor microenvironment, changes in antigen presentation or even additional mutations in genes involved in the immune response.

Pembrolizumab, in monotherapy or combined with Lenvatinib, has demonstrated superiority over conventional QT (Doxorubicin or Paclitaxel) in terms of PFS, OS, and ORR, consolidating its position as a standard option for second-line treatment. Although hypertension is the most common AE, its safety profile is manageable. For its part, Dostarlimab, evaluated in the GARNET trial, has shown a favorable balance between efficacy and safety, especially in patients with dMMR/MSI-H SC. However, future comparative and randomized studies are needed to better define its role in the treatment of advanced SC.

5. Abreviations

ADP-ribose: polypeptide enzyme inhibitors

CE: endometrial cancer

dMMR: MMR protein deficiency

DR: duration of response

AE: adverse events

ICIs: immune checkpoint inhibitors

TKI: receptor tyrosine kinase inhibitors

MMR: DNA mismatch repair mechanism

MSI: microsatellite instability

MSI-H: microsatellite instability-high

MSI-L: microsatellite instability-low

MSS: microsatellite stability

PARP: polymerase chain reaction

pMMR: presence of MMR

PR: disease progression

CT: chemotherapy

CR: complete response

PR: partial response

OS: overall survival

PFS: progression-free survival

TBI: disease control rate

ORR: objective response rate

6. Administrative Information

6.1 Contributions of the Authors

1. Conceptualization: Silvia Vázquez Gómez.
2. Formal analysis: Silvia Vázquez Gómez, Alba Díaz Fernández.
3. Research: Silvia Vázquez Gómez, Alba Díaz Fernández.
4. Methodology: Silvia Vázquez Gómez.
5. Project administration: Silvia Vázquez Gómez.
6. Supervision: Silvia Vázquez Gómez, Alba Díaz Fernández.
7. Validation: Silvia Vázquez Gómez, Alba Díaz Fernández.
8. Visualization: Silvia Vázquez Gómez, Alba Díaz Fernández.
9. Editor - original draft: Silvia Vázquez Gómez.
10. Writing - proofreading and editing: Silvia Vázquez Gómez, Alba Díaz Fernández.

All authors read and approved the final version of the manuscript.

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The authors received no financial recognition for this research work. The authors subsidized the administrative costs of this research.

6.3 Data and material Availability

Data is available upon request to the corresponding author. No other materials are reported.

7. Declarations

The authors declare that the information presented in this manuscript has been obtained and analyzed in an ethical and rigorous manner. However, results and conclusions presented are the sole responsibility of the authors and do not necessarily reflect the opinion of the journal or its editors. The journal and the editors shall not be liable for misuse or misinterpretation of the content of the article.

In addition, authors release the journal from liability for any unintentional errors, omissions, or consequences arising from the publication of this manuscript. Authors assume responsibility for the originality of the work and for possible ethical or legal conflicts.

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Article / Artículo

Association of the Neutrophil-to-Lymphocyte Ratio (NLR) with Survival in Locally Advanced and Metastatic Cervical Cancer: A Longitudinal, Retrospective Study

Asociación del índice neutrófilos/linfocitos con la supervivencia en cáncer de cérvix uterino localmente avanzado y metastásico: estudio retrospectivo

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ABSTRACT

Introduction: Cervical cancer is one of the gynecological tumors with the highest mortality rates. Inflammation plays a crucial role in its initiation and metastatic progression. The neutrophil-to-lymphocyte ratio (NLR) reflects the balance between the tumor and the antitumoral immune response, positioning it as a relevant prognostic factor. Given the high lethality of this cancer, the evaluation of NLR allows for proper patient stratification, facilitating personalized treatment and, consequently, optimizing healthcare resources and costs. **Materials and Methods:** Observational, descriptive study of historical cohorts at the SOLCA Oncology Hospital, Quito, in patients diagnosed with locally advanced (IB2 - IVA) and metastatic (IVB) cervical cancer from January 2010 to 2018. These were anonymized according to current and updated legal regulations. **Results:**The study population included 672 patients with a 180-month follow-up, and the neutrophil-to-lymphocyte ratio was assessed before treatment. Values less than 2.5 were associated with longer overall survival and late recurrence, with data of 37 months (95% CI 26.3–47.6; p < 0.05) and 30 months (95% CI 9.4–50.5; p < 0.05), respectively. Furthermore, a neutrophil-to-lymphocyte ratio ≥ 2.5 is a predictor of recurrence. The hazard ratio (HR) for mortality is 3.09 (95% CI 2.42 to 3.94; p < 0.05) and for recurrence, HR = 3.16 (95% CI 2.47 to 4.05; p < 0.05). Similarly, the Moore criteria, in the intermediate-high risk group, mortality HR 5.39 and recurrence HR 10.66, both p 0.000. **Conclusions:** NLR less than 2.5 is associated with better overall survival and shorter time to recurrence. NLR ≥2.5 is associated with more aggressive tumor behavior with a tendency toward early recurrence and higher mortality.

Keywords: Cervical cancer, lymphocytes, neutrophils, survival, index.

RESUMEN

Introducción: El cáncer de cérvix uterino es uno de los tumores ginecológicos con mayor mortalidad. La inflamación desempeña un papel clave en su iniciación y progresión metastásica. El índice neutrófilo/linfocitos refleja el equilibrio entre el tumor y la respuesta inmunológica antitumoral, por lo que se ha propuesto como un factor pronóstico relevante. Dada la alta mortalidad de este cáncer, evaluarlo permite estratificar adecuadamente a los pacientes, lo que facilita personalizar el tratamiento y, en consecuencia, optimiza los recursos y costos en salud. **Materiales y métodos:** Se llevó a cabo un estudio observacional y descriptivo de cohortes históricas en el Hospital Oncológico de SOLCA, núcleo Quito. Participaron pacientes con diagnóstico de cáncer de cérvix localmente avanzado (IB2-IVA) y metastásico (IVB) desde enero del 2010 hasta enero del 2018. Los datos fueron anonimizados según las normativas legales vigentes y actualizadas. **Resultados:** La población de estudio incluyó a 672 pacientes con un seguimiento de 180 meses y se evaluó el índice neutrófilo/linfocitos antes del tratamiento. Los valores menores a 2,5 se asociaron con un mayor tiempo de sobrevida global y una recurrencia tardía,

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con datos de 37 meses (IC 95 % de26,3-47,6; p < 0,05) y 30 meses (IC 95 % de 9,4-50,5; p < 0,05), respectivamente. Además, un índice neutrófilo/linfocitos ≥ 2,5 es un factor que predice la recurrencia. La razón de riesgos (Hazard ratio, HR) para la mortalidad es de 3,09 (IC95% de 2,42 a 3,94; p< 0,05) y para la recurrencia, HR = 3,16 (IC 95 % de 2,47 a 4,05; p < 0,05). Igualmente, los criterios de Moore, en el grupo de riesgo intermedio-alto, HR mortalidad 5,39 y HR recurrencia 10,66, ambos p 0,000. **Conclusiones:** Un índice neutrófilo/linfocitos menor a 2,5 está relacionado con una mejor sobrevida global y menor tiempo de recurrencia; un índice neutrófilo/linfocitos ≥ 2,5 está relacionado con un comportamiento tumoral más agresivo con tendencia a la recurrencia temprana y mayor mortalidad.

Palabras Clave: cáncer de cérvix uterino, linfocitos, neutrófilos, supervivencia, índice..

