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Prognostic value of miliary versus non-miliary sub-staging in advanced ovarian cancer☆,☆☆

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HIGHLIGHTS

- High-stage ovarian cancers commonly present with miliary disease.
- Miliary disease may be underemphasized by size and location based staging systems.
- Accounting for staging, cases with miliary spread are more likely to recur and have shorter survival.

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ABSTRACT

Objective. The presence of miliary disease during initial ovarian cancer debulking may reflect a distinct mode of peritoneal spread independent from size-based tumor staging and may explain variation in response to treatment and survival outcomes. To infer the prevalence, presentation and clinical implications of miliary disease we reviewed existing surgical records.

Methods. Reports were available for 1008 primary debulking surgeries for ovarian, primary peritoneal or fallopian tube cancer between 2001 and 2015 (685 reports from 2005 to 2015). Clinical outcome data was available for 938 patients. We analyzed a high-stage sub-cohort for survival (N = 436).

Results. Most records were evaluable for miliary disease (761/938); for these, the miliary phenotype was highly prevalent (249/761, 32.7%) and often accompanied by ascites (185/249, 74%). While optimal debulking rates were unaffected by miliary disease, total resection (R0) rates were poorer. Liver, stomach, spleen or bladder appeared to be sporadically involved while the omentum, mesentery, bowel, peritoneum and diaphragm were affected simultaneously (Spearman rho > 0.5). Overall, miliary disease was associated with worse progression free survival, overall survival, and time from relapse to death independent of stage. Survival effects were particularly strong for Stage IV disease where median overall survival varied by over 30 months (log-rank p = 0.002).

Conclusions. Miliary disease is an identifiable surgical phenotype reflecting a distinct clinical trajectory that adds prognostic information to standard disease burden-based staging. These findings should permit further retrospective investigation in a wider cohort and prompt the consideration of prospective structured operative reporting standards and treatment strategies.

1. Introduction

Surgical staging represents one of the strongest prognostic biomarkers for advanced ovarian cancer [1]. While there are multiple staging schemas [2,3], all systems share a site and size based classification where greater disease burden and spread into the peritoneal cavity define higher stages.

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Recognizing the heterogeneity in the involvement of specific abdominal organs, Fagotti and colleagues developed a laparoscopic model for predicting achievement of optimal cytoreduction including mesenteric, bowel, stomach, and liver involvement as highly-specific, primary risk factors [4]. Surprisingly, their recent study noted that peritoneal/diaphragmatic carcinomatosis and omental caking were more accurate predictors for sub-optimal cytoreduction than degree of spread and tumor size [5].

These factors may reflect a miliary-type disease defined by the presence of diffuse spread of sub-centimeter nodules or plaques across multiple organ/peritoneal surfaces resembling tuberculosis peritonitis [6]. This pattern of disease spread is distinct from non-miliary disease in which the growth pattern is large bulky disease with few peritoneal implants demonstrating an exophytic growth pattern (Fig. 1).

