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Factors that influence survival in high-grade serous ovarian cancer: A complex relationship between molecular subtype, disease dissemination, and operability

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HIGHLIGHTS

- Median OS is shortest in patients with upper abdominal/miliary disease and mesenchymal subtype
- Median OS is shortest in patients with RD >1 cm
- RD is the only predictor of OS in multivariable analysis
- Among patients with upper abdominal/miliary disease, there is a survival benefit of achieving RD0, irrespective of tumor biology
- Among patients with upper abdominal/miliary disease, there is a survival benefit of achieving RD0, irrespective of subtype.

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ABSTRACT

Objective. To investigate the relationship between molecular subtype, intraperitoneal (IP) disease dissemination patterns, resectability, and overall survival (OS) in advanced high-grade serous ovarian cancer (HGSOC).

Methods. Patients undergoing primary surgery for stage III-IV HGSOC at Mayo Clinic from 1994 to 2011 were categorized into three IP disease dissemination patterns: upper abdominal or miliary; lower abdominal; and pelvic. Residual disease was defined as 0 (RD0), 0.1–0.5, 0.6–1.0, or >1 cm. Molecular subtypes were derived from Agilent 4x44k tumor mRNA expression profiles and categorized as mesenchymal (MES) or non-mesenchymal (non-MES).

Results. Operative and molecular data was available for 334 patients. Median OS was shorter in patients with MES compared to non-MES subtypes (34.2 vs 44.6 months; $P = 0.009$). Patients with MES subtype were more likely to have upper abdominal/miliary disease compared to non-MES subtype (90% vs. 72%, $P < 0.001$). For patients with upper abdominal/miliary disease, complete resection (RD0) was less common in MES compared to non-MES subtypes (11% vs. 27%, $P = 0.004$). On multivariable analysis, RD was the only factor associated with OS ($P < 0.001$). In patients with upper abdominal/miliary disease, though less commonly achieved, RD0 improved survival irrespective of molecular subtype (median OS of 69.2 and 57.9 months for MES and non-MES subtype).

Conclusions. Our results support a paradigm in which molecular subtype is an important driver of dissemination pattern; this in turn impacts resectability and ultimately survival. Consequently mesenchymal subtype is associated with much lower rates of complete resection, though RD0 remains the most important independent predictor of survival.

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1. Introduction

Molecular classification of high-grade serous ovarian cancer (HGSOC) using tumor mRNA profiling was first described by Tothill et al. [1] and has been independently confirmed by multiple studies, including our own [2, 3]. We subsequently demonstrated that molecular

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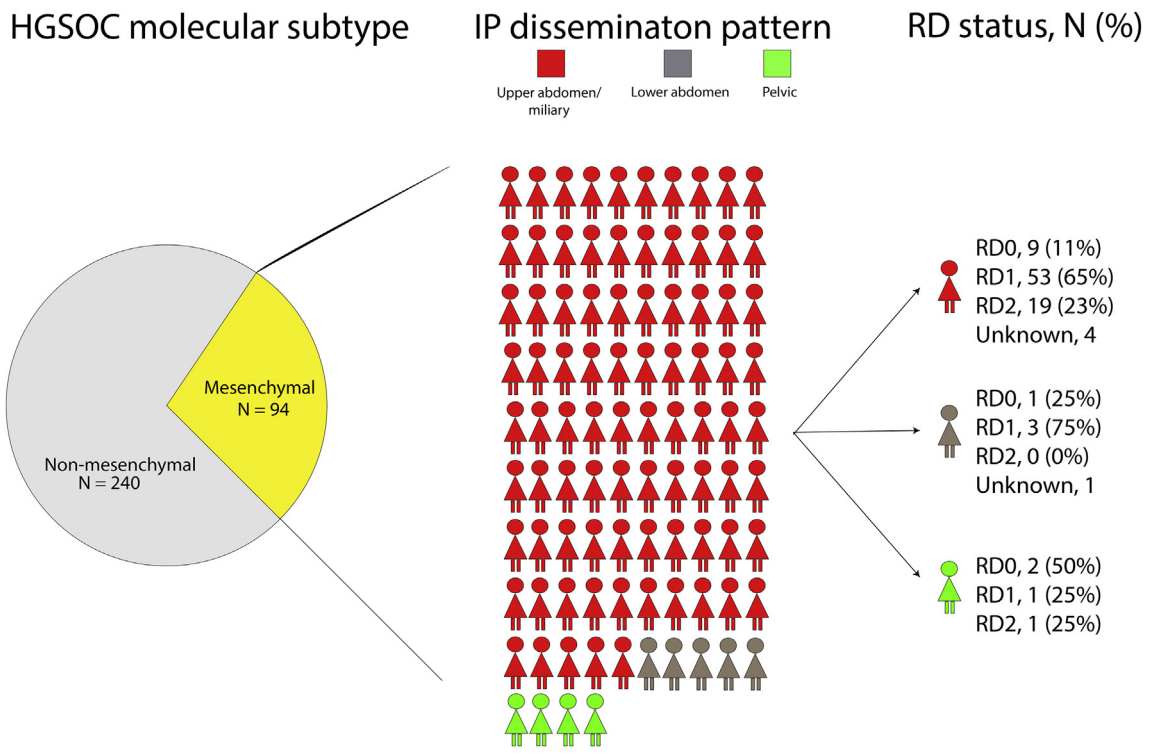