1. Introduction

Cervical cancer (CC) is the second most common type of gynecological cancer worldwide, with approximately 528,000 new cases and 266,000 deaths annually [1,2]. Although its incidence and mortality have declined in developed countries, it remains a leading cause of death in developing regions. It accounts for 84% of cases, with high rates reported in Africa, Central America, Latin America, and the Caribbean. The average age at diagnosis is 48 years, with lower prevalence among women under 20 and over 85 years old [1,2,3]. In Ecuador, it ranks second in incidence and first in mortality, according to data from SOLCA-Quito and GLOBOCAN [4,5,6].

Key prognostic factors include tumor stage (FIGO, International Federation of Gynecology and Obstetrics), lymph node status, tumor size (TNM), and histologic grade. However, clinical staging has limitations, especially in advanced stages, highlighting the need for additional methods such as the neutrophil-to-lymphocyte ratio (NLR) [7]. Inflammation plays a crucial role in tumorigenesis, and NLR has been proposed as a useful marker to predict prognosis in solid tumors [8,9,10]. Several studies have shown that chemotherapy can normalize NLR, which is associated with better treatment responses [11–14].

Human papillomavirus (HPV) is detected in 99.7% of cases, with its persistence being the main factor in cancer development [15–17]. In locally advanced stages (IB2–IVA), recurrence rates reach 50–70%, and metastatic disease occurs in 15–61% of cases [18,19,20]. The standard treatment involves platinum-based chemotherapy combined with radiotherapy. Risk stratification using Moore criteria is essential to individualize treatment [18,19,21–25]. Mizunuma [26] demonstrated that a high pretreatment NLR is associated with poorer overall and progression-free survival [27]. This underscores the importance of this marker in optimizing resource use and improving patients' quality of life.

2. Materials and Methods

This study was conducted as an observational, descriptive, historical cohort study with a longitudinal, retrospective, and analytical approach to survival. It was carried out at the SOLCA Oncology Hospital in Quito, and included patients diagnosed with locally advanced cervical cancer (stages IB2 to IVA) and metastatic disease (stage IVB), treated between January 2010 and January 2018. Inclusion criteria encompassed the availability of complete blood count data, measurable disease on imaging, histologic subtype determination, and having received cancer treatment in accordance with clinical stage.

Prior to its implementation, the study was approved by the Ethics and Human Research Committee (CEISH) of SOLCA Quito. Data were anonymized through a de-identification process that irreversibly removed any information that could identify individuals, using coded identifiers to mask patient identity. Given the retrospective nature of the study, no interventions were performed that could affect patient care, and informed consent was therefore not required.

Statistical analysis was conducted using IBM-SPSS software, which facilitated the application of various statistical tests to examine the relationship between the neutrophil-to-lymphocyte ratio (NLR) and survival in patients with cervical cancer. First, descriptive analyses were performed to obtain measures of central tendency (mean, median) and dispersion (standard deviation) for quantitative variables, as well as frequency distributions for categorical variables.

Overall survival (OS) was defined as the time from the initiation of cancer treatment to the date of death from any cause or the last follow-up visit in censored patients. Recurrence-free survival (RFS) was defined as the interval from treatment initiation to the clinical or radiological detection of the first tumor recurrence. Both variables were analyzed using the Kaplan-Meier method to estimate cumulative survival probability over time. OS and RFS curves were compared between risk groups based on NLR (<2.5 vs. ≥2.5). The log-rank test was used to assess whether differences between groups were statistically significant.

Additionally, a Cox proportional hazards regression model was applied for multivariate analysis, enabling the identification of independent prognostic factors for survival, adjusted for potential confounders. This model calculated hazard ratios (HRs) and their confidence intervals, providing an estimate of the relative risk of survival events. The proportional hazards assumption was verified using the Schoenfeld residuals test. All p-values were two-sided, and a p-value <0.05 was considered statistically significant.

2.1 Inclusion criteria

- Age: between 18 and 80 years.
- Patients diagnosed with cervical cancer, FIGO 2009 clinical stages IB2 to IVB.
- Patients treated at the SOLCA Oncology Hospital – Quito, from 2010 to 2018, with concurrent chemoradiotherapy or chemotherapy alone.
- Measurable oncologic disease according to RECIST 1.0 criteria.

2.2 Exclusion criteria

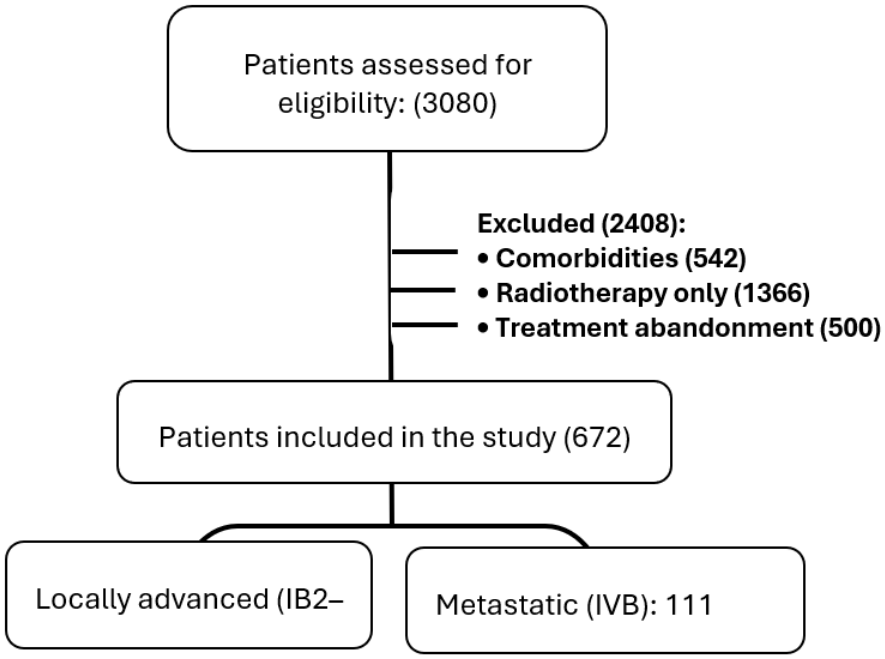
- Non-cancer-related conditions that could alter the NLR, such as pre-existing cardiovascular disease (e.g., hypertension), diabetes mellitus, acute or chronic kidney disease, or infection-related processes (e.g., sepsis, superimposed infection prior to treatment initiation).
- Patients who underwent non-oncologic surgery as treatment.
- Use of alternative therapies or treatment discontinuation.
- Diagnosis of a second primary malignancy.
- Patients who received radiotherapy alone as treatment.

A total of 3,080 patients were initially evaluated. After applying the exclusion criteria, 2,408 were excluded, including patients with comorbidities: 542 (history of cardiovascular disease, acute or chronic kidney disease, metabolic diseases such as diabetes mellitus, and autoimmune disorders), 1,366 (treated with radiotherapy alone), and 500 (treatment discontinuation) (Fig. 1).

All patients had their white blood cell counts assessed before treatment initiation, at treatment completion, and at the time of recurrence. Differential white blood cell counts (neutrophils, lymphocytes, among others) were measured using automated hematology analyzers.

Treatment response was evaluated after the third cycle in patients with metastatic disease, and after the fifth week in patients with locally advanced disease, using full body computed tomography and assessed according to RECIST 1.0 criteria, which were in use at the institution at the time of analysis.

