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Distribution and case-fatality ratios by cell-type for ovarian carcinomas: A 22-year series of 562 patients with uniform current histological classification

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HIGHLIGHTS

- Among 562 ovarian cancers classified by cell-type, high grade serous carcinoma and its variants accounted for 85% of tumor deaths
- Reproducibility of cell-type designation among gynecologic pathology experts was excellent
- 1.7% of type II tumors (high grade serous carcinomas and variants) were FIGO stage I with comprehensive surgical staging

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ABSTRACT

Background. Ovarian carcinoma is comprised of several different cell types reflecting different clinicopathologic features. Pathologic criteria for distinguishing cell types have evolved, and therefore non-contemporary literature on ovarian cancer may have limited current relevance. A new dualistic model of pathogenesis that distinguishes type I (endometrioid, mucinous, clear cell and low grade serous carcinomas) from type II (high grade serous carcinomas and carcinosarcomas) tumors has become widely accepted.

Methods. A cohort of 562 patients with invasive ovarian carcinoma from a large community hospital practice was reviewed. Cell type, FIGO stage, mortality and interpathologist diagnostic reproducibility were analyzed.

Results. Advanced stage ovarian carcinomas were type II in 86% of cases while low stage tumors were most often type I. Only 1.7% of type II tumors were confirmed to be stage I with comprehensive surgical staging. Type II tumors accounted for 85% of deaths, and clear cell carcinomas, 5% of deaths. Cell type-specific case-fatality ratios for type II tumors were 62% and 79% for high grade serous carcinoma and carcinosarcoma, respectively. For type I tumors, case-fatality ratios were 38%, 36%, 27% and 13% for low grade serous, clear cell, endometrioid and mucinous carcinomas, respectively. The kappa value for diagnostic reproducibility among 3 gynecologic pathologists was 0.83.

Conclusions. Current diagnostic criteria confirm that high grade serous carcinoma and carcinosarcoma account for the vast majority (85%) of ovarian cancer deaths. Cell type designation is highly reproducible among gynecologic pathologists. Type II tumors are rarely stage I (<2%) when comprehensively staged by a gynecologic oncologist.

Introduction

Existing paradigms of ovarian cancer have undergone major shifts in the past decade. Morphological and molecular studies have supported a new dualistic model of pathogenesis [1,2]. Concomitantly, the source of most high grade serous carcinomas, which cause most ovarian cancer deaths, appears more and more likely to be the fallopian tubes. The best evidence for this is from women with germline BRCA mutations. These advances have been supported by numerous morphological and molecular biological studies and studies in animal models [1–8]. It is essential for all types of biological studies of cancer to have a firm

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foundation in histopathology to provide the requisite context. Accordingly, accurate histological classification is essential for any meaningful understanding of ovarian cancer.

Both pathological and clinical studies of ovarian cancer have significant limitations that directly depend on histopathology. Central pathologic review, use of standardized diagnostic criteria and verifying interobserver diagnostic reproducibility are all essential components of any study that is expected to produce reliable, biologically accurate and clinically relevant results. Cutting edge molecular biological techniques cannot contribute new information if the tissue from which the specimen was derived has not been properly classified according to current, standardized, accurate and reproducible criteria.

Diagnostic criteria for the major cell types of ovarian carcinoma have undergone significant shifts over the past two decades [1,9–14]. Serous carcinomas have been more clearly distinguished from endometrioid and clear cell carcinomas with which they have often been confused [13,14]. Serous carcinomas have also been divided into two distinct groups, low grade and high grade, which do not appear to be different grades of the same tumor, but rather, based on morphologic, molecular biologic and clinical outcome data, reflect different cell types [1,2,10,15,16]. Finally, mucinous carcinomas have been refined into intraepithelial carcinoma, invasive and metastatic groups. In the past, metastatic mucinous carcinomas have been frequently misclassified as ovarian primaries [17]. Subclassification of ovarian carcinomas into the different cell types is increasing in importance because it is becoming more evident that these histological types reflect major differences in etiology, pathogenesis and tumor biology and are best viewed as different diseases [18]. Importantly, it is possible that the failure of screening studies to specifically search for the clinical features of the cancer cell types associated with the largest numbers of fatalities has contributed to their failure to reduce ovarian cancer mortality.

A decade ago, we reviewed 220 consecutive ovarian carcinomas from a general community hospital applying the latest criteria and made several important observations which included stage-cell type correlations and the rarity of mucinous carcinomas [9]. Based on a continual re-review as newly refined criteria have been accepted into practice, we now update this series to 562 cases to refine these observations and correlate cell type with ovarian cancer deaths.

