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Chemotherapy Response Score (CRS): A comprehensive review of its prognostic and predictive value in High-Grade Serous Carcinoma (HGSC)

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HIGHLIGHTS

- CRS represents a useful prognostic predictor in high grade ovarian serous carcinoma.
- CRS may also predict response to immunotherapy and PARP inhibitors.
- This score can be evaluated both in omental and adnexal tissue.
- Pathologists must be aware of the chemotherapy induced morphological changes following chemotherapy.

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ABSTRACT

Ovarian carcinoma, the second most common gynecological cancer in Western countries, is frequently diagnosed at advanced stages, necessitating complex treatment strategies. While cytoreductive surgery remains the standard for improving survival, neoadjuvant chemotherapy (NACT) has become essential for cases unsuitable for immediate surgery, aiming to reduce tumor burden preoperatively. Introduced in 2015, the Chemotherapy Response Score (CRS) is now a key histopathological tool for assessing response to NACT, stratifying patients into three response categories. CRS3 is associated with improved progression-free survival (PFS) and overall survival (OS), while CRS1 and CRS2 are linked to poorer outcomes. Validated across clinical cohorts, CRS has proven valuable not only as a prognostic tool but also as a predictor for molecular-targeted therapies, such as PARP inhibitors, especially in BRCA wild-type patients. Studies also suggest a potential role for CRS in guiding the use of PD-L1 inhibitors, especially in partial responders (CRS1 and CRS2), where immunotherapy may complement chemotherapy. In the present paper we exlored the actual knowledge on CRS scoring for ovarian carcinoma. Diagnostic and prognostic implications of CRS as well as its correlation with therapeutic response and other biomarkers are discussed.

Contents

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1. Introduction

Ovarian carcinoma is the second most prevalent gynecological malignancy in Western countries, surpassed only by endometrial carcinoma [1]. Unfortunately, the majority of ovarian cancer cases are identified at an advanced stage, which significantly impacts treatment strategies and outcomes [2].

Specifically published guidelines from the National Comprehensive Cancer include neoadjuvant chemotherapy but the first recommendation is for upfront debulking surgery. Neoadjuvant chemotherapy is only recommended in cases where the surgery is unlikely to result in optimal debulking or in patients who are medically unable to undergo upfront debulking surgery.

For these advanced-stage cases, specifically published guidelines from the National Comprehensive Cancer Network (NCNN) include neoadjuvant chemotherapy but the first recommendation is for upfront debulking surgery, with the objective of achieving optimal cytoreduction which is strongly associated with improved survival outcomes [3]. However, in instances where the tumor burden is too extensive or where patients present with clinical contraindications that preclude immediate surgery, the use of neoadjuvant chemotherapy (NACT) has emerged as a strategic intervention [4,5]. The goal of NACT is to reduce tumor volume preoperatively, thereby enhancing the feasibility of subsequent surgical resection and increasing the likelihood of achieving optimal cytoreduction [4,5]. Moreover, NACT may provide survival benefits similar to primar debulking surgery, with fewer surgical morbidities [4,5]. This approach has become a critical component of treatment in cases where initial debulking surgery is not possible due to the advanced disease stage or significant patient comorbidities [3–5].

Until 2015 no uniform consensus regarding the histopathological grading system for assessing NACT response in advanced / unresectable ovarian cancer has been reached. Several studies have proposed regression grading systems with prognostic correlations. However, their findings have shown little reproducibility and have not been validated in an independent external cohort [6–9]. In 2014, Petrillo et al., proposed an easily assessable classification of pathological response, in a large series of unresectable advanced ovarian cancer (AOC) patients (complete – cPR: absence of residual disease; microscopic – microPR: presence of microscopic tumor foci (maximum diameter ≤ 3 mm; macroscopic – macroPR: macroscopic residual disease detected) [10]. In their study, FIGO stage IV emerged as the only negative predictor of cPR, suggesting that extraperitoneal dissemination could represent foci of more aggressive chemoresistant disease, being less prone to be removed by conventional NACT [10]. Similarly, the presence of peritoneal carcinomatosis also emerged as predictor of poor pathological response to NACT but it did not retain an independent prognostic role, thus suggesting that a complete cytoreduction to no gross residual disease at the time of IDS may overcome the negative prognostic impact of a wide initial tumoral diffusion [10].

Finally, in 2015 Böhm et al. developed a reproducible histopathological CRS three-tier grading system based on omental assessment of residual disease after NACT in a cohort of 71 EOC patients [11].

Up to date, Chemotherapy Response Score (CRS), considered a standardized histopathological grading system, has been included into the International Collaboration on Cancer Reporting (ICCR) and the College of American Pathologists (CAP) guidelines for histopathologic reporting of ovarian carcinoma.

CRS was initially developed for evaluating the response to NACT in omental tissue, where tumor response is often more pronounced [11,12]. Over time, its application has expanded to include adnexal tissues (ovaries and fallopian tubes) [13]. CRS categorizes patients into three response groups: CRS3 has consistently been linked to significantly better progression-free survival (PFS) and overall survival (OS) outcomes, making it an essential tool in guiding clinical decisions; patients with CRS1 or CRS2, by contrast, show a higher likelihood of recurrence and poorer prognosis [13].

The aim of the present review is to investigate the prognostic significance of CRS, its integration into clinical practice, and its validation across multiple studies.

2. CRS and its correlation with survival outcomes

The CRS score has been extensively validated as a reliable prognostic tool across diverse clinical settings and patient populations, particularly in high-grade serous carcinoma (HGSC). The first published study by Böhm et al. established that CRS3 is a strong predictor of both progression-free survival (PFS) and overall survival (OS) [11]. Subsequent research has reinforced these findings, confirming the reproducibility and robustness of CRS, particularly in predicting chemotherapy response and long-term outcomes [14–17]. Additionally, Santoro et al., through a systematic review of 691 patients, validated the use of adnexal CRS when omental tissue is unavailable, showing its comparable prognostic utility [18]. In addition to its histopathological implications, CRS has also been linked with molecular-targeted therapies. In this regard, Lee et al. demonstrated that in ovarian cancer patients carrying BRCA 1/2 mutations, CRS3 did not predict survival; by contrast, CRS3 was still a robust prognostic predictor for BRCA wild-type patients [19]. Additional recent studies demonstrated that patients with CRS3, particularly those with BRCA wild-type tumors, had significantly improved survival outcomes when treated with PARP inhibitors (PARPi) [20]. This connection between CRS and personalized therapies suggests

that CRS may represent an useful biomarker for guiding specific targeted treatments.

Overall, the extensive validation of CRS across multiple studies confirms its reliability as a prognostic factor for both PFS and OS. Its reproducibility, combined with its potential integration into molecular and genetic profiling, positions CRS as a valuable tool not only for assessing chemotherapy response but also for informing personalized treatment strategies in HGSC.

3. Chemotherapy Response Score (CRS): pathological definition

The CRS system assesses the extent of tumor regression, focusing on changes in tumor cells and the surrounding stroma. These morphological features, particularly in omental and adnexal tissues (ovaries and fallopian tubes), are categorized according to a three-thiered system: CRS1, CRS2, CRS3 (Fig. 1) [11–13].

Additional CRS scoring systems have also been proposed however, to date, the three-tiered system seem the most reproducible and has been introduced in clinical practice.

In this regard, in 2023 some researchers attempted to investigate a "CRS0" group (defined as those cases with a CRS1 and $R > 1$) vs a "CRS4" group (defined as those with a CRS3 and $R = 0$). "CRS0" patients (CRS1 and R > 1) had a worse OS than CRS1 patients with $R \leq 1$ or R0, though authors recognized this is significantly limited by small numbers [21]. However, regarding CRS1 group, it seems that residual disease status retains its prognostic value even when accounting for CRS status [21]. Moreover, considering the slight prognostic differences between omental CRS1 and CRS2, Rajkumar et al. proposed a binary system (CRS3 vs. CRS1/2) as opposed to a 3-tier score [17].