Figure 1. Patient selection process



2.3 Results

A total of 672 patients met the inclusion criteria, representing 21.81% of the initial cohort. The final study population was stratified into two groups according to clinical stage: 561 patients (IB2–IVA) with locally advanced disease, and 111 patients (IVB) with metastatic disease.

The mean age was 48.7 years (SD ±11.4). The mean white blood cell count was 9,049/µL, with a mean lymphocyte count of 2,453/µL and neutrophil count of 5,438/µL. The mean neutrophil-to-lymphocyte ratio (NLR) was 2.39 (SD ±1.43). Regarding histopathological subtypes, squamous cell carcinoma predominated (85.6%), followed by adenocarcinoma (10%) and adenosquamous carcinoma (4.5%).

Among the 672 patients analyzed, 229 (34.1%) had a high-risk NLR, while 443 (65.9%) had a low-risk NLR. Based on Moore criteria, applied to patients with disease progression and metastasis, two risk groups were identified: an intermediate-to-high-risk group comprising 268 patients (39.9%), and a low-risk group with 34 patients (5.1%) (Table 1).

We conducted a contingency analysis of NLR in relation to vital status (alive, deceased) and disease status (recurrence, no recurrence), using a cutoff value of 2.5 based on previous literature and further supported by the mean NLR observed in our patient population (2.39 ± 1.43). Patients with a low-risk NLR exhibited a mortality rate of 32.7% and a recurrence rate of 32.4%. In comparison, those with a high-risk NLR showed a mortality rate of 35.8% and a recurrence rate of 54.9%. These differences were statistically significant (Table 2).

Table 1. Descriptives of the study population

Variables	Frequency (%)
Clinical stage (FIGO)	
IIB	246 (36,6)
IIIA	1 (0,1)
IIIB	303 (45,1)
IVA	11 (1,6)
IVB	111 (16,5)
Leukocytosis	
> 13000	55 (8,2)
≤ 13000	617 (91,8)
INL risk	
High	229 (34,1)
Low	443 (65,9)
Moore criteria (risk)	
Lowo	34 (5,1)
Intermediate-high	268 (39,9)
Vital status	
Alive	402 (59,8)
Dead	270 (40,2)

*__ECOG__, Eastern Cooperative Oncology Group; **INL, Neutrophil/lymphocyte ratio.**
Source: Medical records from the SOLCA-Quito Cancer Hospital

Table 2. Analysis of recurrence and mortality (Chi-square)

Variables		Recurrence (%)	Mortality (%)	p-value
Neutrophil-to-Lymphocyte Ratio (NLR)	High Risk ≥ 2.5	125 (54,9)	129 (35,8)	0,000
	Low Risk < 2.5	144 (32,7)	143 (32,4)	0,000
Moore Criteria	Intermediate and High Risk	265 (98,9)	249 (92,9)	0,000
	Low Risk	4 (11,4)	5 (14,7)	0,000
Leukocytosis	>13000	33 (60)	33 (60)	0,002
	≤ 13000	237 (38,4)	239 (38,7)	0,002
Neutrophils	> 7500	58 (54,7)	58 (54,7)	0,001
	≤ 7500	212 (37,5)	214 (37,8)	0,001
Lymphocytopenia	> 1000	265 (39,9)	267 (40,2)	0,195
	≤ 1000	5 (62)	5 (62,5)	0,202

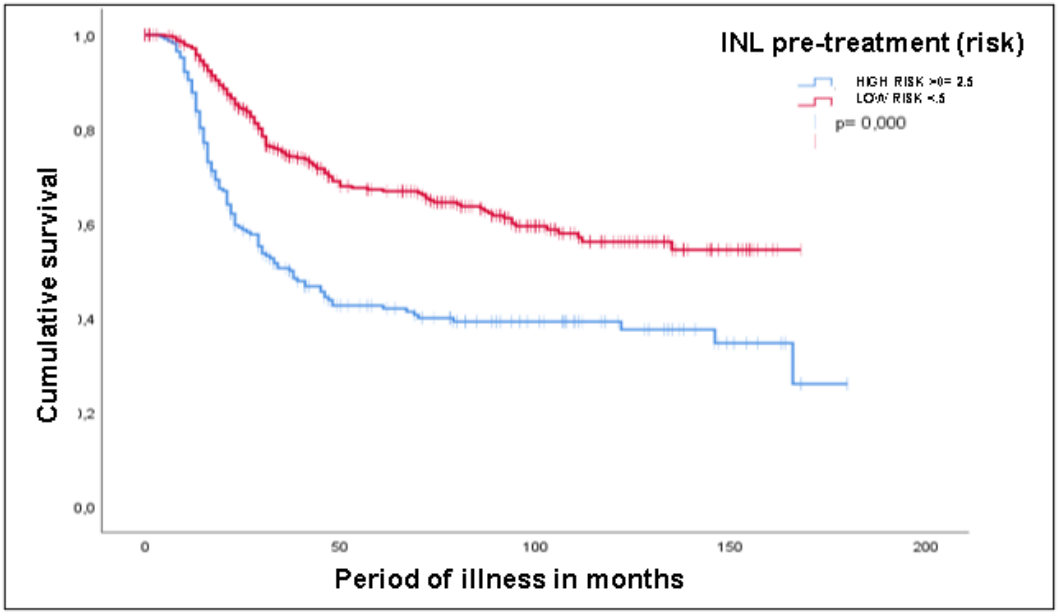
Source: Medical records from the SOLCA-Quito Cancer Hospital

An association analysis using Moore criteria revealed that women classified as intermediate-to-high risk exhibited a recurrence rate of 98.9% and a mortality rate of 92.9% (p = 0.000).

Survival analysis comparing high- and low-risk NLR groups among patients classified as intermediate-to-high versus low risk according to Moore criteria was conducted using the Kaplan–Meier method, with statistical significance evaluated via the log-rank test. The follow-up period extended up to 180 months. Regarding overall survival and NLR, the median survival for patients with NLR ≥ 2.5 was 37 months, with a 95% confidence interval (CI) of 26.3 to 47.6 (p < 0.05) (Figure 2).

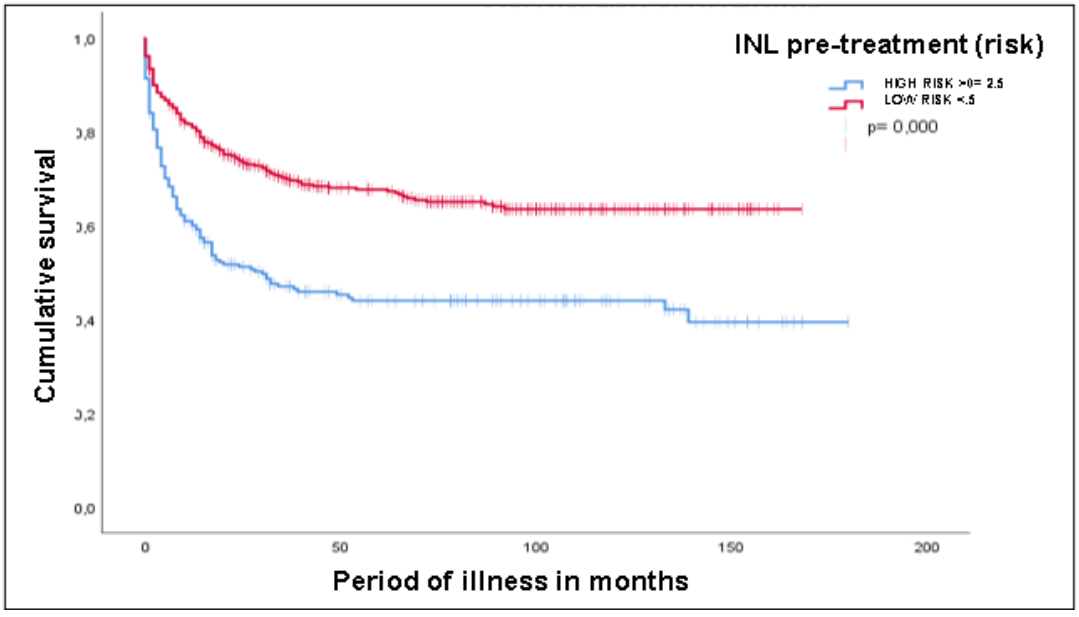
Recurrence-free survival in relation to NLR showed a median of 30 months for patients with NLR ≥ 2.5 (95% CI: 9.4–50.5; p < 0.05) (Figure 3).

