

Cytoreductive surgery in ovarian cancer: an integrative review*

Cirurgia citorrredutora no câncer de ovário: uma revisão integrativa

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ABSTRACT: Ovarian cancer ranks fifth on the list of causes of cancer mortality in women. The most used therapeutic approach for this condition is cytoreductive surgery combined with chemotherapy. This review aims to analyze survival related to cytoreductive surgery in cases of ovarian cancer. This occurred through an integrative review of articles from 2018 to 2022, following the PRISMA criteria, in the PubMed database. In total, 32 articles were found and of these, 18 entered this review. Therefore, cytoreduction followed by platinum/taxane-based chemotherapy is the current standard treatment for ovarian cancer. Survival outcomes are inversely related to initial and residual tumor burden after surgery. It appears that cytoreductive surgery is a viable technique that has been associated with good patient outcomes, including a median survival rate of 53 months.

KEY WORDS: Ovarian Neoplasms; Cytoreductive Surgical Procedures; Chemotherapy, Adjuvants.

RESUMO: O câncer de ovário ocupa o quinto lugar na lista de causas de mortalidade por câncer em mulheres. A abordagem terapêutica mais utilizada para essa condição é a cirurgia citorrredutora combinada com quimioterapia. Esta revisão objetiva analisar a sobrevida relacionada à intervenção cirúrgica citorrredutora em casos de câncer de ovário. Isso ocorreu por meio de uma revisão integrativa com artigos de 2018 a 2022, seguindo os critérios PRISMA, no banco de dados PubMed. Ao total, 32 artigos foram encontrados e desses, 18 adentraram essa revisão. Sendo assim, a citorredução, seguida de quimioterapia à base de platina/taxano, é o tratamento padrão atual para o câncer de ovário. Os resultados de sobrevida estão inversamente relacionados à carga tumoral inicial e residual após a cirurgia. Consta-se que a cirurgia citorrredutora é uma técnica viável que tem sido associada a bons prognósticos aos pacientes, incluindo uma taxa média de sobrevida de 53 meses.

PALAVRAS-CHAVE: Câncer do ovário; Carcinoma de ovário; Cirurgia citorrredutora; Quimioterapia.

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INTRODUCTION

Ovarian, tubal, and primary peritoneal cancers are among the deadliest malignancies in women, with a median survival rate of five years. Epithelial ovarian cancer (EOC) is the most common type, accounting for 90% of all cases¹, making it the fourth leading cause of cancer-related deaths in women².

This high mortality rate is largely due to the fact that most EOC cases are diagnosed at advanced stages, presenting a significant challenge in managing the disease².

Based on histopathology and molecular genetic changes, EOC includes subtypes such as high-grade serous carcinoma, endometrioid, clear cell, mucinous, and low-grade serous carcinoma³.

In this context, biomarkers are essential for understanding and treating cancer, providing measurable characteristics of different cell types. Among these, “CA125” stands out, showing a strong clinical correlation with patient survival, where an elevated CA125 level (>35 U/mL) suggests residual disease⁴. “HE4” is another valuable biomarker that plays a significant role in analyzing progression-free survival⁵. Additionally, “CA 19-9,” traditionally used in the assessment of pancreatic, gastric, and hepatobiliary neoplasms, has shown high sensitivity and specificity in ovarian cancer screening⁶.

Regarding treatment, complete cytoreductive surgery, defined as the absence of residual lesions larger than 1 cm in maximum diameter, is the cornerstone of primary treatment and is preferable when an optimal surgical outcome is achievable. However, when complete cytoreduction is not feasible, neoadjuvant chemotherapy may be employed to improve patient survival outcomes⁷.

Over recent decades, cytoreductive surgery has been extensively studied and refined to enhance clinical outcomes and patient quality of life. Numerous clinical studies have been conducted to assess the efficacy and safety of this therapeutic approach, as well as to establish appropriate criteria for selecting patients who would benefit most from this surgical intervention.

This integrative review aims to compile and critically analyze current scientific literature on cytoreductive surgery for the treatment of ovarian cancer. In doing so, we present a comprehensive and updated synthesis of available evidence, offering a deeper understanding of the advantages and limitations of this therapeutic approach within the context of EOC.