- **CRS3: Complete or Near-Complete Response**
  Patients with CRS3 exhibit a near-total or complete absence of viable tumor cells following chemotherapy, reflecting an excellent therapeutic response [11,13,15,16]. As a guide, pathologists should identify <5 % of residual tumor cells or tumoral deposits up to 2 mm to diagnose CRS3 [11,13,15,16]. The histological hallmark of CRS3 is extensive fibrosis, scarring, and stromal inflammation (Fig. 1) [11,13,15,16]. The replacement of tumor cells with fibrotic tissue indicates that the tumor has undergone significant regression. Dense fibrotic bands may replace the bulk of the tumor, with scattered chronic inflammatory infiltrates composed of macrophages, lymphocytes, and occasional plasma cells [11,13,15,16]. Occasionally, calcification and hyalinization may also occur within the fibrotic areas, indicating older areas of tumor necrosis [11,13,15,16]. Vascular proliferation can be observed in these regions as part of the repair process, further reinforcing the dynamic changes induced by chemotherapy [11,13,15,16]. Importantly, hemosiderin-laden macrophages, indicating previous hemorrhage and iron deposition, are frequently found in the stroma. These features collectively provide strong evidence of a complete or near-complete response, justifying the categorization of CRS3 [11,13,15,16].
- **CRS2: Partial Response**
  In patients classified as CRS2, the response to chemotherapy is intermediate, with both residual tumor cells and signs of regression present [11,13,15,16]. Viable tumor cells may persist in clusters or small nests embedded within fibrotic and necrotic areas (Fig. 1). Although chemotherapy has initiated a significant degree of tumor regression, the presence of these clusters of viable cells indicates that the response has been incomplete. Histological findings in CRS2 include moderate fibrosis, but in contrast to CRS3, the fibrotic tissue is more likely to be interspersed with viable tumor cells [11,13,15,16]. These cells may show signs of chemotherapy-induced stress, such as cytoplasmic vacuolation, cell shrinkage, and nuclear pyknosis, indicating a partially effective therapeutic response [11,13,15,16]. Inflammatory infiltrates are also present but are less dense and widespread than those observed in CRS3. These infiltrates, composed of lymphocytes and macrophages, are typically confined to areas surrounding residual tumor cells, indicating a continued immune response against remaining viable tumor tissue [11,13,15,16].
- **CRS1: Minimal to No Response**
  In CRS1, the tumor has shown minimal to no response to chemotherapy. Histologically, the tumor cells retain their original morphology, with little to no evidence of regression or cell death (Fig. 1) [11,13,15,16]. As a guide, >95 % of tumor should be viable for diagnosing CRS1 [11,13,15,16]. These tumors display dense cellularity, with large areas of viable tumor cells that maintain their pleomorphic and

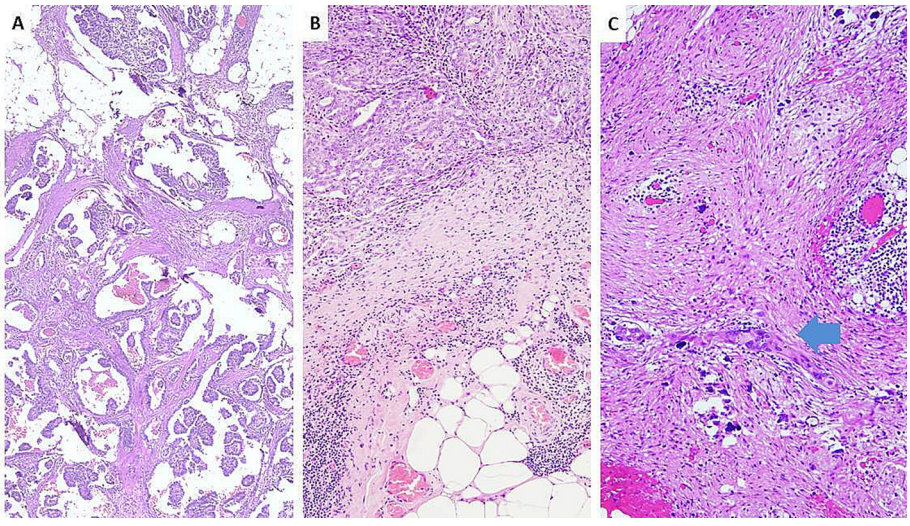

Fig. 1. Chemotherapy response score for high grade ovarian serous carcinoma (haematoxylin and eosin-stained sections).

A) Omental CRS1: omental tissue shows multiple neoplastic foci with papillary and glandular architecture. No evidence of tumor regression is observed.
B) Omental CRS2: neoplastic foci with solid and glandular architecture (top half) are intermixed with the fibrotic tissue and lymphocytic infiltrate (top half) indicating partial tumor regression.
C) Omental CRS3: omental tissue showing extensive fibrosis and stromal inflammation with a single neoplastic focus measuring <2 mm. These findings are consistent with a significant therapeutic response.

hyperchromatic appearance, typical of high-grade serous carcinoma [11,13,15,16]. Mitotic activity may still be observed, reflecting the ongoing proliferative capacity of the tumor despite chemotherapy exposure. The stroma in CRS1 shows few changes, with little to no evidence of fibrosis or inflammatory infiltration [11,13,15,16]. This lack of stromal reaction indicates that the tumor has not engaged the body's immune or reparative mechanisms and suggests a chemoresistant phenotype. The absence of necrosis and minimal signs of apoptosis further support the conclusion that the tumor has not responded to treatment, making CRS1 a marker of poor prognosis.

4. Histopathological features post-NACT

Beyond the specific changes categorized by CRS, chemotherapy can induce a range of additional morphological alterations that are not explicitly included in the scoring system but provide further insights into the tumor's behavior and response [22]. Oncocytic changes and nuclear pleomorphism (marked variation in nuclear size and shape) is frequently seen in tumors post-chemotherapy, particularly in CRS2 cases [23]. Tumor cells may become enlarged, with hyperchromatic nuclei and prominent nucleoli, creating a bizarre appearance (Fig. 2) [23].

Another key feature of chemotherapy-induced changes is the formation of multinucleated giant cells [23]. These cells, which are often a reaction to chemotherapy-induced stress, may resemble tumor cells but do not necessarily indicate active malignancy [23]. Their presence complicates the assessment of residual tumor viability versus therapy-induced atypia, especially in borderline cases between CRS1 and CRS2 [23]. Another additional morpho-phenotypical feature that can also predict patient outcomes is represented by the pattern of infiltration: in large confluent masses, in small foci or in scattered cells [23]. Other Authors showed worse overall survival with both, average Ki-67 > 20 % and highest Ki-67 > 50 %, so that they proposed adding Ki-67 labeling index to CRS to provide additional prognostic separation between patients with CRS1 and CRS2 [24].

5. Practical considerations in histopathological evaluation of CRS

The Chemotherapy Response Score (CRS) provides a structured and validated framework for assessing the histological response of HGSC to NACT. However, the application of CRS in clinical practice involves several challenges, including tissue sampling, morphological variability, and interpretation difficulties. Addressing these issues is essential for achieving consistent and accurate CRS evaluation, which has a direct impact on patient prognosis and treatment decisions.

5.1. Sampling and site selection

The accuracy of CRS evaluation depends heavily on the adequacy and appropriateness of tissue sampling. Since chemotherapy can induce variable responses across different tumor sites, careful selection of tissue samples from multiple regions is crucial to avoid underestimating or overestimating the overall tumor response [22,23]. Ideally, the omental specimen should be evaluated first, as this site is typically more responsive to chemotherapy, providing clearer evidence of tumor regression [11]. However, when omental tissue shows a complete or near-complete response (CRS3), additional sampling from adnexal tissues (ovary and fallopian tubes) is important to assess potential residual disease [13].

