

Homologous Recombination Deficiency as a Potential Predictor of Complete Cytoreduction in High Grade Ovarian Cancer: A Narrative Review

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ARTICLE INFO

Received:  September 24, 2026

Published:  October 07, 2026

Citation: Minas Mahjoub Mohammedein Elhaj, Aref Zribi, Meriem Makhoulfi, Shariq Aman, Rubeya Ahmed, Laila altahir, Mazin Elhassan, Muhammed Ovais, Malaz Mudather, Maryam Gaith, Hayyan Tila Khan, Muhammed Asad, Rahaf Rafea Ammar, Ana Paula Galerani lopes and Sulaiman Mohamed Saif Alsaadi. Homologous Recombination Deficiency as a Potential Predictor of Complete Cytoreduction in High Grade Ovarian Cancer: A Narrative Review. Biomed J Sci & Tech Res 67(1)-2026. BJSTR. MS.ID.010430.

ABSTRACT

Complete cytoreductive surgery (R0) is the strongest modifiable prognostic factor in high-grade ovarian cancer (HGOC). However, pre-operative designation of patients likely to achieve R0 stays challenging, causing suboptimal selection for primary debulking surgery (PDS) or neoadjuvant chemotherapy (NACT). Homologous recombination deficiency (HRD), present in about 50% of HGOC, has been designated in recent papers as a prognostic biomarker for progression-free survival and a predictive marker for platinum sensitivity and PARP inhibitor response. Whether HRD status also predicts surgical resectability is an emerging, clinically relevant question. This review recapitulates current evidence on cytoreductive surgery outcomes and evaluates tools for predicting complete cytoreduction. We also tried to explore the biological rationale linking HRD to disease distribution and operability, and to discuss HRD's potential role within multimodal pre-operative decision-making strategies.

Abbreviations: HGOC: High-Grade Ovarian Cancer; PDS: Primary Debulking Surgery; NACT: Neoadjuvant Chemotherapy; HRD: Homologous recombination deficiency; PIV: Predictive Index Value; IDS: Interval Debulking Surgery

Introduction

High grade ovarian cancer is usually diagnosed at an advanced stage, mostly when the disease invades the peritoneum, and is the leading cause of gynecologic cancer death worldwide [1]. Even with all the progress that's been made in treatments, like targeted therapies and new maintenance options. The biggest factor is still how much tumor is left after surgery. Studies show that if surgeons can remove all visible diseases (what's called R0), patients have better out-

comes, no matter what their cancer stage or the order of treatments [2]. The decision between PDS and NACT followed by interval debulking surgery (IDS) is critical. Randomized trials [3] have shown that, for some patients, starting with chemotherapy and then having surgery can work just as well as going straight to surgery. But no matter which approach is used, the best outcomes still depend on being able to remove all visible tumors. Trying very aggressive surgery in people who probably won't reach R0 can just add more surgical risks without

really helping them. That's why figuring out ahead of time who's likely to benefit from surgery is such a big challenge when treating high-grade ovarian cancer.

Prognostic Significance of Complete Cytoreduction

Residual disease after cytoreductive surgery is an independent prognostic factor in HGOC. Patients achieving R0 have significantly better survival than those left with minimal (<1 cm) or bulky residual disease. (Chase DM) Importantly, the survival advantage conferred by complete cytoreduction continues across treatment strategies, including both PDS and IDS [4]. The emphasis on surgical outcome rather than surgical timing has driven efforts to improve patient selection for upfront surgery. While surgical expertise and center volume are key determinants of R0 rates, biological factors influencing tumor dissemination and resectability are increasingly recognized as potential contributors [5].

Current Approaches to Predict Surgical Resectability

5.1. Imaging Based Assessment

Contrast-enhanced CT scans are still the go-to tool for staging and planning surgery before treatment begins (Sahdev [6]). They give doctors a clear picture of where the cancer has spread, how much ascites is present, it also allows to evaluate enlarged lymph nodes, and if there are any distant metastases. However, its sensitivity for detecting small-volume peritoneal disease is limited, especially at the mesentery, bowel serosa, diaphragm, and porta hepatis—sites that often determine resectability [6]. MRI, particularly when using diffusion-weighted imaging, can give even clearer pictures of soft tissues and might do a better job spotting peritoneal implants. However, it's not always easy to access, can be expensive, and there aren't guidelines for predicting outcomes based on the results [7]. Because of these challenges, relying on imaging alone often means surgeons either overestimate or underestimate whether they'll be able to remove all the tumor during surgery.

5.2. Diagnostic Laparoscopy and Predictive Scoring Systems

Diagnostic laparoscopy is an important method for assessing surgical resectability in advanced diseases. The Fagotti predictive index value (PIV) assesses disease at key intra-abdominal sites and has demonstrated strong predictive performance for optimal cytoreduction [8]. Laparoscopy allows surgeons to see the extent of peritoneal disease and reduces the rate of non-therapeutic laparotomy. Although laparoscopy has advantages, it is invasive, resource-intensive, and not widely available globally. It also offers limited insight into tumor biology, highlighting the need for complementary non-invasive markers.

Radiomics and Machine Learning

These last years, newer approaches like radiomics and machine learning are exciting because they might help doctors figure out, just from pre-op scans, whether it's possible to remove all the tumor [9].

