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Histotype classification of ovarian carcinoma: A comparison of approaches

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HIGHLIGHTS

- Older studies can reclassify histotypes to align with the new guidelines.
- Survival patterns are generally similar across histotype assignment approaches.
- The most notable differences in classification were for the less common histotypes.

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ABSTRACT

Objective. Major changes in the classification of ovarian carcinoma histotypes occurred over the last two decades, resulting in the current 2014 World Health Organization (WHO) diagnostic criteria that recognize five principal histotypes: high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous carcinoma. We assessed the impact of these guidelines and use of immunohistochemical (IHC) markers on classification of ovarian carcinomas in existing population-based studies.

Methods. We evaluated histotype classification for 2361 ovarian carcinomas diagnosed between 1999 and 2009 from two case-control studies using three approaches: 1. pre-2014 WHO ("historic") histotype; 2. Standardized review of pathology slides using the 2014 WHO criteria alone; and 3. An integrated IHC assessment along with the 2014 WHO criteria. We used Kappa statistics to assess agreement between approaches, and Kaplan-Meier survival curves and Cox proportional hazards models to evaluate mortality.

Results. Compared to the standardized pathologic review histotype, agreement across approaches was high (kappa = 0.892 for historic, and 0.849 for IHC integrated histotype), but the IHC integrated histotype identified more low-grade serous carcinomas and a subset of endometrioid carcinomas that were assigned as high-grade serous ($n = 25$). No substantial differences in histotype-specific mortality were observed across approaches.

Conclusions. Our findings suggest that histotype assignment is fairly consistent regardless of classification approach, but that progressive improvements in classification accuracy for some less common histotypes are achieved with pathologic review using the 2014 WHO criteria and with IHC integration. We additionally recommend a classification scheme to fit historic data into the 2014 WHO categories to answer histotype-specific research questions.

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1. Introduction

Ovarian carcinoma is heterogeneous, consisting of distinct histotypes with unique epidemiologic characteristics, molecular features, clinical presentations, and prognostic outcomes [1,2]. In the past twenty years, there has been a considerable evolution in how histotypes are defined. Older classification systems, including the 1973 and 2003 World Health Organization (WHO) Classification of Tumors of Female Reproductive Organs [3,4], identified eight principal histotypes: serous, mucinous, endometrioid, clear cell, transitional cell, undifferentiated, unclassified, and mixed ovarian surface epithelial malignant tumors. However, these classification systems showed only moderate reproducibility among pathologists [5–8], highlighting the need for refinement of diagnostic criteria to make them clinically useful. Recent molecular evidence demonstrates that serous carcinomas are two separate histotypes, high- and low-grade [9]. Further, many high-grade endometrioid and undifferentiated carcinomas diagnosed using morphology alone are high-grade serous carcinomas based on protein expression [10], and transitional cell carcinomas are indistinguishable from high-grade serous carcinomas [11]. It has also become clear that true mixed carcinomas are exceedingly rare [12]. In 2014, the new WHO criteria [13] incorporated these histopathological insights, recognizing five principal ovarian carcinoma histotypes: high-grade serous carcinoma (HGSC), low-grade serous carcinoma (LGSC), endometrioid carcinoma (EC), clear cell carcinoma (CCC), and mucinous carcinoma (MC).

A recent study by Kommoss et al. [14] used data from a clinical trial to evaluate the extent to which histotype diagnosis assigned by a gynecologic pathologist in 2002 changed when the same slides were re-reviewed by the same pathologist using the 2014 WHO criteria. Upon re-review, the histotype diagnoses were confirmed for only 54% of patients. However, when two pathologists independently assessed the same diagnostic slides using the 2014 WHO guidelines, an identical histotype was assigned by the pathologists for 98% of patients, which suggests high reproducibility of the 2014 WHO criteria. The low concordance between historical histotype diagnoses and the pathologic re-review using the 2014 criteria prompted Kommoss et al. [14] to conclude: "it is completely unacceptable to use historical histotype diagnosis for research purposes." Given that the majority of epidemiologic studies of ovarian cancer were conducted prior to publication of the WHO 2014 criteria and include histotype diagnoses determined by the earlier WHO classification schemes [15], this assertion by Kommoss et al. [14] has major implications for any histotype-specific analyses or research using existing data sources.