Methods

All tumors classified as primary ovarian, fallopian tubal, peritoneal carcinomas and carcinosarcomas (malignant mixed mullerian tumors) accessioned to the Department of Pathology, Washington Hospital Center, during 1991–2013 were re-reviewed for the current study in 2013. This study was approved by the IRB of the Washington Hospital Center (MedStar Research Institute) under expedited review for minimal risk studies. Some of these patients have been previously reported in earlier studies [9,17,19,20]. Microinvasive tumors and carcinomas arising in germ cell or stromal tumors were excluded as were extramural cases reviewed in consultation. FIGO stage was based on surgical findings as documented in the operative note in conjunction with review of all available pathologic specimens. The 1988 FIGO staging was used, as this study was completed before the 2014 staging went into effect. Histological classification was based on current standard criteria [10–12] with particular attention to the following problematic areas:

1. High grade serous carcinoma was distinguished from low grade serous carcinoma using criteria reported by Malpica et al. [15].
2. High grade serous carcinoma is recognized as having focal or occasionally extensive areas with clear cytoplasm. Clear cell carcinoma is not diagnosed unless the classical tubulocystic, tubulopapillary and/or hobnail patterns predominate [10,13,14].
3. So-called transitional cell carcinoma is considered a high grade serous carcinoma with transitional cell features [21-23].
4. Nonspecific poorly differentiated gland-forming carcinomas are classified as high grade serous [1,10,22].
5. Bonafide endometrioid adenocarcinoma displays classical features of eutopic endometrial adenocarcinoma; squamous (morular) metaplasia and origin within endometriosis can be used as supportive features [1,10].
6. Primary mucinous adenocarcinoma of the ovary is quite uncommon and should be diagnosed with caution. The majority of mucinous adenocarcinomas involving the ovaries prove to be metastatic. All available clinical information should be considered in this assessment [17].
7. Undifferentiated carcinoma is characterized by diffuse, solid growth without any glandular or papillary foci and without psammomatous calcification [24].

All sections were initially reviewed and classified by the senior author (JDS). To evaluate reproducibility, a subset of 114 cases was reviewed by two additional gynecological pathology experts (RV, BMR). This subset was created by accruing 60 consecutively accessioned cases and then enriching for the less common (i.e. non-high grade serous) subtypes. For the initial reproducibility review, 1–3 representative sections of the primary ovarian tumor and/or peritoneal tumor were selected by the primary reviewer. Whenever possible, representative sections were preferentially selected to include the invasive component in tumors containing a noninvasive component. Reviewers were instructed to assume an ovarian, peritoneal or tubal primary site, and were asked to classify tumors as high grade serous, low grade serous, clear cell, mucinous, endometrioid, seromucinous, carcinosarcoma, Brenner or mixed. Reviewers were also given the option of requesting more slides, in which case up to 5 representative sections were then provided when available. For this analysis, high grade serous carcinomas were combined with undifferentiated carcinoma and high grade or poorly differentiated adenocarcinoma NOS or unclassified. Mixed subtypes each were considered a unique cell type. Accordingly, endometrioid/mucinous, endometrioid/seromucinous, serous/endometrioid and clear cell/endometrioid were considered 4 separate types. Clear cell carcinoma was classified as type I for this analysis. A fourth gynecological pathology expert (AY) reviewed all cases in which the first 3 reviews were not unanimous.

Reproducibility data were analyzed with the online tool available at http://dfreelon.org/utils/recalfront/recal3/ (accessed May 29, 2014). Clinical follow-up/vital status was obtained from a publicly available database (social security death index, accessed 2013). Survival data were based on the original diagnosis except for those for which there was a consensus diagnosis that differed from the original diagnosis. Case-fatality ratios were calculated as the fraction of deaths based on the total number of cases of each cell type. To evaluate for length of follow-up bias, the cell type distribution was compared between two time periods divided by the median date of diagnosis of the cohort.

Results

Histologic type and stage distribution are shown in Table 1. Mortality by cell type is shown in Table 2. There were 303 deaths after a mean follow-up of 4.8 years (median 5.5 yr, range 0.1–20 yr). A total of 63 of 86 stage I patients (73%) and 27 of 45 stage II patients (60%) were comprehensively staged by a gynecological oncologist.

Type II tumors accounted for 85% of deaths, and type I tumors, 15% ($P < 0.001$). The case-fatality ratios ranged from 13.3% for mucinous carcinoma to 79.4% for carcinosarcoma. The case-fatality ratio for carcinosarcoma was not significantly different from that for high grade serous carcinoma which was 62% (chi square with Yates correction, $P = 0.067$). The cell type-distribution in the two time periods studied was virtually identical (Table 3), and therefore there is no reason to suspect length of follow-up bias. As previously reported in an earlier cohort which included most of these patients, the 5-year