It is recommended to sample tumor areas that show the least response, as they represent the true extent of residual disease. If no tumor is identified in the omentum, it is critical to verify whether the patient had pre-existing omental involvement before chemotherapy, as the absence of residual tumor may reflect the original disease distribution rather than a therapeutic response [8]. Radiological and clinical data should be consulted to ensure the sampled tissues are representative of the disease burden before chemotherapy [11,13,15–17]. If there was no omental involvement prior to starting chemotherapy, then a CRS score cannot be applied [11,13,15–17].

Moreover, tissue block selection can affect the CRS outcome. Pathologists must carefully choose the blocks that exhibit minimal fibrosis and necrosis, as these provide better insights into the extent of viable tumor cells [11,13,15–17]. In contrast, heavily fibrotic or necrotic areas may lead to overinterpretation of tumor regression, as the presence of fibrosis may not accurately reflect the extent of residual malignancy [11,13,15–17].

5.2. Tumor heterogeneity

It is well-known that HGSC shows marked intratumoral heterogeneity [25]. Specifically, a wide variety of morphological patterns and tissue architectures as well as different molecular signatures may be encountered within the same tumor mass [25]. Initial biopsy specimens, typically obtained from limited tumor regions, may not fully represent the entire tumor's biological behavior. Following NACT, the distribution of residual disease and the tumor microenvironment can change significantly, potentially altering histological features and chemotherapy response scores (CRS) [22]. This underscores the importance of extensive sampling of post-NACT resection specimens to ensure a more comprehensive representation of the tumor's response to treatment.

The differential responses observed between omental and adnexal tissues further highlight the importance of considering tissue-specific factors, such as variations in tumor burden, vascularization, and drug penetration, which may influence CRS interpretation [13,18]. While omental tissue is often preferred for CRS evaluation due to its substantial tumor burden and accessibility, adnexal tissue assessment can also offer valuable prognostic information, especially when omental specimens are unavailable [13,18]. Recognizing the potential discordance between these tissues underscores the need for comprehensive sampling to capture tumor heterogeneity and optimize treatment evaluation.

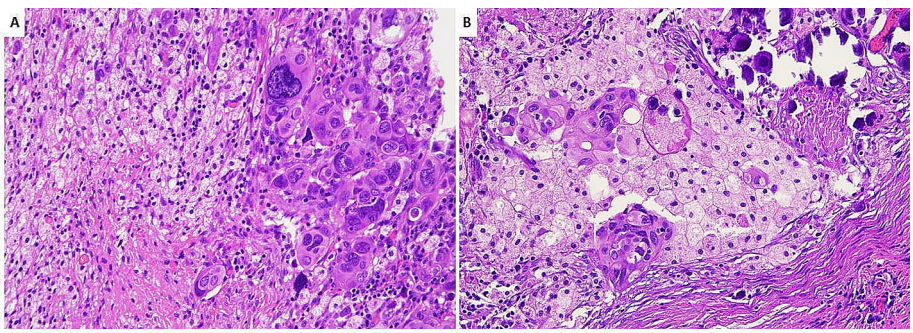

Fig. 2. Residual markedly atypical neoplastic cells in omental (A) and adnexal (B) samples categorized as CRS3.

5.3. Morphological variability and interpretation challenges: fibro-inflammatory changes and psammoma bodies

The morphological changes induced by chemotherapy present significant challenges in the evaluation of CRS. The distinction between chemotherapy-induced fibrosis and tumor-associated desmoplasia represents one of the most common challenges [22–24,26]. Both can appear as dense collagenous stroma, but only chemotherapy-induced fibrosis reflects a true therapeutic response, while desmoplasia may indicate a reactive stromal change associated with viable tumor cells [22–24,26]. Desmoplasia may be part of the natural biology of the tumor rather than a response to therapy [27]. Misinterpreting desmoplastic stroma as post-treatment fibrosis may lead to an overestimation of tumor regression. Additionally, necrosis, a common feature after chemotherapy, can vary widely in its presentation. In some cases, large areas of necrosis may suggest a significant therapeutic response, but in others, it may be an artifact of tumor ischemia rather than a direct effect of chemotherapy cells [28]. Careful correlation with viable tumor cells at the periphery of necrotic areas is necessary to assess the true response. CRS2, which represents an intermediate response, may contain a mix of necrotic, fibrotic, and viable tumor elements, making it difficult to distinguish between these morphologies [28].

Fibro-inflammatory changes indicative of tumor regression are characterized by the presence of macrophages, lymphocytes, and plasma cells, which facilitate the removal of necrotic tumor debris and promote tissue repair [22–24,26,29]. In some instances, the presence of fibro-inflammatory changes in regressed areas may lead to an overestimation of the treatment effect, particularly if underlying viable tumor cells are not accurately assessed [22–24,26,29].

Additionally, the occurrence of multinucleated giant cells and nuclear pleomorphism following chemotherapy complicates evaluation. These features, commonly observed in cases classified as CRS1 or CRS2, may reflect chemotherapy-induced atypia rather than true residual malignancy [23,29]. It is crucial to recognize these atypical cells as non-viable to prevent misclassification as residual disease.

Furthermore, the presence of psammoma bodies—calcified deposits typically found in high-grade serous carcinoma—can aid in evaluating tumor response [22,30]. These structures, formed in areas of previous tumor activity, may increase in density in regions undergoing tumor regression, serving as markers of past tumor burden [22,30]. The identification of psammoma bodies in post-NACT specimens can provide additional confirmation of tumor presence, especially in areas that are now devoid of viable tumor cells [22,30].

The most relevant morphological changes induced by chemotherapy are summaryzed in Table 1.

Table 1
Chemotherapy-induced morphological chenges in ovarian cancer.

Feature	Description	Implication
Oncocytic changes	Seen frequently post-chemotherapy, especially in CRS2 cases	Indicates response to chemotherapy, complicates malignancy assessment
Nuclear pleomorphism	Marked variation in nuclear size and shape	Suggests tumor response to treatment
Multinucleated giant cells	Reaction to chemotherapy-induced stress	Complicates assessment of residual tumor viability vs. therapy-induced atypia
Infiltration patterns	Large confluent masses, small foci, or scattered cells	Predicts patient outcomes and guides treatment decisions
Ki-67 labeling index	Average Ki-67 > 20 % and highest Ki-67 > 50 %	Higher index indicates poor prognosis, proposed addition to CRS for prognostic separation
Chemotherapy-induced fibrosis	Dense collagenous stroma	Reflects true therapeutic response
Tumor-associated desmoplasia	Reactive stromal change associated with viable tumor cells	May lead to overestimation of tumor regression if misinterpreted
Necrosis	Common feature post-chemotherapy	Requires careful correlation with viable tumor cells to assess true response
Fibro-inflammatory changes	Presence of macrophages, lymphocytes, and plasma cells	May lead to overestimation of treatment effect if underlying viable tumor cells are not assessed
Psammoma bodies	Calcified deposits indicating past tumor activity	Aids in evaluating tumor response and confirms presence of residual disease

5.4. Immunohistochemistry as a supplementary tool

Given the complexity of the morphological changes post-chemotherapy, immunohistochemistry (IHC) serves as an invaluable tool to complement the histological evaluation of CRS [31].

Numerous studies demonstrated a strong correlation between the expression of the human Ki-67 protein and cellular proliferation [24,32]. Consequently, elevated Ki-67 levels within neoplastic tissues are generally regarded as an unfavorable prognostic indicator [32]. However, these elevated levels have also been identified as a positive predictor of response to chemotherapy.

The relationship between Ki-67 expression within tumor cells and therapeutic outcomes has been examined across various malignancies, including non-Hodgkin lymphoma, bladder cancer, endometrial cancer, cervical cancers, neuroendocrine tumors, and sarcomas [32–34]. These studies demonstrated a positive association between higher Ki-67 expression levels and improved chemotherapeutic response.