METHODS

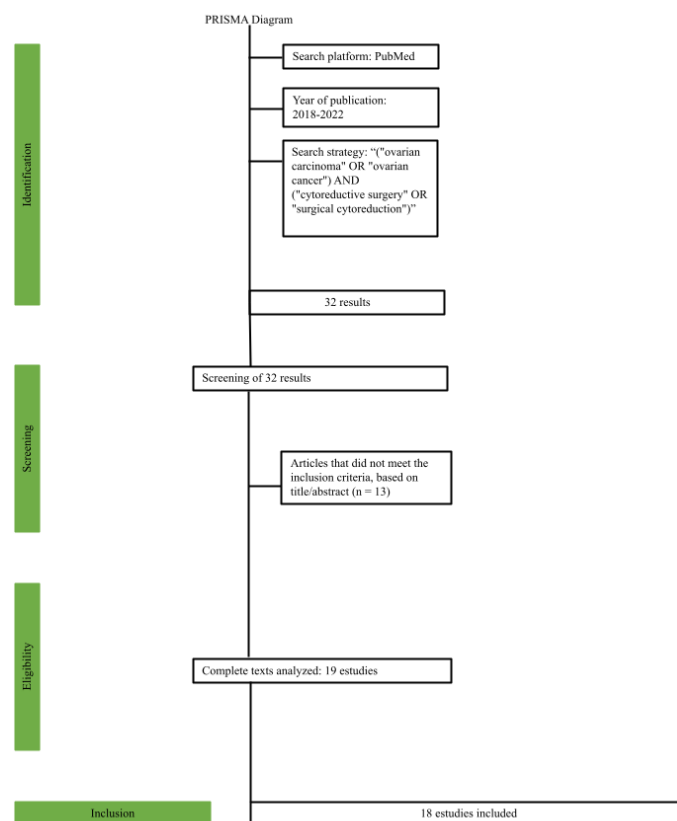
This study is an Integrative Literature Review based on searches in the PubMed database. Searches were conducted using the following Health Sciences Descriptors (DeCS): “ovarian carcinoma,” “ovarian cancer,” “cytoreductive,” and “surgical cytoreduction,” combined as follows: “(ovarian carcinoma) OR (ovarian cancer)” AND “(cytoreductive surgery) AND (surgical cytoreduction)”.

Inclusion criteria included studies published within the last five years, with initial selection based on titles and abstracts to align with the study’s purpose, and with a preference for

clinical and epidemiological studies. Studies that did not meet the research objective were excluded. A total of 32 studies were found in the databases used, and after applying selection criteria, 18 articles were chosen for full analysis.

This methodology is visualized in Figure 1.

Figure 1 - PRISMA Flow Diagram for Study Screening and Selection



RESULTS

This study identified a significant increase in survival rates among patients who underwent the analyzed surgical approach, with an average survival time of 53 months across all reviewed studies.

Additionally, we assessed the survival probabilities for patients who underwent cytoreductive surgery alone compared to those who received chemotherapy alone, as evidenced by the Kaplan-Meier curve shown in Figure 2, with data sourced from the articles^{8 9}.

Accordingly, there is an approximate 56% probability of survival at 84 months for patients who underwent cytoreductive surgery. In comparison, the probability of survival at 84 months is less than 20% for patients who received chemotherapy alone.

This study also evaluated patient survival probabilities based on the extent of residual disease, as illustrated by the Kaplan-Meier curve in Figure 3, with data derived from Article⁸.

Thus, survival probability decreases as the extent of residual disease increases, with a five-year survival probability of 70% for complete cytoreduction, under 40% for cytoreduction leaving 1 to 9 mm of residual disease, and less than 30% for cytoreduction with residual disease greater than 10 mm.

