Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Intraperitoneal disease dissemination patterns are associated with residual disease, extent of surgery, and molecular subtypes in advanced ovarian cancer

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HIGHLIGHTS

- Patients with upper abdominal and miliary disease have similar RD0 rates.
- IP disease dissemination patterns are associated with molecular subtypes.
- >90% of patients with MES tumors have either upper abdominal or miliary disease.
- Patients with MES tumor subtype were significantly less likely to achieve RD0.

ARTICLE INFO

Article history:
Received 1 August 2017
Received in revised form 14 September 2017
Accepted 18 September 2017
Available online xxxx

ABSTRACT

Objective. To investigate the association between intraperitoneal (IP) disease dissemination patterns, residual disease (RD), surgical complexity, and molecular subtypes in advanced high-grade serous ovarian cancer (HGSOC).

Methods. 741 patients with operable stage III-IV HGSOC undergoing primary debulking surgery at Mayo Clinic from 1994 to 2011 were categorized into four mutually exclusive IP disease dissemination patterns: upper abdominal (60%), miliary (16%), lower abdominal (15%), and pelvic (9%). Surgical complexity was classified as high, intermediate, or low; RD status was defined as 0, 0.1–0.5, 0.6–1.0, or >1 cm; molecular subtype assignments were derived from expression profiling of tumors from 334 patients.

Results. Patients with either miliary or upper abdominal dissemination patterns were less likely to achieve RD0 compared to patients with pelvic and lower abdominal dissemination patterns (25% vs. 9% and 62%, each $P < 0.001$) despite higher surgical complexity (39% vs. 6% and 20%, each $P < 0.001$). Among the subset with molecular subtype data, patients with mesenchymal subtype of tumors were more likely to have upper abdominal or miliary dissemination patterns compared to patients with differentiated, proliferative, or immunoreactive subtypes (90% vs. 77%, 70%, 69%, respectively, $P < 0.05$).

Conclusions. IP disease dissemination patterns are associated with RD, surgical complexity, and tumor molecular subtypes. Patients with upper abdominal or miliary dissemination patterns are more likely to have mesenchymal HGSOC and in turn achieve lower rates of complete resection. This provides a plausible model for how the biologic behavior of molecular subtypes is manifest in disease and oncologic outcomes.

1. Introduction

High-grade serous ovarian cancer (HGSOC) is the most common histology of epithelial ovarian cancer (EOC) [1]. Most diagnoses are made in patients with advanced stage disease, and treatment is usually aggressive primary debulking surgery (PDS) followed by platinum-based adjuvant chemotherapy [2–4]. Patients without visible residual disease

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https://doi.org/10.1016/j.ygyno.2017.09.021
0090-8258/

(RD0) after PDS have the longest overall survival (OS). If RD0 is not obtained, patients with RD ≤1 cm (i.e. optimal debulking) have a significantly longer OS than patients with RD >1 cm (suboptimal debulking) [5,6]. Therefore, the goal of PDS is to achieve the lowest gross RD when RD0 debulking is not feasible.

Several studies have consistently reported the impact of disease distribution on surgical outcomes in advanced stage disease, irrespective of RD. Disease in the upper abdomen is more difficult to resect and is associated with a higher number of procedures to achieve RD ≤1 cm [7–10]. Patients with upper abdominal disease are more likely to have shorter progression-free survival (PFS) and OS [9]. These findings raise the possibility that the association between survival outcomes and disease spread may be at least partially explained by differences in RD.

HGSOC molecular subtypes have been independently confirmed by multiple studies [11–13]. Our previous studies [13] demonstrated resectability of disease differs by molecular subtype. HGSOC patients with the mesenchymal (mesenchymal) subtype had the lowest RD0 rates and required more complex surgery to achieve RD ≤1 cm compared to patients with other subtypes of tumors. Patients with mesenchymal subtype had the shortest OS even after adjusting for age, stage, and grade [11,13]. Despite a significant association between surgical and clinical outcomes across molecular subtypes, it is unclear as to how the molecular subtype affects the behavior of disease. To date, no studies have investigated the influence of molecular subtypes on patterns of disease dissemination in HGSOC. This is partly due to a lack of detailed operative findings and surgical outcomes in existing databases. This knowledge is important to better understand the manifestation of molecular subtypes on disease phenotype and to discern the factors underlying the prognostic significance of molecular subtypes [11,13]. If molecular subtypes are associated with intraperitoneal (IP) disease dissemination patterns, preoperative molecular profiling may serve as an adjunct to radiologic imaging and intraoperative laparoscopic scoring systems to assist gynecologic oncologists in determining extent of disease and assessing the probability of optimal PDS. Using molecular subtypes to predict dissemination patterns and lack of resectability of disease may have implications in triaging patients to neoadjuvant chemotherapy (NACT) vs. PDS. Given the biologic differences between molecular subtypes [12], we hypothesize that different subtypes of HGSOC may in part contribute to various types of IP disease dissemination patterns, resectability of disease, and in turn oncological outcomes.