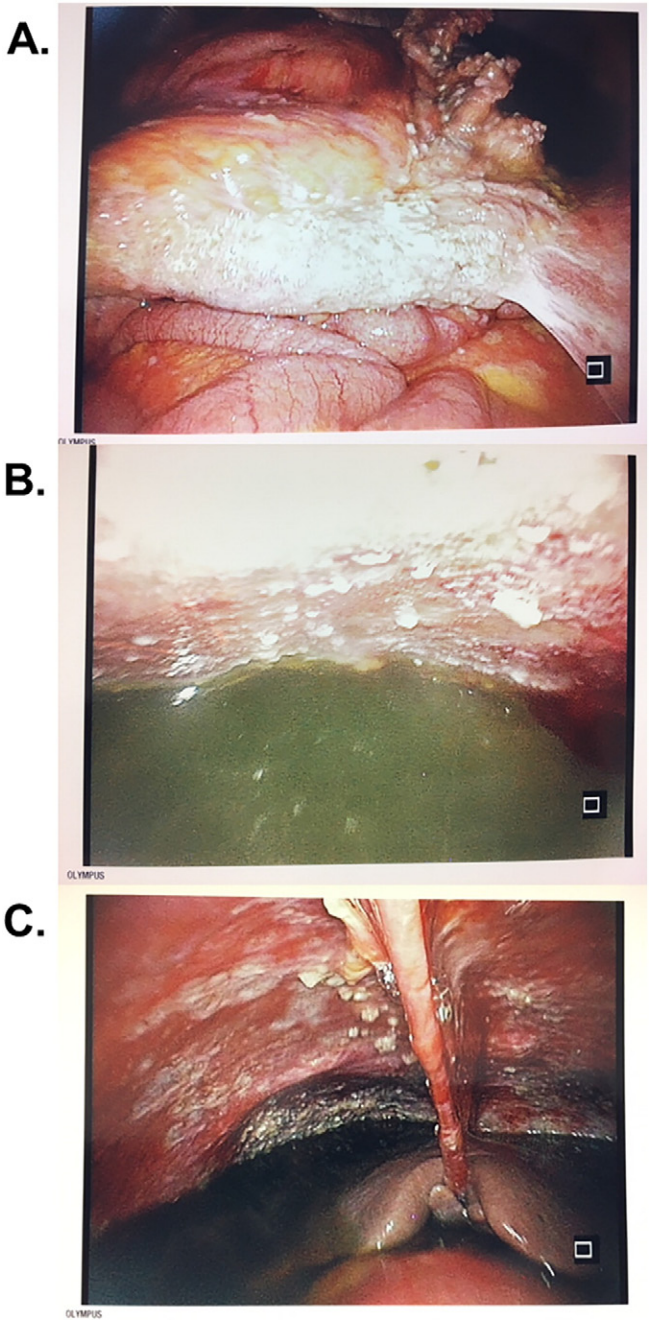

Fig. 1. Representative laparoscopic views showing tumor bulk above retracted mesentery (A), pooled ascites below peritoneal miliary disease (B) and a representative gradient of miliary disease to confluent plaque again with ascites (C).

Recognizing that despite many surgical and critical care advances, significant variations in debulking rates remain [7,8], it is tempting to speculate that miliary disease is both the source of suboptimal cytoreduction [4] and a major predictor of poor clinical outcomes [9]. Deliberate intervention to improve total resection (R0) rates [10] suggests that moving debulking goals from resecting all bulky disease (optimal) to achieving R0 may or may not improve survival [11,12] and the difference in residual disease size roughly fits the miliary component.

It may be an oversimplification to consider simply the *size and location* of intra-abdominal metastases. Auer and colleagues have presented evidence in a medium number of cases that miliary disease is a molecularly distinct subtype of metastasis [11,13]. Because cases can present with miliary-type spread alone or in combination with heavy tumor burden, and the latter are upstaged algorithmically, there might be important to sub-stratify heavy burden tumors with and without miliary disease.

To understand the clinical trajectory associated with miliary versus non-miliary disease, we undertook a retrospective study of surgical records from patients undergoing maximal debulking surgery for ovarian cancer. We reviewed these patients' surgical and adjuvant chemotherapy outcomes as well as time to progression or relapse and time following relapse to death. Our objective was to compile outcomes data to evaluate whether a miliary disease constitutes a distinct clinical phenotype.

2. Materials and methods

2.1. Patient cohort

Following institutional review board (IRB) approval, we identified 1008 records of primary debulking surgeries with matching surgical pathology records for epithelial ovarian cancer conducted by the gynecologic oncology service at Roswell Park Cancer Institute between January 2001 and December 2015. Of these, n = 938 patients were eligible for evaluation (20 were recorded as not cancer, 70 were determined to have a non-qualifying primary site after surgery). No patients received neoadjuvant chemotherapy. Of these, 177 operative reports were excluded because they lacked sufficient detail to determine the extent of disease; we were able to assess the pattern of disease spread in 81% of cases (761/938).

2.2. Surgical record review

We developed a set of variables and a protocol for standardized abstraction: miliary disease was defined by the direct mention of miliary disease, the description of small nodules and/or plaques consistent with the images used in the MITO-13 study [14]. We trained three physician abstracters (DC, AK, LA) using these images and they scored individual surgical records for the presence of miliary disease, organ site involvement, and ascites. Independently, we applied a natural language processing algorithm that identified context relevant mention of nodular disease. The automatic and human scoring agreed in 78% of the cases with 62% specificity and 85% sensitivity (using human scoring as the gold standard). We estimated moderate inter-rater reliability for a random subset of 666 overlapping cases (Kappa = 0.46, $p < 0.001$). The rate of miliary disease scoring was similar across raters ($p = 0.726$) and the rate of scorable records was similar ($p = 0.449$). Miliary disease was consistently defined across year of diagnosis with no change in relative frequency (chi-square test $p = 0.30$). Using the set of Stage I through IIIA cases as a negative control, we note that only 25 were incorrectly scored (2.4% overall) and a handful were subsequently upstaged.

2.3. Clinical correlates

We adhered to the FIGO 2014 staging scheme throughout the study [2]. We summarized patient characteristics in Table S2, which details