Figure 2. Pre-treatment INL Overall Survival



Source: Medical records from the SOLCA-Quito Cancer Hospital

Figure 3. Recurrence-free survival



Source: Medical records from the SOLCA-Quito Cancer Hospital

The analysis of recurrence and mortality revealed significant associations with several prognostic factors. A high-risk NLR (≥2.5) was strongly associated with increased risk of disease recurrence (HR: 3.16, 95% CI: 2.47–4.05, p < 0.000) and mortality (HR: 3.09, 95% CI: 2.42–3.94, p < 0.000). Moore criteria (intermediate and high risk) showed a markedly higher risk, particularly for recurrence (HR: 10.66, 95% CI: 3.97–28.64, p < 0.000) and mortality (HR: 5.39, 95% CI: 2.00–14.48, p = 0.001). Leukocytosis (>13,000) and elevated neutrophil counts (>7,500) were also associated with increased risk in both outcomes, with hazard ratios of 2.11 and 1.79, respectively (p < 0.000). Finally, lymphocytopenia (≤1,000) was significantly associated with both recurrence and mortality risk (HR: 2.43, p < 0.000). These findings highlight the prognostic value of these hematologic biomarkers as predictors of poor outcomes (Table 3).

Table 3. Hazard Ratio

	Recurrence			Mortality		
VARIABLES	**HR**	**IC 95%**	**p-value**	**HR**	**IC 95%**	**p-value**
High-risk NLR ≥ 2.5	3,16	2,47-4,05	0,000	3,09	2,42-3,94	0,000
Moore criteria (Intermediate and High)	10,66	3,97-28,64	0,000	5,39	2,00-14,48	0,001
Leukocytosis (>13,000)	2,14	1,48-3,08	0,000	2,11	1,48-3,08	0,000
Neutrophils (>7,500)	1,79	1,34-2,40	0,000	1,79	1,34-2,40	0,000
Lymphocytopenia (≤ 1,000)	2,43	1,00-5,90	0,000	2,43	1,00-5,90	0,000

Source: Medical records from the SOLCA-Quito Cancer Hospital

3. Discussion

This study assessed the prognostic value of hematological and inflammatory markers in patients with cervical cancer (CC). The main findings indicate that a pre-treatment neutrophil-to-lymphocyte ratio (NLR) ≥ 2.5 is associated with a higher risk of early recurrence and reduced overall survival (OS), with medians of 30 and 37 months, respectively, and a significant hazard ratio (HR) for recurrence (3.16) and OS (3.09).

These results are consistent with those reported by Mizunuma et al. [13], who identified NLR ≥ 2.5 as a prognostic factor for both OS and progression-free survival (PFS), although with slightly longer periods (PFS of 35.9 months and OS of 37.7 months). Wang et al. [27] also reported differences in OS for NLR ≥ 2.5 values, while Onal et al. [28] confirmed the relevance of NLR as a predictor for both OS and PFS.

Other markers, such as leukocytosis and neutrophilia, were also associated with worse prognosis [29]. In this study, leukocytosis doubled the risk of recurrence and mortality (HRs of 2.14 and 2.11), in line with Cho et al. [30] and Mabuchi et al. [31], who reported significantly reduced OS in patients with tumor-associated leukocytosis. Neutrophilia was associated with earlier recurrence (HR 1.79) and shorter OS (38 months, HR 2.43), similar to findings by Matsumoto et al. [32] in granulocyte-colony stimulating factor (G-CSF)-producing tumors.

Regarding lymphocytopenia, although it did not show statistical significance on its own, it was associated with early recurrence and reduced OS when combined with other factors. This aligns with findings from studies such as that of Clark et al. [33] in pancreatic cancer.

The validity of the Moore risk model was also highlighted. This model stratifies patients into low-, intermediate-, and high-risk categories, showing a direct correlation between increased risk and worse prognosis. These findings are supported by the study by Tewari [34], in which patients in the intermediate- and high-risk groups derived significant OS benefit from treatment with bevacizumab.

Systemic inflammatory response is characterized by an imbalance in white blood cell populations, mainly neutrophilia with relative lymphocytopenia [35–37]. Although isolated counts of lymphocytes or neutrophils may hold prognostic value in CC [38,39], their variability limits their standalone utility; therefore, it is recommended to combine them with other parameters to enhance their accuracy as prognostic indicators.

Finally, it is emphasized that elevated NLR is associated with impaired antitumor immune response. Lymphocytes play a crucial role in immune surveillance, while tumor-associated neutrophils promote tumor progression by inducing an inflammatory and immunosuppressive microenvironment. Moreover, chronic systemic inflammation mediated by cytokines such as IL-6, TNF-α, and G-CSF is believed to contribute to CC progression [40,41].

The results of this study should be validated in larger, multicenter prospective studies. Since the study was conducted in a single institution, there is a potential risk of selection bias, which may limit the generalizability of the findings to other populations. Including multiple centers could yield a more diverse and representative sample and improve the external validity of the results.

4. Conclusions

This study demonstrated that a low-risk NLR (< 2.5) is associated with higher survival rates and fewer cases of recurrence across all stages of cervical cancer. This evaluation enables a more precise stratification of patients, facilitating the personalization of treatment and optimizing healthcare costs related to this pathology. In contrast, an NLR ≥ 2.5 was associated with more aggressive tumor behavior, as evidenced by a higher probability of early recurrence and increased mortality.

Moreover, the importance of applying Moore criteria as a routine practice for prognostic evaluation in patients with recurrent and metastatic cervical cancer was highlighted. The study also revealed that leukocytosis has significant prognostic value in terms of survival and recurrence. Since the presence of infections was an exclusion criterion, it is concluded that treatment delays due to these conditions increase complications and accelerate disease progression.

5. Administrative Information

5.1 Acknowledgements

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5.2 Author Contributions

Edison A. Carrasco-Rubio: Conceptualization, validation, visualization, methodology, project management, writing: review and editing. Henry Caballero: Conceptualization, validation, visualization, methodology Statistics: SPSS Institutional. Edison A. Carrasco-Rubio

5.3 Funding

Self-funded

6. Declarations

6.1 Conflicts of Interest

None declared

6.2 Ethics Approval

The study was approved by the Ethics and Research Committee for Human Beings at SOLCA – Quito (Code: CEISHSOLCAQ.OBS.18.060).