In the present study, we evaluated the above statement by Kommoss et al. [14] using data from two population-based case-control studies of ovarian carcinoma which were conducted prior to the publication of the 2014 WHO guidelines. We compared the agreement of histotypes assigned according to three different classification approaches: 1. pre-2014 WHO ("historic") histotype; 2. Standardized pathology review of H&E slides applying the 2014 WHO criteria alone; and 3. An integrated immunohistochemical (IHC) assessment along with the 2014 WHO criteria. We also evaluated the extent to which histotype-specific survival patterns differed across histotype assignment approaches.

2. Methods

2.1. Study population

This study comprised data from two population-based case-control studies, the Diseases of the Ovary and their Evaluation (DOVE) Study and the North Carolina Ovarian Cancer Study (NCOCS), described in detail elsewhere [16–19]. Briefly, the DOVE study was conducted in 13 counties of Washington State. Cases were identified through the local Surveillance, Epidemiology, and End Results (SEER) cancer registry, the Cancer Surveillance System (CSS), and eligible cases, aged 35–74 years, were diagnosed with primary ovarian carcinoma between 2002 through 2009. The NCOCS was conducted in 48 counties of North Carolina, and cases were identified by the North Carolina Central Cancer Registry (NCCCR) using rapid case ascertainment. Eligible cases were diagnosed with primary ovarian carcinoma during 1999–2008, aged 20–74 years, and residents of the 48-county study area. For both studies, cases had no prior history of ovarian cancer and spoke English. All DOVE and NCOCS participants provided signed, informed consent and each study was approved by the Institutional Review Board at their site (DOVE: Fred Hutchinson Cancer Research Center; NCOCS: Duke University Medical Center).

2.2. Histotype assignment approaches

We assigned tumors into the five principal histotypes of ovarian carcinomas (HGSC, LGSC, MC, EC, CCC) using the following three classification approaches:

2.2.1. Historic histotype

The historic histotype was derived using a two-step process. The first step utilized the histology and tumor grade assigned at the time of diagnosis for each case (diagnoses between 1999 and 2009). For DOVE, community pathologists assigned histology and tumor grade for each case, and this information was recorded according to the International Classification of Diseases for Oncology (ICD-O) [20] codes for morphology and tumor grade by trained CSS staff. For NCOCS, H&E stained slides were centrally reviewed and assigned ICD-O codes and tumor grade by the expert study pathologist (R.B.). Second, a gynecological pathologist (M.K.) grouped the ICD-O codes for all cases into histology categories (serous, endometrioid, mucinous, clear cell) using the schema provided in Supplementary Table 1 [21]. ICD-O codes originally included in the DOVE and NCOCS studies but no longer considered as one of the principal histotypes were categorized as "other epithelial" (e.g., carcinoma, NOS; adenocarcinoma, NOS; mixed tumors). Cases with serous histology and tumor grade 1 were further categorized as LGSC and those with tumor grade ≥ 2 or unknown grade were categorized as HGSC. This reclassification scheme was completed to best match the historic data to the 2014 WHO criteria.

2.2.2. Standardized pathologic review

Expert pathologists (C.B.G. and T.M.N.) re-reviewed representative H&E stained slides of tumors from both the DOVE and NCOCS, and assigned histotype de novo using the 2014 WHO diagnostic criteria [13]. Cases were initially reviewed by T.M.N. and if her review conflicted with the historic histotype or was inconsistent in any way, then the case was referred onto C.B.G. as arbitrator (review based on morphology alone). If the initial review was consistent and in agreement with historic histotype, no additional review was completed by C.B.G.

2.2.3. IHC integrated histotype

Histotype assigned by the standardized pathologic review was compared with histotype predictions from an IHC biomarker panel using tissue microarrays (TMAs), which were available for the DOVE study only. We used an extended IHC biomarker panel (CDKN2A (p16), TFF3, ARID1A, and VIM (Vimentin)) in addition to biomarkers used as the clinical standard (WT1, TP53 (p53), NAPSA (Napsin A), PGR (PR)). Binary IHC expression results, as defined in Köbel et al. [22], were analyzed using the most recent version of the Calculator of Ovarian Subtype Probability, Version 3 (COSPv3) [22–24], which assigned the histotype with the highest probability to each case. When the standardized pathologic review and COSPv3-based histotype assignment did not agree, "arbitration" was performed by a gynecological pathologist (M.K.), who assigned a final, integrated histotype based upon the combination of additional pathologic review, consideration of all previous histotype assignments, and all IHC biomarker expression results reflecting current diagnostic practice.

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