These methods can pull out detailed, quantitative features from the images, things like how varied the tumor looks or its exact pattern, that might give even better predictions than standard imaging. Still, these approaches aren't quite ready for everyday use yet because there's no standard way to do them, they haven't been widely validated, and different hospitals might use different protocols.

Homologous Recombination Deficiency in High Grade Ovarian Cancer

Homologous recombination deficiency, or HRD, happens when there are mutations either inherited or acquired in genes like BRCA1 or BRCA2, or other genes involved in the homologous recombination repair process. Sometimes, it's not even a gene mutation but an epigenetic change that ends up affecting how well this repair system works. Interestingly, about half of all high-grade ovarian cancers show signs of HRD [10]. HRD is a well-established prognostic biomarker for progression-free survival. It is also a predictive marker for response to platinum chemotherapy and PARP inhibitors [11]. HRD tumors exhibit genomic instability, increased DNA damage, and greater sensitivity to DNA-damaging agents [12]. However, the possible impact of HRD on tumor growth patterns, spread, and surgical resectability is less well defined.

Biological Rationale Linking HRD to Surgical Outcomes

The hypothesis that HRD may influence surgical resectability is biologically plausible. Several mechanisms could explain this association:

1. Patterns of disease dissemination Genomic instability with HRD may influence metastatic behavior. This could result in differences in peritoneal spread, tumor volume, or implant distribution [13].
2. Tumor microenvironment and stromal interaction HRD tumors may have different stromal composition, fibrosis, and invasiveness. These factors can affect surgical complexity and the ability to achieve complete resection [14].
3. Chemosensitivity and treatment response HRD tumors are more sensitive to platinum-based chemotherapy. In patients receiving NACT, this may mean greater tumor regression and a higher likelihood of achieving R0 at interval surgery [15].

These hypotheses suggest HRD may change disease phenotype rather than directly determine resectability. This sustains evaluating HRD within predictive models that merge multiple factors.

Evidence Linking HRD Status and Cytoreductive Outcomes

Few studies have examined the relationship between HRD status and surgical outcomes. Most data are retrospective and vary in patient selection, HRD assays, and surgical endpoints. Some cohorts

suggest HRD patients have more consistent outcomes regardless of residual disease, while HR-proficient (HRP) tumors show worse prognosis when residual disease is present [16]. This reinforces the importance of achieving R0 in HRP disease and suggests HRD status could help stratify surgical risk. Other studies report similar rates of complete gross resection between HRD and HRP tumors [17]. This indicates HRD alone is unlikely to predict resectability. Instead, HRD may add prognostic or predictive value when combined with disease burden and clinical factors.

Impact of Neoadjuvant Chemotherapy on HRD Assessment

An important consideration in evaluating HRD as a predictive biomarker (a biological feature that helps predict treatment response) is the timing of testing. Neoadjuvant chemotherapy has been shown to alter genomic scar signatures (patterns left on DNA by past repair errors) and reduce detectable HRD positivity, particularly in BRCA wild type (without BRCA mutations) tumors [18]. This occurrence may reflect chemotherapy induced clonal selection (survival of certain cell groups) or technical limitations of genomic scar assays (tests that measure DNA changes) in post treatment samples [19]. To evaluate HRD as a predictor of surgical outcome, pre-treatment tissue analysis is essential. Neglecting treatment-induced changes may impact what we observe as associations between HRD status and resectability.

Integrating HRD into Multimodal Predictive Systems

Since surgical resectability is multifactorial, HRD is unlikely to replace current prognostic tools. Its value may come from inclusion in multimodal pre-operative models that include:

- Clinical parameters (performance status, comorbidities)
- Radiologic or radiomic features
- Laparoscopic assessment, where available
- Molecular biomarkers, including HRD and HRR gene status

Bringing all these factors together could really help doctors decide who's a better fit for surgery first and who might do better starting with chemotherapy. This kind of approach is especially helpful for those "in-between" cases, where it's not clear-cut and making the right call is toughest.

Clinical Implications

The increasing availability of gene panel testing has made HRD assessment feasible in routine clinical practice. [20]. Incorporating HRD status into pre operative discussions could potentially:

- Refine risk stratification for surgical planning.
- Inform of multidisciplinary treatment decisions.
- Reduce unnecessary surgical morbidity.
- Support customized treatment pathways.

However, premature use without strict validation may lead to poor decisions. HRD should be seen as an adjunct marker until more evidence emerges.

Future Directions

Prospective studies are needed to clarify HRD's role in predicting surgical outcomes. Key methodological considerations include:

- Standardized definitions of surgical endpoints (R0 vs <1 cm)
- Stratification by treatment sequence (PDS vs IDS)
- Adjustment to disease burden, surgical complexity, and center expertise
- Uniform HRD testing platforms and cutoffs

Emerging technologies, including AI based histopathologic prediction of HRD and liquid biopsy approaches, may further enhance pre operative risk assessment and postoperative monitoring.

Conclusion

Being able to remove all visible tumors still makes the biggest difference in survival for people with high-grade ovarian cancer. While the tools we have for predicting who's a good candidate for complete surgery aren't perfect, looking at homologous recombination deficiency (HRD) could add some helpful insight. HRD seems like a promising and meaningful biomarker that might work well alongside our current ways of making decisions. Even though the research is still early, combining HRD status with other predictive tools could help tailor surgery plans to each patient's biology. Of course, we'll need more studies to confirm this before HRD can become a routine part of predicting surgical outcomes.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2026.67.010430

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