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Article / Artículo

Characteristics of asbestos exposure in employees of a company in Azuay - Ecuador

Características de la exposición al amianto en los empleados de una empresa en Azuay, Ecuador

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ABSTRACT
Background: Asbestos or amianto which can cause cancer and lung diseases such as asbestosis, according to the WHO, are still used to make fiber cement. This puts workers at risk of respiratory problems in the short, medium, and long term. **Objective:** The aim of this study is to determine the characteristics of asbestos exposure in workers of a company in the city of Cuenca - Azuay, Ecuador during the period 2022-2023. **Materials and methods:** Observational, descriptive, cross-sectional study, including a total of 25 workers. Four processes were carried out: collection of demographic data, review of the morbidity and absenteeism matrix, collection of environmental samples for asbestos analysis, and verification of compliance with biosafety measures by means of a check-list. Subsequently, data were entered into Microsoft Excel and analyzed using statistical methods such as mean, median, and mode. **Results:** It was found that 84% of the studied population had not completed secondary school, and 60% were between 18 and 31 years of age. The rate of absenteeism was 1.35% due to respiratory tract diseases. All workers are exposed to asbestos (0.35 f/cc; 0.45 f/cc). Finally, 60% of the population does not adequately comply with biosafety measures. **Conclusions:** This study identified a population at high risk of asbestos exposure, who, in addition, lack adequate personal protective measures. Although this exposure could have contributed to the rate of absenteeism due to respiratory tract diseases, it is not possible to establish a direct proportional relationship.

Keywords: Asbestos, asbestosis, pneumoconiosis.

RESUMEN
Antecedentes: El amianto o asbesto, que según la Organización Mundial de la Salud puede causar cáncer y enfermedades pulmonares como la asbestosis, todavía se usa para hacer fibrocemento. Esto pone a los trabajadores en riesgo de sufrir problemas respiratorios a corto, mediano y largo plazo. El objetivo de este estudio fue determinar las características de la exposición al asbesto en los trabajadores de una empresa en la ciudad de Cuenca, Azuay, Ecuador, durante el 2022-2023. **Materiales y métodos:** Estudio descriptivo observacional, de corte transversal, que incluyó un total de 25 trabajadores. Se llevaron a cabo cuatro procesos: 1) recolección de datos demográficos, 2) revisión de la matriz de morbilidad y de ausentismo laboral, 3) toma de muestras ambientales para análisis de amianto y 4) verificación del cumplimiento de medidas de bioseguridad mediante una lista de chequeo. Posteriormente, los datos se ingresaron a Microsoft Excel y se analizaron utilizando métodos estadísticos como media, mediana y moda. **Resultados:** Se evidenció que el 84 % de la población estudiada no ha cursado la secundaria y el 60 % tiene un rango de edad entre 18 y 31 años. El índice de

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ausentismo laboral fue de 1,35 % por enfermedades del tracto respiratorio. Todos los trabajadores se encuentran expuestos al amianto (0,35 f/cc; 0,45 f/cc). El 60 % de la población no cumple adecuadamente con las medidas de bioseguridad. **Conclusiones:** Este estudio identificó una población con alto riesgo de exposición al amianto, la cual, además, carece de las medidas adecuadas de protección personal. Aunque esta exposición podría haber contribuido al índice de ausentismo por enfermedades del tracto respiratorio, no se puede establecer una relación directamente proporcional.

Palabras Clave: amianto, asbestosis, pneumoconiosis.

1. Introduction

Asbestos is a group of fibrous minerals made up of double-chain silicates, they are naturally found in nature and have various commercial uses in different types of industry including construction, automotive, textile, electrical, chemical, and demolition work [1]. Asbestos is also known as *amianto* in some regions of America and are divided into two classes: serpentines, which are flexible, elongated and coiled fibers; and amphiboles, which are short, straight, rigid, and generally sharp fibers [2]. Among the serpentines, there are chrysotile, a hydrated magnesium silicate, grey-white in color; amphiboles, including crocidolite, iron and sodium silicates (blue asbestos); anthophyllite, including magnesium silicates; tremolite including calcium and magnesium silicates; amosite and actinolite [3]. Due to their fibrous characteristics, asbestos can cause three types of respiratory pathologies in the organism: asbestosis or alveolar fibrosis, lung cancer, and the appearance of mesotheliomas or cancers in the pleura and other endothelia [4]. The World Health Organization (WHO) considers that there is sufficient evidence to classify all types of asbestos as carcinogenic for humans who are exposed to them in different industries without any protective barriers or controls at the source, in the environment or in the person [5]. In Latin American countries such as Argentina, Colombia, and Peru, there are restrictions on the use of asbestos due to the serious health problems it has caused in the working population, especially in construction activities, as well as in the air near emitting points or inside homes and premises built with friable materials containing asbestos. The WHO mentions that there are about 125 million people exposed in the workplace and that 107,000 people die each year due to chronic respiratory pathologies developed as a result of this exposure. Unfortunately, these pathologies develop after continuous and prolonged exposure and do not necessarily present symptoms in primary and secondary prevention stages, but in a tertiary stage where the disease is already developed and it is incurable. In Ecuador, the use of asbestos is permitted. There is little information about this fiber; however, the Ecuadorian Technical Regulation of the Ecuadorian Institute of Standardization RT INEN 052: 2011 mentions mandatory guidelines on safety and health in work activities related to their use. It is vital to investigate the exposure to asbestos in depth given the serious consequences on the health of workers, especially in the construction sector where people start their working life at a very early age and without any protective barrier. The main objective of this study is to determine the characteristics of asbestos exposure in a small population of a construction company operating in the country through a descriptive study. Through the identification of risk factors using the triple criteria matrix method of the National Institute for Safety and Health at Work (INSST) and the implementation of Operational Hygiene, environmental monitoring was carried out to determine objectively whether there is a hygienic risk for the exposed workers. Results were compared with the threshold limit value (TLV)-time-weighted average (TWA) of the American Conference of Governmental Industrial Hygienists (ACGIH) for an exposure of eight hours. It was complemented by an analysis of health surveillance with respect to the rate of absenteeism and monthly morbidity of workers. In Ecuador, the relationship between workers' compliance with biosafety measures and exposure to certain chemical compounds such as asbestos has not been sufficiently studied. This study could contribute to filling this gap, which has been underestimated in the country, and highlight the importance of research in this area, urging the adoption of preventive and protective measures for the worker.

2. Materials and methods

2.1 Study Design

This is an observational, descriptive, cross-sectional study.

2.2 Population and Sample

Given the small number of workers exposed to asbestos in the company where the study was carried out, a census sample was chosen, including the 25 workers exposed in the period 2022-2023.

2.3 Inclusion Criteria

- Workers with documented exposure to asbestos.
- Aged between 18 and 65 years old.
- Both sexes.
- At least 3 months of seniority in the company.

2.4 Exclusion Criteria

- Workers who did not give informed consent.
- History of chronic pulmonary pathology other than occupational exposure.

2.5 Study Variables

- **Socio-demographic data:** sex, age, educational attainment.
- **Absenteeism rate:** total hours of absence due to morbidity in relation to the established working hours.
- **Asbestos monitoring:** environmental concentration of asbestos fibers (f/cc).
- **Compliance with biosecurity measures:** use of personal protective equipment and preventive measures.