KI-76 expression in HGSC represents a useful tool to identify residual tumor activity [24]. In CRS3 cases, low to absent Ki-67 expression indicates minimal to no proliferative activity, consistent with effective chemotherapy response [24]. In contrast, elevated Ki-67 expression in CRS1 and CRS2 indicates ongoing tumor cell division, reflecting incomplete or minimal chemotherapy efficacy [24].

Other important markers include p53 and WT1. TP53 mutations, which are frequent in HGSC, often result in the overexpression of the protein, and this can be detected even after chemotherapy [35]. However, chemotherapy-induced changes can alter p53 expression patterns, which can complicate interpretation [22,29]. In such cases, the loss of p53 expression may indicate an emerging subclonal population resistant to therapy [22,29]. WT1, a key marker for diagnosing HGSC, remains consistently expressed post-chemotherapy and helps to confirm the presence of residual disease, even when regressive changes obscure the original tumor morphology [22,29].

Additionally, markers of apoptosis, such as Caspase-3, are useful in identifying tumor cell death induced by chemotherapy [32]. An increase in Caspase-3 expression indicates that apoptosis has been successfully triggered by chemotherapy, further supporting the classification of CRS3 [36]. Conversely, Bcl-2, an anti-apoptotic protein, may be overexpressed in CRS1, suggesting that the tumor has activated survival pathways to evade chemotherapy-induced cell death [37]. This knowledge helps in understanding tumor resistance mechanisms and potentially guides further treatment strategies.

Recently, some Authors evaluated the expression of β-catenin and AQP1 in the preoperative peritoneal biopsies of 32 patients with peritoneal carcinosis by ovarian HGSC carcinoma [38]. They investigated their potential association with chemotherapeutic response evaluated at the omental site, as well as with clinico-pathological parameters. They concluded that HGSC patients could be categorized in two different predictive groups: AQP+ and AQP- [38]. AQP+ cases may represent a subset

of poor responders who could be considered more eligible for cytoreductive surgery rather than for NACT [38]. The most relevant immunohistochemical markers and their correlation to chemotherapy response have been summarized in Table 2.

5.5. Endometrial carcinoma as a mimicker of ovarian carcinoma in peritoneal biopsies: Impact on CRS

In clinical practice, distinguishing between endometrial carcinoma and high-grade serous ovarian carcinoma in peritoneal biopsies can pose significant diagnostic challenges due to the overlapping histopathological features of these malignancies [39,40]. Both cancers can involve the peritoneum and exhibit similar morphological characteristics, such as high-grade nuclear atypia, glandular or papillary architectural patterns, and psammoma body formation [39,40]. These similarities complicate the accurate identification of the tumor's primary origin, particularly in cases where the patient's clinical history is unclear or when both the ovary and endometrium are affected [39,40]. Misidentifying endometrial carcinoma as ovarian carcinoma can have significant implications on the treatment management decisions and on the assessment of chemotherapy response [39–42]. In this regard, applying CRS to endometrial carcinoma, which may show different chemotherapy responses and morphological changes, could lead to an inaccurate evaluation of treatment efficacy. Endometrial carcinoma, particularly the high-grade serous and endometrioid subtypes, may present with similar morphological features after chemotherapy, including areas of necrosis and fibrosis, complicating the interpretation of residual disease (Fig. 3) [43].

Accordingly, the CRS1 score may hold diagnostic utility in addition to its prognostic significance. Specifically, in cases where morphological and clinical findings are discordant, the presence of a CRS1 score could suggest an alternative histotype, such as endometrial carcinoma. In this scenario, immunohistochemistry can help resolve this diagnostic challenge.

Although some authors have argued that accurately defining histotype and tumor grade is challenging post-chemotherapy, we consider it essential to attempt a precise characterization of residual tumors to ensure appropriate treatment [22]. This can be accomplished through comprehensive morphological and immunohistochemical evaluation on multiple tumor sections.

Key markers such as WT1, which is typically positive in HGSC but often negative in endometrial carcinoma, and ER/PR receptors, which are more commonly expressed in endometrial carcinoma, can aid in distinguishing between these two malignancies [44]. However, we have to keep in mind that WT1 immunohistochemical expression is not limited to serous histotype and/or ovarian origin. In fact, a significant proportion of endometrial adenocarcinomas can also show WT1 immunoreactivity [41]. However, even with IHC, the overlapping expression of certain markers like p53 and PAX8 can further complicate the differentiation, emphasizing the need for careful evaluation of all available clinical and pathological data [39–41]. Misapplication of the CRS system in the context of endometrial carcinoma could lead to inappropriate clinical decisions, as CRS has been validated for use in ovarian carcinoma and may not reflect the true chemotherapy response in other malignancies.

Thus, accurate differentiation between ovarian and endometrial carcinomas or between serous and other hystotypes in peritoneal biopsies is crucial for the proper application of CRS and the subsequent management of patient care. In particular, a CRS1 pathological feature (minimal to no Response) should be immunohistochemically investigated when morphology seems to not fit with a real high grade serous carcinoma diagnosis. Finally, a multidisciplinary approach, incorporating morphological assessment, IHC profiles, and clinical history, is essential to avoid misclassification and ensure that patients receive the most appropriate treatment based on their tumor's origin and response to therapy.

Table 2
Useful immunohistochemical markers in ovarian cancer following chemotherapy.

Marker	Description	Implication
Ki-67	Marker of cellular proliferation; identifies residual tumor activity	Low to absent in CRS3 indicates effective chemotherapy elevated in CRS1 and CRS2; reflects ongoing cell division
p53	Overexpressed due to TP53 mutations in HGSC	Altered expression patterns complicate interpretation; loss of expression may indicate therapy-resistant subclones
WT1	Key marker for diagnosing HGSC, remains consistently expressed post-chemotherapy	Confirms presence of residual disease despite regressive changes
Caspase-3	Marker of apoptosis, indicates tumor cell death induced by chemotherapy	Increase supports classification of CRS3, showing successful apoptosis
Bcl-2	Anti-apoptotic protein, may be overexpressed in CRS1	Suggests activation of survival pathways to evade chemotherapy-induced cell death
β-catenin	Investigated for association with chemotherapeutic response in peritoneal biopsies	Potentially linked with chemotherapeutic response and can categorize patients into different predictive groups
AQP1	Investigated in preoperative peritoneal biopsies	AQP+ cases may be poor responders more eligible for cytoreductive surgery rather than NACT.

6. Omental versus adnexal CRS

While CRS was initially developed for use with omental tissue, its application has expanded to include adnexal tissues [18]. In a systematic review and meta-analysis of ovarian cancer patients, Santoro et al. demonstrated that CRS2–3, when applied to both omental and adnexal tissues, significantly improved the ability to predict PFS and OS, broadening CRS's applicability beyond ovarian cancer [18]. In detail, CRS, when applied on the omentum, adnexa, and as a combined score (omental and adnexal), was significantly associated with PFS but not with OS; adnexal CRS1/2 is more likely to develop platinum-resistant disease. Finally, the modified 2-tier CRS (CRS1/2 versus CRS3) was significantly associated with survival (OS and PFS), independently of scoring site (omental vs. adnexal) [18].

While omental CRS has been well-validated, adnexal tissues may exhibit a different response pattern to chemotherapy, with residual viable tumor cells often persisting in the adnexa even when the omental disease has regressed (CRS3) [13,18]. Therefore, assigning a CRS1 or CRS2 in adnexal tissues may carry more prognostic significance than a similar score in omental tissue.

Studies suggest that minimal or absent tumor response (CRS1) in adnexal tissues is a strong indicator of chemoresistance and is associated with higher rates of recurrence and worse survival outcomes [13,18]. Adnexal sites may be more resistant to chemotherapy due to differences in tumor microenvironment and vascularization, which limits the penetration of chemotherapeutic agents.