Figure 2 - Comparison of Survival in Ovarian Cancer Patients According to Treatment Strategy

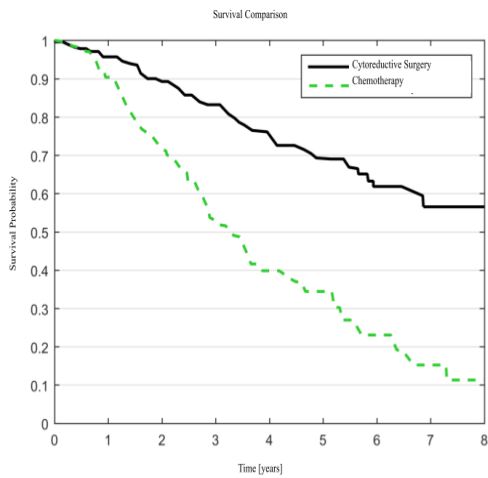
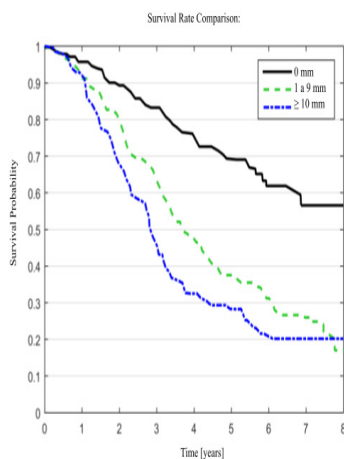


Figure 3 - Survival Rate Comparison Based on the Extent of Residual Disease after Cytoreductive Surgery



DISCUSSION

This integrative review summarizes high-quality evidence from the oncology literature on the effectiveness of cytoreductive surgery and the prognosis for ovarian cancer patients undergoing this treatment.

Cytoreductive surgery is considered the first line of treatment for patients with platinum-sensitive ovarian cancer, as platinum-resistant patients generally are not surgical candidates due to limited life expectancy and high rates of surgical morbidity/mortality¹⁰.

Some studies indicate that cytoreductive surgery alone is more effective than surgery combined with chemotherapy^{11, 12}, especially in the early stages, while delayed surgery after neoadjuvant chemotherapy is an option for patients with stage IIIC or IV cancer¹³.

Our study showed that the five-year survival probability is about 30% for patients undergoing chemotherapy alone; however, when patients undergo surgery alone, this probability increases to an average of 70%.

Thus, following diagnosis and staging, the next step is cytoreductive surgery, which typically includes hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of all metastatic lesions, given that ovarian cancer is usually diagnosed at advanced stages with confirmed metastases¹⁴.

Our study further demonstrated that patients with no residual disease (0 mm) post-surgery had the best survival rates, while those with 1 to 9 mm of residual disease had better survival rates compared to patients with suboptimal cytoreduction, where the residual disease was 10 mm or more [Figure 2]. This factor is significant, as achieving complete cytoreduction may be unfeasible for surgeons. However, attaining a 1 to 9 mm margin is viable, making it worthwhile to pursue to improve patient survival rates.

This point is even more apparent in quantitative analysis: the five-year survival probability is 70% for patients who underwent complete cytoreduction, drops to around 40% with a 1 to 9 mm residual disease, and falls to approximately 30% if the residual disease is 10 mm or more.

Although cytoreduction offers proven prognostic benefits supported by multiple studies and summarized here, it is not without risks, necessitating careful patient selection. Factors such as advanced age, poor functional status, high tumor burden, extensive disease, and poor preoperative nutritional status are predictors of worse postoperative morbidity¹².

As our understanding of disease heterogeneity deepens, a personalized approach to each patient becomes increasingly justified, always considering primary and recurrent disease contexts.

Furthermore, for patients with very advanced disease, cytoreductive surgery may be contraindicated due to the likelihood of incomplete resection and substantial residual tumor burden.

It is worth mentioning that this study has limitations, including its retrospective data analysis approach. Additionally, this study did not specify individual patient characteristics for stratification, nor did it differentiate groups by specific treatment regimens. Finally, the study was temporally and locally limited, analyzing only studies published within a certain period and on the specified scientific search platform.

CONCLUSION

In summary, recognizing oncology as a continually evolving field, cytoreductive surgery remains an effective treatment approach for ovarian cancer.

Moreover, the presence of residual disease negatively impacts patient survival.

Early diagnosis limits disease progression, making preventive medicine essential in this care process.

Finally, we recommend further studies with high levels of scientific evidence to improve cytoreduction techniques and enhance patient quality of life.