2.6 Procedures and Data Collection

The study was approved by the Committee on Ethics and Research in Human Health (CEISH) with the code 2023-024-MST-MLF (Oficio No. CEISH-UC-2023-096). Subsequently, data collection was carried out using the following techniques:

1. Structured interview and validated questionnaire:

- Individually applied after informed consent.
- It contained questions on socio-demographic data and working conditions.

2. Structured observation:

- The absenteeism rate was assessed using monthly company records.
- A morbidity and absenteeism matrix were used.

3. Environmental monitoring of asbestos:

- It was carried out on 12 May 2023 in collaboration with ABGES Environmental Analytic Laboratory Cia Ltda.
- A vacuum pump with membrane filter and phase contrast optical microscopy were used.
- Results were expressed in fibers per cubic centimeter of air (f/cc) and compared with the limits set by ACGIH and NIOSH.

4. Assessment of biosecurity compliance:

- A 12-item checklist was applied.

- Eight items on respiratory protection, one on body protection, and three on other equipment were included.

5. **Occupational risk assessment:**

- The methodology of the Spanish National Institute for Safety and Health at Work (INSST) was used.
- Risks were classified according to likelihood of exposure and expected consequences.

2.7 Data Analysis

The collected data were entered into Microsoft Excel 2016 and analyzed using descriptive statistics, calculating frequencies and percentages for qualitative variables. Results of the environmental monitoring were compared with international references.

2.8 Ethical Considerations

Data confidentiality was ensured by anonymous identification codes. All participants gave informed consent prior to inclusion in the study.

3. Results

3.1 Socio-demographic characteristics

The socio-demographic characteristics of workers included in the study are detailed in Table 1. The entire sample (n = 25) was composed of men. Sixty per cent of the participants were between 18 and 30 years old. With regard to educational attainment, 40% did not complete basic education and 8% did not complete secondary education.

Table 1. Demographic variables

Variables		**F**	**%**
Age Ranges	18 to 30	15	60
	31 to 45	7	28
	46 to 65	3	12
Sex	Male	25	100
Educational attainment	None	2	8
	Incomplete basic education	10	40
	Complete basic education	9	36
	Bachelor's degree	4	16

Source: Author

3.2 Rate of absenteeism due to illness

The rate of absenteeism due to respiratory tract diseases was 1.35%, higher than the 0.25% recorded for digestive tract diseases. The total all-cause absenteeism rate reached 2.05%. Despite the higher incidence of absenteeism due to respiratory diseases, a direct relationship with asbestos exposure cannot be established without considering other factors.

Table 2. Comparison of absenteeism and morbidity

Disease	Absenteeism rate (%)
Digestive tract	0.25
Respiratory tract	1.35
Musculoskeletal	0.1
COVID-19	0.25
Other	0.1
Total	**2.05**

Source: Author

3.3 Environmental monitoring of asbestos

The environmental measurement determined that workers were exposed for approximately 8 hours per day, accumulating 40 hours per week and 160 hours per month. The weighted asbestos concentrations were 0.45 f/cc in the cement hopper and 0.35 f/cc in the operating cabin. These figures exceed the permissible exposure limit (0.1 f/cc) established by NIOSH and ACGIH, thus indicating an intolerable risk according to INSST criteria.

Table 3. Monitoring of asbestos in a cement hopper

Parameter	Value
Concentration 15 min	0.35 f/cc
Weighted concentration (8h)	0.45 f/cc
NIOSH/ACGIH Limit	0.1 f/cc
Risk level	**Intolerable**

Table 4. Asbestos monitoring in operator's cabs

Parameter	Value
Concentration 15 min	0.25 f/cc
Weighted concentration (8h)	0.35 f/cc
NIOSH/ACGIH Limit	0.1 f/cc
Risk level	**Intolerable**

3.4 Compliance with occupational health and safety measures

The analysis of current regulatory compliance (Standard 044/2022) at the company revealed deficiencies in technical management and basic process control, both with a moderate risk of 25% and 30%. This shows a lack of adequate corrective measures to reduce the risk of asbestos exposure.

Table 5. Level of risk in compliance with regulations

Management area	High risk	Moderate risk	Low risk	No risk
Documentary management	-	-	15%	-
Technical management	-	25%	-	-
Basic process control	-	30%	-	-
Administrative management	-	-	30%	-

3.5 Use of personal protective equipment

In relation to the use of personal protective equipment, it was found that 52% of the workers used an N95 mask, while 48% did not use any type of respiratory protection. As for hand protection, 68% used nylon gloves with polyurethane coating. No workers used adequate body protection equipment, such as airtight suits or boots. In addition, a general lack of knowledge about the use and replacement of protective equipment was identified.

These findings show deficiencies in the implementation of occupational health and safety measures, which represent a continuing risk for workers exposed to asbestos.

Table 6. Use of personal protective equipment

Type of protection	Indicator	Yes (%)	No (%)
Respiratory	Mask N95	52	-
	None	-	48
Hands	Coated nylon gloves	68	-
	None	-	32
Corporal	Airtight suit	0	100
	Safety boots	0	100

4. Discussion

Exposure to asbestos without adequate protection or above safe working limits causes serious lung diseases such as asbestosis, mesothelioma, and various types of cancer [6]. This study analyzed 25 construction workers by assessing socio-demographic factors, shared responsibility for protective equipment, levels of asbestos fibers in the work environment, and their possible relationship with absenteeism.

A study conducted by Donostia (2018) analyzed 55 patients exposed to asbestos, being 98% men and 2% women, all older than 55 years [7]. The University of Valladolid reported that, in 2016, 8 people developed occupational diseases from asbestos dust and 14 from related carcinogens, all men aged 20-45 years with incomplete education [8]. The current study shows that all participants are men (100%) between 18-65 years old, 60% of them are under 30 years old, being a younger population than in previous studies, and 84% did not complete secondary education.

A 1987 Serbian study of workers in an asbestos textile factory showed significantly higher rates of absenteeism than the control group over four years, with rates for respiratory diseases ranging from 99-117.4 versus 22.9 for the control group [9]. The current study shows a similar correlation, with absenteeism due to respiratory diseases accounting for 1.35%, being the most frequent cause of absence from work.

Although 1.35% seems low, it is the highest rate among all causes of absenteeism in the population studied, which could indicate a future increase for this reason.

The study detected asbestos levels of 0.45f/cm^3 in the cement hopper and 0.35f/cm^3 in the operating cabin, exceeding the ACGIH limits. This is evidence of the lack of control in Ecuador compared to developed countries such as the USA, where a 2011 study in mechanics showed concentrations between 0.005-0.049f/cc, well below the permitted limit [10]. A Slovakian study from 2020 measured asbestos fibers during demolition of asbestos-cement buildings, finding concentrations between 0.010-0.020 f/cm^3, with the highest values during demolition, but still well below the permitted limits [11]. Both studies showed asbestos concentrations significantly lower than those found in the present study and below the limits set by ACGIH.

A 2013 Iranian study assessed asbestos exposure during demolitions of old houses, detecting levels between 0.02-0.42 f/cm^3 by optical microscopy, considerably higher than the limits set by ACGIH [12]; both studies, although in different contexts, analyzed construction workers using the same methodology

and found asbestos levels above safe limits. This suggests that, in the construction sector in developing countries such as Ecuador and Iran, exposure levels are still not adequately controlled, and that it will take years to effectively implement international regulations to reduce asbestos-related occupational diseases.