According to Santoro et al., absent or minimal tumor response in the adnexal samples (adnCRS1) has higher potential to influence the prognosis when compared to an absent or minimal response in omental samples (Om1Adn2: PFS 15 m; Om2Adn1: PFS 10 m); a partial tumor response in omental samples (omCR2) seems to be related with a worse outcome when compared to a partial response in adnexal samples (Om2Adn3: PFS 21 m; Om3Adn2: PFS 36 m) [13].

This spatial heterogeneity underscores the importance of evaluating multiple tissue sites and not relying solely on omental response to determine the overall CRS score.

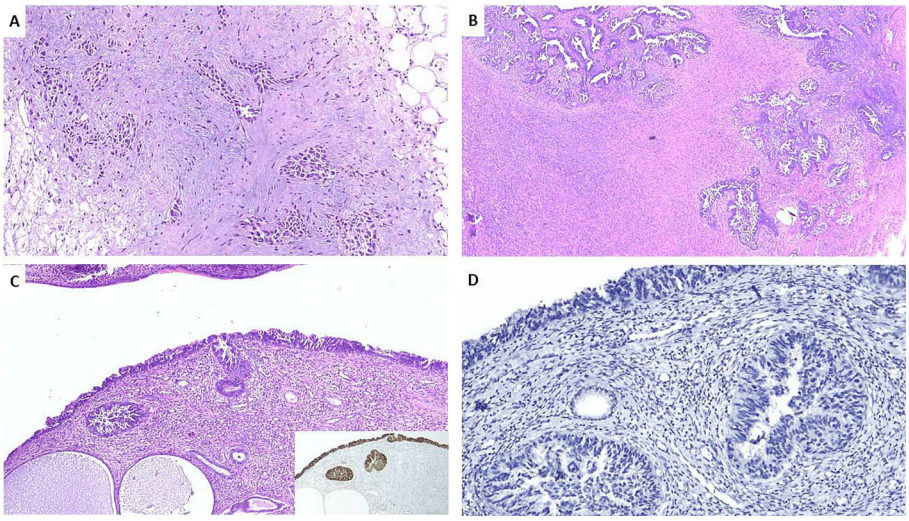

Fig. 3. Diagnostic pitfall in CRS score. A 58 year old woman underwent adjuvant chemotherapy after a pre-operative peritoneal biopsy indicating a diagnosis of high-grade ovarian serous carcinoma (images taken from author's pathological archives).

A) Omental CRS1 score: omental tissue exhibiting several neoplastic foci with solid and glandular architecture, without evidence of fibro-inflammatory changes related to tumor response.
B) Ovarian CRS1 score: ovarian tissue of the same patient showing multiple neoplastic foci without evidence of tumor regression.
C) Hysterectomy specimen following chemotherapy: the superficial endometrial tissue from the same patient showed atypical high grade nuclei with pleomorphism, hyperchromasia. Neoplastic cells wer diffusely stained with p16.
D) A null-type pattern for p53 immunohistochemistry was also observed. Overall, these findings suggested that the initial pre-chemotherapy diagnosis of ovarian carcinoma was incorrect; conversely, the patient was affected by a superficial serous endometrial carcinoma.

7. CRS in clinical practice

CRS has not only been validated but also successfully integrated into clinical practice, particularly in determining the treatment and prognosis of HGSC.

CRS can be enhanced by combining it with other clinical and molecular markers, including CA125 levels, RECIST 1.1 imaging, and BRCA mutation status. In this regard, Liang et al., showed that patients with CRS3 had the most significant reductions in CA125, underscoring the value of CRS in conjunction with other markers [45]. Moreover, integrating Ki-67 labeling index with CRS could provide further insights for patients with intermediate responses, such as those with CRS1–2 [45]. Recently, two treatment algorithms have been established for selecting maintenance therapy in the first-line management of advanced ovarian cancer, specifically for good and moderate responders [45,46]. These algorithms are informed by the timing and outcomes of surgery, response to platinum-based chemotherapy, and biomarker status [46]. A scoring system for assessing chemotherapy response has been proposed, although its validation is still in progress [46]. Notably, the authors indicate that for patients undergoing interval debulking surgery (IDS) following neoadjuvant chemotherapy (NACT), the assessment of response to chemotherapy should consider the Chemotherapy Response Score (CRS), the KELIM score, and the completeness of resection following IDS [42].

7.1. CRS, PARP inhibitor therapy and BRCA mutations

Several studies have highlighted the relationship between CRS and the effectiveness of PARP inhibitors (PARPi), particularly in BRCA-mutated and BRCA wild-type patients [19,20,47,48]. However, it is important to note that the interplay between CRS, BRCA mutations, and PARP inhibitors therapy in ovarian cancer is still an emerging area of research. Further investigation is needed to fully understand these complex interactions and to determine the optimal treatment strategies for individual patients.

Concerning the relationship between BRCA mutations and CRS, a recent paper by Lee et al. explored the role of BRCA1/2 mutations in determining chemotherapy response and survival outcomes in advanced ovarian cancer patients treated with neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) [20]. In this study authors demonstrated that in ovarian cancer patients with BRCA1/2 mutations, CRS does not significantly predict progression-free survival (PFS) or overall survival (OS) [20]. By contrast, for BRCA wild-type patients, a CRS 3 score after NAC was associated with significantly better PFS and OS, highlighting the prognostic value of CRS for this group [20]. Additionally, in patients with CRS 1 or 2 (indicating lesser tumor response), BRCA1/2 mutation carriers demonstrated better survival outcomes than those with the wild-type genotype [20]. This suggests that while a high CRS may not be crucial for predicting survival in BRCA mutation carriers, their inherent sensitivity to platinum-based chemotherapy could compensate for a lower chemotherapy response score. The findings underscore the importance of individualized treatment approaches for ovarian cancer. For BRCA wild-type patients, achieving a CRS 3 may suggest better prognosis and guide further therapeutic decisions. However, for BRCA1/2 mutation carriers, alternative markers or treatment strategies may need to be considered, as CRS does not have the same prognostic value [20].

In 2023, during the ASCO Annual Meeting, Marchetti et al. presented an abstract highlighting the role of Chemotherapy Response Score (CRS) in predicting responses to PARP inhibitors (PARPi) among patients with high-grade serous ovarian cancer undergoing neoadjuvant chemotherapy (NACT) [49]. The study also explored the correlation between CRS and Homologous Recombination status (HR status) [49]. Patients with a CRS of 3 receiving PARPi maintenance exhibited the most favorable prognosis [49]. In the BRCA wild-type population, a CRS of 3 was associated with prolonged survival, with a median progression-free survival (PFS) of 24 months for the CRS3 + PARPi BRCA wild-type group, compared to 15 months for the CRS1/2 + PARPi BRCA wild-type group ($p = 0.041$) [49]. Furthermore, 59.1 % of patients with HRD+ status had a CRS of 3, while only 22.7 % of HRD- patients achieved this score

($p = 0.048$) [45]. The authors concluded that a higher CRS at the time of interval cytoreduction correlates with improved responses to subsequent PARPi therapy [49]. As CRS correlates with PARPi response in a manner similar to HRD testing in other clinical trials, it may serve as a surrogate marker for HRD status [49].

An open question remains regarding the potential correlation between Chemotherapy Response Score (CRS) and treatment outcomes in newly diagnosed non-BRCA-mutated high-grade FIGO stage III-IV ovarian cancer patients. With the evolving therapeutic landscape, particularly the combination of Durvalumab and Olaparib as maintenance therapy, and the observed 51 % disease reduction in homologous recombination deficiency (HRD) cohorts, there is a need for further investigation. Given its effectiveness, ease of definition, and cost-effectiveness, could CRS serve as a biomarker to predict responses to this novel therapeutic protocol? This emerging opens the way for future studies exploring the utility of CRS in this context.