Our objective was to investigate the relationship between IP disease dissemination patterns, RD, surgical complexity, and tumor molecular subtypes in advanced HGSOC. First, we hypothesized that more aggressive and diffuse IP disease dissemination patterns are associated with increased RD and surgical complexity. Second, we hypothesized that IP disease dissemination patterns vary by HGSOC molecular subtype. As the survival differences among molecular subtypes may be driven by relative lack of resectability, our two-pronged hypothesis provides a plausible model for how the biologic behavior of molecular subtypes is manifested in disease spread and influences oncologic outcomes.

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 maintained databases of patients undergoing PDS from 1994 to 2011. Inclusion criteria were high-grade serous or mixed high-grade (grade 2–4) serous histology, ovarian, fallopian, or primary peritoneal cancer, and operable stages III-IV. Patients with stage I-II disease, borderline tumors, those who were treated with NACT, and those without research consent were excluded.

We referenced previously described disease distributions [7–10], and the consensus among all gynecologic oncologists in the Division of Gynecologic Surgery at Mayo Clinic was to divide IP disease dissemination patterns in patients with stage III and operative stage IV HGSOC into four categories: pelvic disease, lower abdominal disease, upper abdominal disease, and miliary disease. Since patients with stage I-II disease were excluded, pelvic disease represented gross adnexal disease microscopic extrapelvic disease and/or lymphadenopathy. A gynecologic oncology physician (DT) reviewed the operative reports and assigned each patient to one of four mutually exclusive dissemination patterns as defined in Table 1. Inter-observer variation in the pattern assignment was assessed by having another gynecologic oncology physician (SW) independently review 89 randomly-selected operative reports.

Four RD groups were defined, RD0, RD 0.1–0.5 cm, RD 0.6–1.0 cm, RD >1 cm, based on the largest residual tumor diameter. Surgical complexity was assigned using previously published methods and classified as low, intermediate, or high complexity surgery [14]. Since patients with miliary disease often have disease in the upper abdomen, we combined upper abdominal and miliary disease into one disease spread for the statistical comparisons to account for the potential overlap between the two IP disease dissemination patterns. Gene expression profiles of the primary tumor were measured using Agilent Whole Human Genome 4x44K Expression Arrays. Expression data normalization and molecular subtype assignment were done as described in past publications [11,13]. Patients with molecular profiling data available were assigned to one of four HGSOC molecular subtypes: mesenchymal, immunoreactive, proliferative, or differentiated.

Associations between molecular subtype, IP disease dissemination pattern, RD, and surgical complexity, and were quantified using odds ratios (OR) and corresponding 95% confidence intervals (CI) estimated from univariate and multivariable logistic regression models. All calculated P values were two-sided and P values <0.05 were considered statistically significant. SAS version 9.3 package (SAS Institute, Inc.; Cary, NC) was used for the analysis.

3. Results

During the study period, 741 patients met inclusion criteria; their perioperative characteristics are summarized in Table 2.

We began by investigating the relationship between IP disease dissemination patterns, surgical complexity, and RD (Fig. 1). Intraperitoneal disease dissemination patterns were assigned as follows: pelvic disease (9%), lower abdominal (15%), upper abdominal (60%), and miliary (16%); inter-observer variability was 91% (81/89) with substantial concordance (kappa K = 0.78, 95% CI 0.64–0.92). Not surprisingly, patients with pelvic disease had the highest RD0 rate (91%), followed by patients with lower abdominal disease (62% RD0), those with upper abdominal disease (28% RD0), and those with miliary disease (18% RD0). Patients with either miliary or upper abdominal disease were less likely to achieve RD0 compared to patients with pelvic disease (25% vs. 91%, OR 0.03, 95% CI 0.01–0.08, $P < 0.001$) or lower abdominal disease (25% vs. 62%, OR 0.21, 95% CI 0.14–0.33, $P < 0.001$) (Fig. 2). Further, patients with either miliary or upper abdominal disease were more likely to be suboptimally debulked compared to patients with pelvic disease (17%

Table 1
Intraperitoneal disease dissemination definitions for stage III and operable stage IV disease.

Category	Definition
Pelvic disease	Tumor present in the adnexa with or without bulky pelvic and/or paraaortic lymph nodes
Lower abdominal disease	Tumor present in the abdomen (including omentum) and pelvis but sparing the diaphragm, liver, pancreas, stomach, lesser sac, mesenteric root, spleen, and lesser curvature of the stomach
Upper abdominal disease	Tumor present in or on the diaphragm, liver, pancreas, stomach, lesser sac, mesenteric root, spleen, and lesser curvature of the stomach
Miliary disease	Diffuse abdominal and pelvic tumor studding (<1 cm in greatest dimension) with or without omental caking in the absence of bulky pelvic and abdominal disease

Please cite this article as: D. Torres, et al., Intraperitoneal disease dissemination patterns are associated with residual disease, extent of surgery, and molecular subtypes in ..., Gynecol Oncol (2017), https://doi.org/10.1016/j.ygyno.2017.09.021