A study conducted in Quito, Ecuador, on environmental exposure to asbestos in residents near an industrial plant detected by optical microscopy 443 asbestos fibers in the first filter and 221.5 in the second [13]. This study, although not conducted in the construction sector, highlights the importance of implementing continuous monitoring and measurements in both construction companies and factories using asbestos-containing materials.

There is currently no literature that verifies compliance with biosafety measures in workers exposed to asbestos. This study proposes to compare the actual use of personal protective equipment with the recommendations of articles, good practice guides, and current legislation on asbestos management.

In this study, only 52% of workers wore N95 masks and 68% wore nylon gloves with polyurethane, while the rest did not use protection. This is evidence of company negligence, since according to Royal Decree 773/1997, employers must identify positions requiring protection, select suitable equipment, provide it free of charge, replace it when necessary, and ensure its correct use and maintenance [14].

According to Royal Decree 396/2006, workers must wear personal protective equipment, especially respiratory protective equipment, even when asbestos exposure limits are not exceeded, for two reasons: any exposure, no matter how small, represents a risk, and in work environments the absence of unforeseen accidental exposure cannot be guaranteed [15,16].

The INSST recommends different respiratory protection equipment according to duration and concentration: for short work at levels below the Environmental Limit Value (VLA), FFP3 masks or adapters with P3 filters; for concentrations not exceeding the VLA, facepieces with P3 filters; for levels exceeding the VLA, filtering equipment with assisted ventilation (TMP3/THP3); and for concentrations much higher than the VLA, semi-autonomous or autonomous compressed air isolation equipment [14-16]. Company employees did not use even the minimum recommended respiratory protective equipment, even in situations where exposure levels could be low.

Appropriate protective clothing must prevent the penetration of asbestos fibers, cover the whole body, comply with European classification, be certified according to RD 1407/1992 and CE marked. It is crucial to follow the manufacturer's instructions on use, maintenance and compatibility with another PPE. The suits can be disposable or reusable, requiring specific protocols for disposal or decontamination, and workers must keep them on throughout the exposure [15]. They also did not use the basic body protective equipment recommended in the literature, such as airtight clothing and appropriate gloves.

The Agreement N° 0100 in Ecuador regulates safety for the handling of asbestos, requiring adequate protective equipment and a respiratory protection program to be developed with technical advice from IESS, but does not specify the types of equipment to be used [17-19].

5. Conclusions

The study characterized asbestos exposure in 25 masonry workers, evaluating specific tasks, biosafety measures, absenteeism, and fiber concentration in the environment. It is recommended to replace fiber cement with asbestos-free alternatives or to reinforce controls at source, environment, and people. In addition, it is essential to improve ventilation, provide adequate protective equipment, train workers, and carry out regular environmental assessments to ensure regulatory compliance and early detection of diseases associated with exposure.

6. Abbreviations

- **ACGIH** Conference of Governmental Industrial Hygienists
- **TLV** Threshold Limit Values
- **VLA** Environmental Limit Value
- **TWA** Time – Weighted Average

7. Administrative Information

7.1 Additional Files

None

7.2 Acknowledgments

I thank my family for their unconditional support.

7.3 Contributions of the Authors

The authors declare that the responsibilities contributed to the article are described using the CRediT taxonomy. Conceptualization: V.J.; data curation: V.J. and E.D.; formal analysis: V.J. research and methodology: V.J. and E.D.; project management: V.J.; software: V.J.; writing - original draft: V.J.; supervision: E.D.; validation: V.J. and E.D.; visualization: E.D.; writing - revision: E.D.; editing V-J. And E.D.; The authors declare that this research was self-financed and did not receive financial support from any public or private entity.

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7.5 Data and Material Availability

Data is available upon request to the corresponding author. No other materials are reported.

8. Declarations

8.1 Conflict of Interest

The author declares no conflicts of interest.

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ONCOLOGÍA

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GASTRIC ADENOCARCINOMA, A LOOK AT A DECADE

ADENOCARCINOMA GÁSTRICO, MIRADA A UNA DÉCADA

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Introduction: Gastric adenocarcinoma (ADK) is a type of cancer that originates in the glandular cells of the gastric mucosa. It is the most common type of stomach cancer, approximately 95% of cases. According to the IARC (International Agency for Research on Cancer) from 2017 to 2022, stomach cancer ranked fifth in prevalence, incidence and mortality worldwide and in South America, and at the level of Ecuador it is the third most common cancer (second in men and fourth in women), representing 8.7% of all types of cancer.

This cancer is associated with risk factors such as H. pylori infection, diets rich in salted, smoked and preserved foods, alcohol and tobacco consumption. It has a great impact on public health due to its high incidence and mortality rate, in addition to the economic and social impact due to treatment costs. The main measures to reduce the burden of this disease are based on early detection programs, education and awareness.

Objective: To establish the clinical-anatomical, histological and sociodemographic characteristics of gastric adenocarcinoma cases diagnosed at SOLCA Núcleo Machala from 2012 to 2022.

Methodology: A descriptive and retrospective study was conducted. The population included patients with existing medical records of upper gastrointestinal endoscopy biopsies, plate or block review, and surgical interventions, of gastric adenocarcinoma cases diagnosed at SOLCA Núcleo Machala between 2012and 2022. The variables used were anatomical location, histological type according to Lauren's classification (2), sex, and the number of cases per year.

Results: The study included 425 patients diagnosed with gastricadenocarcinoma, males accounted for 56% compared tofemales, with 44%; the most frequent location was the antrumwith 94 cases (22%); the clinical stage that prevailed wasstage IV with 40.9%; regarding the histological type, theintestinal type was found in 211 patients (49.6%) and the diffusetype in 214 (51.4%); in turn, the year in which the most cases ofgastric adenocarcinoma were registered was 2014 with 51cases (12%) while the year with the lowest number of cases was2021 with 28 (6.5%).

Conclusion: It is concluded that there is a slight prevalence ofdiffuse gastric adenocarcinoma over intestinaladenocarcinoma and that men have a higher riskof developing this type of cancer. In addition, mostcases are detected in advanced stages and theantrum is a key location to consider in diagnosisand treatment. These data may be crucial to guidefuture research and prevention strategies.