7.2. PD-L1 expression and CRS

PD-L1 (Programmed Death-Ligand 1) is a key molecule in immune evasion mechanisms used by many cancers, including high-grade serous carcinoma (HGSC) [50,51]. In ovarian cancer, PD-L1 is expressed in tumor cells and tumor-infiltrating lymphocytes (TILs), with studies showing that approximately 43 % of ovarian cancer cases exhibit PD-L1 expression [50,51].

The relationship between chemotherapy and PD-L1 expression is an emerging area of research. Chemotherapy can modulate the tumor microenvironment in ways that affect PD-L1 levels [50,51]. For example, in CRS1 and CRS2 tumors, where there is incomplete or minimal response to chemotherapy, residual tumor cells may upregulate PD-L1 as a defensive mechanism to evade immune detection [52]. This upregulation may be linked to chemotherapy-induced DNA damage and the activation of immune checkpoint pathways [52]. By contrast, CRS3 tumors, may have lower PD-L1 expression due to the reduction in viable tumor burden.

Given the potential for PD-L1 upregulation after chemotherapy, the use of PD-L1 inhibitors (such as pembrolizumab or nivolumab) in combination with chemotherapy is being actively studied [52–54]. Clinical trials have shown that single-agent PD-L1 inhibitors have limited efficacy in ovarian cancer, with objective response rates (ORR) of around 9 % [52–54]. However, when immune checkpoint inhibitors are combined with chemotherapy or other agents like anti-angiogenics, the response rates improve significantly, with some trials showing ORRs as high as 30 % [52–54]. This combination approach is particularly promising for patients with CRS1 and CRS2, where residual tumor cells remain following chemotherapy. By using PD-L1 blockade, the immune system may be reactivated to eliminate the remaining cancer cells, improving progression-free survival (PFS) and overall survival.

Ongoing studies are exploring the combined use of PD-L1 inhibitors and chemotherapy in ovarian cancer, particularly in platinum-resistant cases.

While preclinical and early clinical investigations have begun to explore the potential interplay between PD-L1 expression, CRS, and the efficacy of immunotherapy in ovarian cancer, the current literature data are limited and primarily based on preliminary observations. Further clinical trials with larger sample sizes are needed to investigate these complex interactions, elucidate the predictive value of these biomarkers, and establish their clinical utility in guiding individualized treatment decisions for patients with ovarian cancer. Understanding how CRS scoring and PD-L1 expression interact will help refine treatment strategies, offering more personalized therapy options for patients with HGSC.

8. Conclusion

CRS is a reproducible - validated 3-tiered system currently recommended by the ICCR Ovary Carcinoma DAC, only applicable to adnexal HGSC at this time, in omental site and in post NACT setting. It represents a key component in proposed multidisciplinary algorhythm / decisional process for maintenance therapy. While the CRS system provides a structured and validated framework for assessing tumor response to chemotherapy, the incorporation of additional morphological features and immunohistochemical markers offers a more comprehensive and nuanced evaluation of tumor behavior. The ability to differentiate between viable tumor cells, therapy-induced atypia, and apoptotic remnants enhances the accuracy of the assessment, particularly in borderline CRS cases. The investigation of scoring values in ovarian and other extraovarian sites also revealed significant differences between cases with and without residual diseases. Since epithelial ovarian cancer cells gradually become polyclonal and the genetic heterogeneity of metastatic lesions has already been established, it would be prudent to evaluate the actual summative CRS in various sites, including the omentum, ovarian tissue, and peritoneal disease. This way, future research might be able to identify patients with a favorable CRS score from omental biopsies who actually have less responsive extra-omental lesions and, therefore, a higher tendency to relapse.

Author contributions

Conception and design: GFZ,AS.
Resources and methodology: GA, GT.
Collection and assembly of data: EB, AS.
Data analysis and interpretation: FF,SS.
Writing—original draft preparation: AS, GA.
Writing—review and editing: GFZ.
Supervision: GT, FF.
Project administration: GFZ.
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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] M.-A. Lisio, L. Fu, A. Goyeneche, Z.-H. Gao, C. Telleria, High-grade serous ovarian Cancer: basic sciences, clinical and therapeutic standpoints, Int. J. Mol. Sci. 20 (2019) 952, https://doi.org/10.3390/ijms20040952.

[2] J. Prat, Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features, Virchows Arch. 460 (2012) 237–249, https://doi.org/10.1007/s00428-012-1203-5.

[3] J. Liu, A. Berchuck, F.J. Backes, J. Cohen, R. Grisham, C.A. Leath, et al., NCCN guidelines® insights: ovarian Cancer/fallopian tube Cancer/primary peritoneal Cancer, version 3.2024, J. Natl. Compr. Cancer Netw. 22 (2024) 512–519.

[4] S. Kehoe, J. Hook, M. Nankivell, G.C. Jayson, H. Kitchener, T. Lopes, et al., Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial, Lancet 386 (2015) 249–257, https://doi.org/10.1016/S0140-6736(14)62223-6.

[5] I. Vergote, C.G. Tropé, F. Amant, G.B. Kristensen, T. Ehlen, N. Johnson, R.H.M. Verheijen, M.E.L.V.D. Burg, A.J. Lacave, P.B. Panici, et al., Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer, N. Engl. J. Med. 363 (2010) 943–953, https://doi.org/10.1056/NEJMoa0908806.

[6] S. Sassen, B. Schmalfeldt, N. Avril, W. Kuhn, R. Busch, H. Höfler, et al., Histopathologic assessment of tumor regression after neoadjuvant chemotherapy in advanced-stage ovarian cancer, Hum. Pathol. 38 (6) (2007 Jun) 926–934, https://doi.org/10.1016/j.humpath.2006.12.008.

[7] T. Le, K. Williams, M. Senterman, L. Hopkins, W. Faught, M. Fung-Kee-Fung, Histopathologic assessment of chemotherapy effects in epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and delayed primary surgical debulking, Gynecol. Oncol. 106 (1) (2007 Jul) 160–163, https://doi.org/10.1016/j.ygyno.2007.03.029.

[8] J.G. Ferron, C. Uzan, A. Rey, S. Gouy, P. Pautier, C. Lhommé, et al., Histological response is not a prognostic factor after neoadjuvant chemotherapy in advanced-stage ovarian cancer with no residual disease, Eur. J. Obstet. Gynecol. Reprod. Biol. 147 (1) (2009 Nov) 101–105, https://doi.org/10.1016/j.ejogrb.2009.07.016.

[9] M. Muraji, T. Sudo, S. Iwasaki, S. Ueno, S. Wakahashi, S. Yamaguchi, et al., Histopathology predicts clinical outcome in advanced epithelial ovarian cancer patients treated with neoadjuvant chemotherapy and debulking surgery, Gynecol. Oncol. 131 (3) (2013 Dec) 531–534, https://doi.org/10.1016/j.ygyno.2013.09.030.

[10] M. Petrillo, G.F. Zannoni, L. Tortorella, L. Pedone Anchora, V. Salutari, A. Ercoli, et al., Prognostic role and predictors of complete pathologic response to neoadjuvant chemotherapy in primary unresectable ovarian cancer, Am. J. Obstet. Gynecol. 211 (6) (2014 Dec), https://doi.org/10.1016/j.ajog.2014.06.034 632.e1–8.

[11] S. Böhm, A. Faruqi, I. Said, M. Lockley, E. Brockbank, A. Jeyarajah, et al., Chemotherapy response score: development and validation of a system to quantify histopathologic response to neoadjuvant chemotherapy in Tubo-ovarian high-grade serous carcinoma, J. Clin. Oncol. 33 (2015) 2457–2463, https://doi.org/10.1200/JCO.2014.60.5212.

[12] P.A. Cohen, A. Powell, S. Böhm, C.B. Gilks, C.J.R. Stewart, T.M. Meniawy, et al., Pathological chemotherapy response score is prognostic in tubo-ovarian high-grade serous carcinoma: a systematic review and meta-analysis of individual patient data, Gynecol. Oncol. 154 (2019) 441–448, https://doi.org/10.1016/j.ygyno.2019.04.679.