Fig. 1. Breakdown of intraperitoneal (IP) disease dissemination pattern and residual disease (RD) among patients with high-grade serous ovarian cancer (HGSOC) and mesenchymal subtype. RD0, completely resected; RD1, 0.1–1 cm; RD2, >1 cm.

subtypes are associated with intraperitoneal (IP) disease dissemination patterns and surgical outcomes in advanced HGSOC [2–4]. The relationship between molecular subtype, dissemination patterns, and residual disease (RD) is complex. Patients with mesenchymal (MES) subtype are more likely to present with disease in the upper abdomen [4] and, in turn, disease in the upper abdomen is more difficult to resect [4–7]. Irrespective of dissemination pattern, MES tumors are more difficult to completely resect (RD0) than non-MES tumors (Fig. 1). Even among patients with upper abdominal/miliary disease, the rate of complete resection (RD0) is lower in patients with MES compared to non-MES tumors [4]. This appears to reflect, in part, both the driving effect of molecular characteristics on disease spread, and the complex interaction between tumor biology and resectability of disease in advanced HGSOC.

HGSOCs that present with upper abdominal disease or are MES subtype have worse OS [2, 3, 5, 8]. Both of these factors appear to impact residual disease (RD) at primary surgery: RD is a consistently important factor across molecular subtype and disease pattern [3, 9–11]. Collectively this implies that while subsets of MES HGSOC will benefit from aggressive primary debulking surgery (PDS), many will not, owing to limitations of disease spread and resectability. As we approach the era of preoperative molecular tumor testing [12], it will be important to understand which subsets of patients may benefit from alternative approaches.

Few studies are available to examine the independent association between IP disease dissemination pattern, molecular subtype, and RD on OS. Most of the large cohort studies with molecular profiling lack detailed data or primary surgical factors such as initial volume of disease and residual disease [13]. Our primary hypothesis is that all three factors (molecular subtype, IP disease dissemination pattern, and RD) *independently* impact survival in advanced HGSOC. In addition, among patients with upper abdominal or miliary disease and MES subtype, minimizing RD remains an important goal to improve OS when feasible. As improved molecular characterization becomes available and is obtainable preoperatively [12], understanding these complex relationships becomes more important to individualize treatment of patients with advanced HGSOC.

2. Methods

The Mayo Clinic Institutional Review Board approved this single institution, retrospective study. Perioperative patient characteristics and surgical outcome variables were collected from prospectively

Table 1
Patient characteristics among 334 advanced HGSOC patients.

Characteristic	
Age at surgery (years), mean (SD)	63.5 (11.4)
ASA score	
<3	174 (52.1%)
≥3	160 (47.9%)
Preoperative albumin (% of 179)	
≥3.5 g/dL	140 (78.2%)
<3.5 g/dL	39 (21.8%)
FIGO stage	
IIIA/B	27 (8.1%)
IIIC	228 (68.3%)
IV	79 (23.7%)
Residual disease (% of 323)	
0 cm	101 (31.3%)
0.1–0.5 cm	131 (40.6%)
0.6–1.0 cm	36 (11.1%)
>1.0 cm	55 (17.0%)
Surgical complexity (% of 333)	
Low	67 (20.1%)
Intermediate	157 (47.1%)
High	109 (32.7%)
Intraperitoneal dissemination pattern	
Pelvic	29 (8.7%)
Lower abdominal	48 (14.4%)
Upper abdominal/miliary	257 (76.9%)
Molecular subtype	
Proliferative	92 (27.5%)
Differentiated	73 (21.9%)
Mesenchymal	94 (28.1%)
Immunoreactive	75 (22.5%)

Abbreviations: ASA, American Society of Anesthesiologists; FIGO, International Federation of Gynecology and Obstetrics; HGSOC, high-grade serous ovarian cancer.

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