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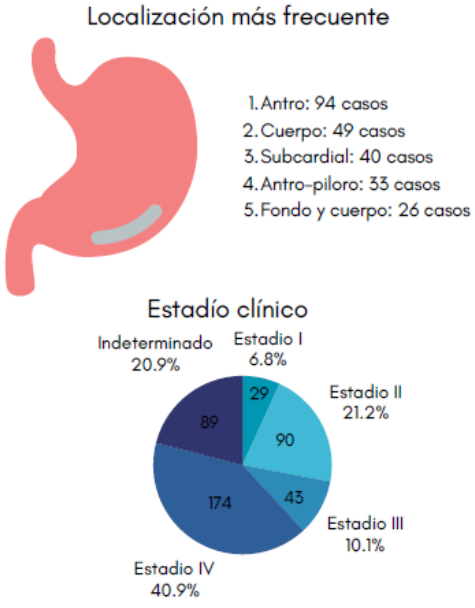
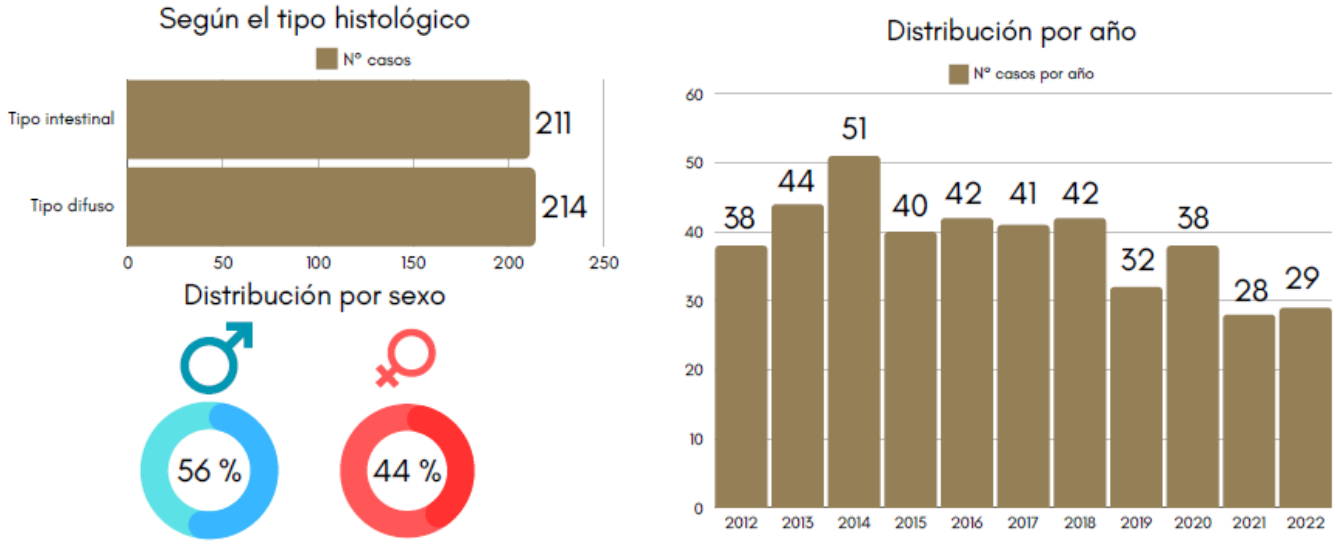
Figure 1. Clinical stage and gender distribution



Source: SOLCA Machala Center

Figure 2. Histological type, distribution by sex and year from 2012 to 2022



Source: SOLCA Machala Center

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BILATERAL MASTECTOMY IN A 23-YEAR-OLD PATIENT PLUS BREAST RECONSTRUCTION WITH LIPOGRAFT: A CASE REPORT

MASTECTOMIA BILATERAL EN PACIENTE DE 23 AÑOS MAS RECONSTRUCCION MAMARIA CON LIPOINJERTO: A PROPOSITO DE UN CASO

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Introduction: Breast cancer is the most common malignant tumor in women, with approximately 1.2 million cases diagnosed each year in the world. It has a tendency to produce about 500,000 deaths per year worldwide, being the first or second cause of cancer death in women depending on the country.

This global problem radically alters the physical and psychological appearance of women. Different oncological procedures such as mastectomy or radiotherapy drastically change the physical appearance of women, producing a decrease in their self-esteem. The different breast reconstruction techniques would be considered the process of restoring the body image and psychological well-being of the patients. It is argued that breast reconstruction should be considered an essential part of the treatment and rehabilitation of patients with breast cancer.

Objective: Recognize when onco-reconstructive surgery is indicated in breast cancer.

To demonstrate the efficacy of onco-reconstructive surgery in the treatment of breast cancer and its influence on women's self-esteem.

Methology: A 24-year-old female patient with APF: grandmother, aunts and sister with breast cancer. In May 2023, he presented a tumor at Hour 12-3 AB of 4.5 x 3 cm without the presence of lymphadenopathy. Breast ultrasound reported a nodule at hour 12 A of 3.0 x 2.2 cm BI-RADS 4B with enlarged adenopathy, so a trucut biopsy was performed, a clip was left in the tumor and left axillary FNA reported *luminal infiltrating ductal carcinoma B, FNA negative*. Patient goes to neoadjuvant chemotherapy receives 4 cycles of AC protocol. Breast MRI was reassessed to define surgical treatment, which reported nodular lesion at hour 12 A of 1.5 x 0.8 cm (20% reduction). With infiltration of the adjacent skin. BRCA 1 and 2 were requested, which were negative, it was decided to transfer the patient to the mastology committee where together it was decided *to have a skin-sparing mastectomy with expander reconstruction plus risk-reducing mastectomy with CAP preservation in the contralateral breast and reconstruction with prosthesis plus bilateral lipograft plus left axillary lymphadenectomy.*

Results: The definitive diagnosis of the left breast was a G2 infiltrating ductal carcinoma, in contact with the skin and rest of the free margins with tumor size of 2.5 x 1.5 cm, 0/8 free axillary nodes. Right breast negative for malignancy.

The patient received radiotherapy in the left breast area and is currently receiving hormone therapy (tamoxifen). In her control examinations, the patient has not had a recurrence.

Discussion: Oncoplastic surgery is of great importance since through the oncology part cancer is fought together with the aesthetic, functional and social benefit of the patient. Currently, the molecular classification of breast cancer is of great consideration to determine which patients will benefit from chemotherapy with the already known predictive factors or in turn from surgery, so we try to resolve in a single time the radical oncology part plus the aesthetic and functional part (3). The hybrid reconstruction, which consists of the use of prosthetic implants plus autologous grafts, in this case adipose tissue from the abdomen was used as a donor site and grafted into the subcutaneous of the left mammary gland in order to improve the flap that covered the expander, thus avoiding rejection of the expander, and improves the tissue, in addition to reducing the complications caused by radiotherapy.

Conclusion: Currently, the treatment of breast cancer involves a multidisciplinary team, which opens up more possibilities in terms of lines of treatment, including oncoplastic surgery, since it fights cancer and can preserve aesthetics, thus increasing self-esteem, giving patients a better quality of life. Remembering that the oncological criterion will always prevail over the aesthetic one.

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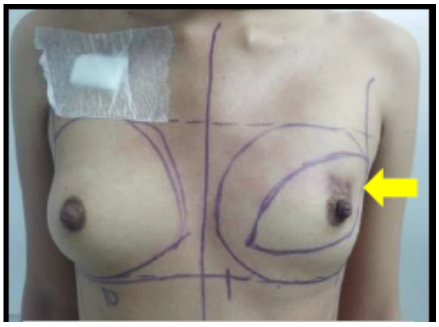
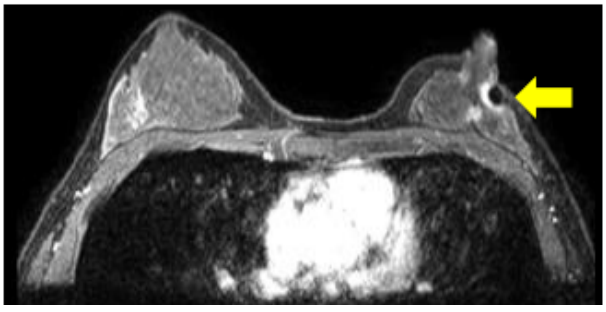
Figure 1. Preoperative design



Source: SOLCA - Guayaquil

Figure 2. Breast MRI



Soure: SOLCA - Guayaquil

Figure 3. Post-surgical control after 3 months

Source: SOLCA - Guayaquil