[13] A. Santoro, G. Angelico, A. Piermattei, F. Inzani, M. Valente, D. Arciuolo, S. Spadola, A. Mulè, P. Zorzato, A. Fagotti, et al., Pathological chemotherapy response score in patients affected by high grade serous ovarian carcinoma: the prognostic role of omental and ovarian residual disease, Front. Oncol. 9 (2019) 778, https://doi.org/10.3389/fonc.2019.00778.

[14] W.G. McCluggage, M.J. Judge, B.A. Clarke, B. Davidson, C.B. Gilks, H. Hollema, et al., International collaboration on Cancer reporting. Data set for reporting of ovary, fallopian tube and primary peri-toneal carcinoma: recommendations from the international collaboration on Cancer reporting (ICCR), Mod. Pathol. 28 (2015) 1101–1122, https://doi.org/10.1038/modpathol.2015.77.

[15] M. Liang, E. Prendergast, J. Staples, C. Holschneider, I. Cass, Complete pathologic response at interval debulking surgery following neoadjuvant chemotherapy predicts improved survival in women with advanced epithelial ovarian cancer in a Mul-ti-institutional cohort, Gynecol. Oncol. 143 (2016) 197, https://doi.org/10.1016/j.ygyno.2016.08.247.

[16] J.-Y. Lee, Y.S. Chung, K. Na, H.M. Kim, C.K. Park, E.J. Nam, et al., External validation of chemotherapy response score system for histopathological assessment of tumor regression after neoadjuvant chemotherapy in tubo-ovarian high-grade serous carcinoma, J. Gynecol. Oncol. 28 (2017), e73, https://doi.org/10.3802/jgo.2017.28.e73.

[17] S. Rajkumar, A. Polson, R. Nath, G. Lane, A. Sayasneh, A. Jakes, et al., Prognostic implications of histological tumor regression (Böhm's score) in patients receiving neoadjuvant chemotherapy for high grade serous tubal & ovarian carcinoma, Gynecol. Oncol. 151 (2018) 264–268, https://doi.org/10.1016/j.ygyno.2018.08.042.

[18] A. Santoro, A. Travaglino, F. Inzani, P. Straccia, D. Arciuolo, M. Valente, et al., Prognostic value of chemotherapy response score (CRS) assessed on the adnexa in ovarian high-grade serous carcinoma: a systematic review and Meta-analysis, Diagnostics (Basel). 12 (3) (2022 Mar 4) 633, https://doi.org/10.3390/diagnostics12030633.

[19] Y.J. Lee, H.S. Kim, J.H. Rim, J.Y. Lee, E.J. Nam, S.W. Kim, S. Kim, Y.T. Kim, Germline BRCA, chemotherapy response scores, and survival in the neoadjuvant treatment of ovarian cancer, BMC Cancer 20 (1) (2020 Mar 4) 185, https://doi.org/10.1186/s12885-020-6688-8.

[20] Y.J. Lee, Y.K. Shin, N.R. Kim, S.I. Kim, Y.Y. Lee, J.Y. Park, J.W. Kim, H.W. Cho, J.Y. Lee, Chemotherapy response score no longer predicts survival outcomes in high-grade serous ovarian cancer patients with *BRCA* mutation and/or maintenance therapy, J. Gynecol. Oncol. (2024 Mar 18), https://doi.org/10.3802/jgo.2024.35.e73.

[21] L.A. Marsh, T.H. Kim, M. Zhang, K. Kubalanza, C.L. Treece, D. Chase, et al., Pathologic response to neoadjuvant chemotherapy in ovarian cancer and its association with outcome: a surrogate marker of survival, Gynecol. Oncol. 177 (2023 Oct) 173–179, https://doi.org/10.1016/j.ygyno.2023.09.002.

[22] W.G. McCluggage, R.W. Lyness, R.J. Atkinson, S.P. Dobbs, I. Harley, H.R. McClelland, J.H. Price, Morphological effects of chemotherapy on ovarian carcinoma, J. Clin. Pathol. 55 (1) (2002 Jan) 27–31, https://doi.org/10.1136/jcp.55.1.27.

[23] Y. Zhong, J. Liu, X. Li, S.N. Westin, A. Malpica, B.C. Lawson, et al., A modified 2 tier chemotherapy response score (CRS) and other histopathologic features for predicting outcomes of patients with advanced Extrauterine high-grade serous carcinoma after neoadjuvant chemotherapy, Cancers 13 (2021) 704, https://doi.org/10.3390/cancers13040704.

[24] M. Heayn, L.B. Skvarca, L. Zhu, R.P. Edwards, A.B. Olawaiye, F. Modugno, et al., Impact of Ki-67 labeling index on prognostic significance of the chemotherapy response score in women with Tubo-ovarian Cancer treated with neoadjuvant chemotherapy, Int. J. Gynecol. Pathol. 40 (3) (2021 May 1) 278–285, https://doi.org/10.1097/PGP.0000000000000706.

[25] E. Azzalini, G. Stanta, V. Canzonieri, S. Bonin, Overview of tumor heterogeneity in high-grade serous ovarian cancers, Int. J. Mol. Sci. 24 (2023) 15077.

[26] P. Mhawech-Fauceglia, D. McCarthy, A. Tonooka, G. Scambia, Y. Garcia, P. Dundr, et al., The association of histopathologic features after neoadjuvant chemo-immunotherapy with clinical outcome: sub-analyses from the randomized double-blinded, placebo-controlled, phase III IMagyn050/GOG3015/ENGOT-ov39 study, Gynecol. Oncol. 186 (2024 Jul) 17–25, https://doi.org/10.1016/j.ygyno.2024.03.022.

[27] Q. Hu, Y. Wang, S. Yao, Y. Mao, L. Liu, Z. Li, et al., Desmoplastic reaction associates with prognosis and adjuvant chemotherapy response in colorectal Cancer: a multicenter retrospective study, Cancer Res Commun. 3 (6) (2023 Jun 15) 1057–1066, https://doi.org/10.1158/2767-9764.CRC-23-0073.

[28] T. Le, P. Shahriari, L. Hopkins, W. Faught, Fung Kee Fung, M., Prognostic significance of tumor necrosis in ovarian cancer patients treated with neoadjuvant chemotherapy and interval surgical debulking, Int. J. Gynecol. Cancer 16 (3) (2006 May-Jun) 986–990, https://doi.org/10.1111/j.1525-1438.2006.00594.x.

[29] F. Inzani, D. Arciuolo, G. Angelico, A. Santoro, A. Travaglino, N. D'Alessandris, et al., Assessing post-treatment pathologic tumor response in female genital tract carcinomas: an update, Front. Oncol. 10 (12) (2022 Feb), https://doi.org/10.3389/fonc.2022.814989 814989.

[30] T. Motohara, H. Tashiro, Y. Miyahara, I. Sakaguchi, H. Ohtake, H. Katabuchi, Long-term oncological outcomes of ovarian serous carcinomas with psammoma bodies: a novel insight into the molecular pathogenesis of ovarian epithelial carcinoma, Cancer Sci. 101 (6) (2010 Jun) 1550–1556, https://doi.org/10.1111/j.1349-7006.2010.01556.x.

[31] V. Manu, T.A. Hein, D. Boruah, V. Srinivas, Serous ovarian tumors: Immunohistochemical profiling as an aid to grading and understanding tumorigenesis, Med. J. Armed Forces India 76 (1) (2020 Jan) 30–36, https://doi.org/10.1016/j.mjafi.2018.06.014 (Epub 2018 Oct 10).

[32] M.G. Davey, S.O. Hynes, M.J. Kerin, N. Miller, A.J. Lowery, Ki-67 as a prognostic biomarker in invasive breast Cancer, Cancers (Basel) 13 (2021) 4455.