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REFERENCES

- Laios A. prediciting complete cytoreduction alexandro laios - Google Search [Internet]. www.google.com. <https://www.google.com/search?client=safari&rls=en&q=prediciting+complete+cytoreduction+alexandro+laios&ie=UTF-8&oe=UTF-8>
- Gorodnova TV, Sokolenko AP, Kuligina E, Berlev IV, Imyanitov EN. Principles of clinical management of ovarian cancer. *Chinese Clin Oncol*. 2018;7(6):56-6. Doi: <https://doi.org/10.21037/cco.2018.10.06>
- Kurman RJ. Blaustein's pathology of the female genital tract - Catalog - UW-Madison Libraries [Internet]. Wisc.edu. 2024. <https://search.library.wisc.edu/catalog/999947979402121>
- Bottoni P, Scatena R. The Role of CA 125 as Tumor Marker: Biochemical and Clinical Aspects. *Adv Exp Med Biol*. 2015;867:229-44. Doi: https://doi.org/10.1007/978-94-017-7215-0_14
- Chudecka-Głaz A, Cymbaluk-Płoska A, Wężowska M, Menkiszak J. Could HE4 level measurements during first-line chemotherapy predict response to treatment among ovarian cancer patients? Ahmad A, editor. *PLOS ONE*. 2018;13(3):e0194270. Doi: <https://doi.org/10.1371/journal.pone.0194270>
- Ali FT, Soliman RM, Hassan NS, Ibrahim AM, El-Gizawy MM, Mandoh AAY, et al. Sensitivity and specificity of microRNA-204, CA125, and CA19.9 as biomarkers for diagnosis of ovarian cancer. Christie E, editor. *PLOS ONE*. 2022;17(8):e0272308. Doi: <https://doi.org/10.1371/journal.pone.0272308>
- Cardillo N, Devor EJ, Pedra Nobre S, Newtson A, Leslie K, Bender DP, et al. Integrated Clinical and Genomic Models to Predict Optimal Cytoreduction in High-Grade Serous Ovarian Cancer. *Cancers*. 2022;14(14):3554. Doi: <https://doi.org/10.3390/cancers14143554>
- May T, Altman A, McGee J, Lu L, Xu W, Lane K, et al. Examining Survival Outcomes of 852 Women With Advanced Ovarian Cancer: A Multi-institutional Cohort Study. *International Journal of Gynecological Cancer: Official J Internat Gynecol Cancer Soc*. 2018;28(5):925-31. <https://pubmed.ncbi.nlm.nih.gov/29621126/>
- Ding T, Tang D, Xi M. The survival outcome and complication of secondary cytoreductive surgery plus chemotherapy in recurrent ovarian cancer: a systematic review and meta-analysis. *J Ovarian Res*. 2021;14(1). Doi: <https://doi.org/10.1186/s13048-021-00842-9>
- Jiang C, Li Z. Prediction Models for Complete Resection in Secondary Cytoreductive Surgery of Patients With Recurrent Ovarian Cancer. *Front Oncol*. 2021;11:674637. Doi: <https://doi.org/10.3389/fonc.2021.674637>
- Gockley A, Melamed A, Cronin A, Bookman MA, Burger RA, Cristae MC, et al. Outcomes of secondary cytoreductive surgery for patients with platinum-sensitive recurrent ovarian cancer. *Am J Obstet Gynecol*. 2019;221(6):625.e1-14. Doi: <https://doi.org/10.1016/j.ajog.2019.06.009>
- Goldberg RM, Kim SR, Fazelzad R, Li X, Brown TJ, May T. Secondary cytoreductive surgery for recurrent low-grade serous ovarian carcinoma: A systematic review and meta-analysis. *Gynecologic Oncology*. 2022;164(1):212-20. Doi: <https://doi.org/10.1016/j.ygyno.2021.10.080>
- Vergote I, Tropé CG, Amant F, Kristensen GB, Ehlen T, Johnson N, et al. Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIc or IV Ovarian Cancer. *NEJM*. 2010;363(10):943-53. Doi: <https://doi.org/10.1056/nejmoa0908806>
- Luna-Abanto J, García Ruiz L, Laura Martínez J, Álvarez Larraondo M, Villoslada Terrones V. Liver Resection as Part of Cytoreductive Surgery for Ovarian Cancer. *J Gynecol Surg*. 2020;36(2):70-5. Doi: <https://doi.org/10.1089/gyn.2019.0074>

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