[33] S. Wajid, F.A. Samad, A.S. Syed, F. Kazi, Ki-67 and its relation with complete pathological response in patients with breast Cancer, Cureus 13 (2021), e16788.

[34] R. Sales Gil, P. Vagnarelli, Ki-67: more hidden behind a 'Classic proliferation Marker', Trends Biochem. Sci. 43 (2018) 747–748.

[35] M. Köbel, A.M. Piskorz, S. Lee, S. Lui, C. LePage, F. Marass, et al., Optimized p53 immunohistochemistry is an accurate predictor of *TP53* mutation in ovarian carcinoma, J. Pathol. Clin. Res. 2 (4) (2016 Jul 13) 247–258, https://doi.org/10.1002/cjp2.53. PMID: 27840695; PMCID: PMC5091634.

[36] T. Tenev, M. Marani, I. McNeish, N.R. Lemoine, Pro-caspase-3 overexpression sensitises ovarian cancer cells to proteasome inhibitors, Cell Death Differ. 8 (3) (2001 Mar) 256–264, https://doi.org/10.1038/sj.cdd.4400808.

[37] N.S. Anderson, L. Turner, S. Livingston, R. Chen, S.V. Nicosia, P.A. Kruk, Bcl-2 expression is altered with ovarian tumor progression: an immunohistochemical evaluation, J. Ovarian Res. 25 (2) (2009 Oct) 16.

[38] G. Angelico, A. Ieni, R. Caltabiano, A. Santoro, F. Inzani, S. Spadola, et al., Evaluation of Beta-catenin subcellular localization and Water Channel protein AQP1 expression as predictive markers of chemo-resistance in ovarian high-grade serous carcinoma: comparative study between preoperative peritoneal biopsies and surgical samples, Diagnostics (Basel). 11 (3) (2021 Mar 5) 452, https://doi.org/10.3390/diagnostics11030452.

[39] R. Murali, B. Davidson, O. Fadare, J.A. Carlson, C.P. Crum, C.B. Gilks, et al., High-grade endometrial carcinomas: morphologic and Immunohistochemical features, diagnostic challenges and recommendations, Int. J. Gynecol. Pathol. 38 Suppl 1(Iss 1 Suppl 1):S40-S63 (2019 Jan), https://doi.org/10.1097/PGP.0000000000000491.

[40] H. Assem, P.F. Rambau, S. Lee, T. Ogilvie, A. Sienko, L.E. Kelemen, M. Köbel, High-grade Endometrioid carcinoma of the ovary: a Clinicopathologic study of 30 cases, Am. J. Surg. Pathol. 42 (4) (2018 Apr) 534–544, https://doi.org/10.1097/PAS.0000000000001016.

[41] G. Angelico, A. Santoro, P. Straccia, F. Inzani, F. Cianfrini, S. Spadola, et al., Diagnostic and prognostic role of WT1 Immunohistochemical expression in uterine carcinoma: a systematic review and Meta-analysis across all endometrial carcinoma Histotypes, Diagnostics (Basel). 10 (9) (2020 Aug 26) 637, https://doi.org/10.3390/diagnostics10090637.

[42] I. Jani, R.R. Lastra, K.S. Brito, C. Liao, I. Lazo, N.K. Lee, S.D. Yamada, K.C. Kurnit, Chemotherapy response score as a prognostic tool in patients with advanced stage endometrial carcinoma treated with neoadjuvant chemotherapy, Int. J. Gynecol. Cancer 31 (6) (2021 Jun) 852–858, https://doi.org/10.1136/ijgc-2020-002202.

[43] A.T. Williams, R. Ganesan, Role of the pathologist in assessing response to treatment of ovarian and endometrial cancers, Histopathology 76 (1) (2020 Jan) 93–101, https://doi.org/10.1111/his.13994.

[44] S. Gupta, S. Ahuja, D.S. Kalwaniya, Immunohistochemistry markers in ovarian and fallopian tube neoplasms: a comprehensive review, Indian J. Surg. Oncol. 15 (Suppl. 3) (2024 Sep) 465–480, https://doi.org/10.1007/s13193-024-02049-y (Epub 2024 Jul 25).
[45] W.F. Liang, H. Li, J.Y. Wu, C.H. Liu, M.F. Wu, J. Li, Identification of ovarian Cancer patients Most likely to achieve chemotherapy response score 3 following neoadjuvant chemotherapy: development of a predictive nomogram, Front. Oncol. 10 (2020 Oct 5), 560888, https://doi.org/10.3389/fonc.2020.560888.
[46] N. Colombo, A. Gadducci, F. Landoni, D. Lorusso, R. Sabbatini, G. Artioli, et al., Consensus statements and treatment algorithm to guide clinicians in the selection of maintenance therapy for patients with newly diagnosed, advanced ovarian carcinoma: results of a Delphi study, Gynecol. Oncol. 175 (2023 Aug) 182–189, https://doi.org/10.1016/j.ygyno.2023.05.065.
[47] C.H. Lau, K.M. Seow, K.H. Chen, The molecular mechanisms of actions, effects, and clinical implications of PARP inhibitors in epithelial ovarian cancers: a systematic review, Int. J. Mol. Sci. 23 (15) (2022 Jul 23) 8125, https://doi.org/10.3390/ijms23158125.
[48] A. Gadducci, S. Cosio, F. Landoni, A.A. Lissoni, P. Zola, M.E. Laudani, et al., Response to chemotherapy and clinical outcome of patients with recurrent epithelial ovarian Cancer after PARP inhibitor maintenance treatment: a multicenter retrospective Italian study, Anticancer Res. 42 (4) (2022 Apr) 2017–2022, https://doi.org/10.21873/anticanres.15681.
[49] C. Marchetti, R. Ergasti, F.M. Capomacchia, D. Giannarelli, C.M. Sassu, G.F. Zannoni, et al., The role of Chemotherapy Response Score (CRS) in the decision-making process for patients with advanced high-grade serous ovarian cancer undergoing neoadjuvant chemotherapy. Meeting Abstract: 2023 ASCO annual meeting I, Gynecologic Cancer (May 31, 2023), https://doi.org/10.1200/JCO.2023.41.16_suppl.559.
[50] A. Santoro, G. Angelico, F. Inzani, D. Arciuolo, A. d'Amati, F. Addante, et al., The emerging and challenging role of PD-L1 in patients with gynecological cancers: an updating review with clinico-pathological considerations, Gynecol. Oncol. 184 (2024 May) 57–66, https://doi.org/10.1016/j.ygyno.2024.01.032.
[51] Z. Peng, M. Li, H. Li, Q. Gao, PD-1/PD-L1 immune checkpoint blockade in ovarian cancer: dilemmas and opportunities, Drug Discov. Today 28 (8) (2023 Aug), https://doi.org/10.1016/j.drudis.2023.103666 103666.
[52] M.C. Merlano, N. Denaro, D. Galizia, F. Ruatta, M. Occelli, S. Minei, et al., How chemotherapy affects the tumor immune microenvironment: a narrative review, Biomedicines 10 (8) (2022 Jul 28) 1822, https://doi.org/10.3390/biomedicines10081822.
[53] J.W. Woo, E.K. Han, K.J. Suh, S.H. Kim, J.H. Kim, S.Y. Park, Alteration of PD-L1 (SP142) status after neoadjuvant chemotherapy and its clinical significance in triple-negative breast cancer, Breast Cancer Res. Treat. 207 (2) (2024 Sep) 301–311, https://doi.org/10.1007/s10549-024-07359-x (Epub 2024 May 16).
[54] I. Colombo, K. Karakasis, S. Suku, A.M. Oza, Chasing immune checkpoint inhibitors in ovarian Cancer: novel combinations and biomarker discovery, Cancers (Basel) 15 (12) (2023 Jun 16) 3220, https://doi.org/10.3390/cancers15123220.