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Histotype classification of ovarian carcinoma: A comparison of approaches

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Author Contributions

Mary Anne Rossing, Jennifer A. Doherty, and Joellen M. Schildkraut designed the study. Mary Anne Rossing, Jennifer A. Doherty, Joellen M. Schildkraut, Kristine Wicklund, and Andrew Berchuck contributed to data collection. Michael Anglesio, Rex Bentley, C. Blake Gilks, Tayyeb M. Nazeran, David G. Huntsman, and Martin Köbel contributed to the pathologic and immunohistochemical assessment of tumors. Kara L. Cushing-Haugen completed all data analysis, and Lauren C. Peres drafted the manuscript. All authors contributed to and approved the final version of the manuscript.

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Conflict of Interest

The authors have no conflicts of interest to disclose.

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 2,361 ovarian carcinomas diagnosed between 1999–2009 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.

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.

Methods

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).

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:

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 1999–2009). 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.

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.

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), NAPS A (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.

Statistical Analysis

Sankey flow diagrams were created using the “sankeyNetwork” function in the “networkD3” R package [25] to depict the changes in histotype assignment across each

approach. The width of the “ribbon” or arrow is directly proportional to the flow quantity, and represents the proportion of cases that move across histotype categories from one histotype assignment approach to the next. We also evaluated the concordance of histotype assignment between the historic histotype and the standardized pathologic review as well as between the standardized pathologic review and IHC integrated histotype. The kappa statistic was used to assess the agreement of the histotype assignment approaches beyond what would be expected by chance. The range of values for the kappa statistic is less than or equal to one, with a value of one indicating perfect agreement between histotype classification approaches and a value of zero indicating no agreement between approaches other than what would be expected by chance

Information on vital status and date of death was obtained from the Social Security Death Index or the NCCCR for NCOCS, and from the CSS for DOVE. The period of follow-up used in the survival analyses was from the time of diagnosis to date of death, loss to follow-up, or the end of the study (December 31, 2015 for DOVE and December 31, 2014 for NCOCS). For each histotype assignment approach, we estimated unadjusted Kaplan Meier survival curves and used Cox proportional hazards regression modelling to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between histotype (HGSC as the referent group) and survival using Stata Version 14.0 (Stata Corporation, College Station, TX). All survival estimates are presented separately by SEER summary stage (localized/regional stage, distant stage) due to the markedly different survival experiences [26]. *A priori* confounders included study site (DOVE, NCOCS), age at diagnosis (5-year age categories), and race (white, black, other) for all models as well as stage (localized, regional) for models examining women with localized and regional stage (combined) disease. The proportional hazards assumption was evaluated using Schoenfeld residuals. We included all confounders in the ‘strata’ command in Stata’s ‘stcox’ statement. We observed a violation of the proportional hazards assumption among women with distant stage disease ($p < 0.05$), which appeared to be due to markedly worse survival for women with MC and CCC in the first two years after diagnosis. Therefore, the survival analyses among women with distant stage disease were stratified into two time intervals: 0–2 years after diagnosis and >2 years after diagnosis.

Results

After excluding 32 women with unknown stage disease and 2 women with non-epithelial histology, a total of 2,361 women with ovarian carcinoma were identified from DOVE and NCOCS (Supplementary Figure 1). Supplementary Table 2 shows participant characteristics by age, race, study, and tumor stage. For historic histotype, 403 were classified as other epithelial, and 1,958 tumors were assigned one of the five principal histotypes: 1,273 HGSC (65%), 66 LGSC (3%), 92 MC (5%), 334 EC (17%), 193 CCC (10%). Standardized pathology review was performed on the 1,909 women with available tissue. Histotype could not be determined for 58 of these women because the tissue block did not contain invasive disease or had insufficient tissue for review. Of the remaining 1,851 women, 62 were assigned a histology other than the five principal histotypes (e.g., carcinoma, NOS; adenocarcinoma, NOS; Mullerian mesodermal mixed tumors), and 1,789 women were assigned to one of the principal histotypes based upon the standardized pathologic review:

1,264 HGSC (71%), 38 LGSC (2%), 69 MC (4%), 250 EC (14%), and 168 CCC (9%). Successful IHC staining was completed for DOVE cases with TMA blocks (N=1,031). Following COSPv3 prediction, 128 cases (12%) were discordant with the histotype assigned by standardized pathologic review, and subsequent arbitration resulted in a change in the COSPv3 prediction for 71 of the 128 cases (56%). Supplementary Table 3 shows the expression of each marker by histotype as designated by the IHC integrated histotype approach. Of the 1,031 women that were assigned a histotype by the IHC integrated approach, 15 women were assigned a histotype other than the five principal histotypes, and 1,016 cases were assigned to one of the five principal histotypes: 700 HGSC (69%), 30 LGSC (3%), 25 MC (2%), 164 EC (16%), and 97 CCC (10%).

Figure 1 provides two Sankey diagrams: Panel A depicts the changes in histotype assignment across the historic histotype and standardized pathologic review approaches for all DOVE and NCOCS cases (N=2,361), and Panel B depicts the changes in histotype assignment across all three approaches, restricted to DOVE cases assigned one of the principal histotypes by standardized pathology review (N=1,106). Histotype assignment was largely retained across historic histotype and standardized pathologic review approaches (Panels A and B), as well as IHC integrated histotype (Panel B). The greatest number of histotype assignment changes were from EC, or from other epithelial histology, to HGSC. However, we also observed changes from HGSC upon standardized review to EC using IHC integrated histotype (Panel B).

To evaluate the pair-wise agreement of the historic histotype with the standardized pathologic review, we restricted the analysis to women who had tumors classified as one of the five principal histotypes for both the historic assignment and the standardized pathologic review, N=1,600 (Table 1). Substantial agreement was observed between the historic histotype and standardized pathologic review ($\kappa=0.892$), with 95% of tumors in each of the historically assigned five principal histotypes remaining in the same category upon standardized pathologic review. The most notable sources of discordance between these two approaches were: the 37 tumors historically classified as EC (37 of 266 EC tumors; 14%) that were reclassified to HGSC upon standardized pathologic review; and the 10 of 38 (26%) LGSC tumors classified by standardized pathologic review which were originally designated as HGSC.

For the pair-wise agreement of the IHC integrated histotype and the standardized pathologic review approach, we restricted the analysis to women who had tumors classified as one of the five principal histotypes from the standardized pathologic review and had successful IHC staining (N=1,016). Substantial agreement was also observed between the standardized pathologic review and the IHC integrated histotype ($\kappa=0.849$), with 93% of the tumors remaining as the same principal histotype. Of the 748 tumors assigned as HGSC by standardized pathologic review, 7% (55 of 748) were reassigned to one of the other four histotypes by the IHC integrated approach. Notably, 25 HGSC tumors based on standardized pathologic review were re-classified as EC in the IHC integrated approach. The agreement between these two approaches was low for LGSC (40%), with more LGSC assigned by IHC integrated histotype than standardized pathologic review (30 vs. 16, respectively). More than half of the tumors classified as LGSC by the IHC integrated histotype approach were

considered HGSC by standardized pathologic review (18 of 30, 60%), while 75% (12 of 16) of tumors classified as LGSC by standardized pathologic review remained as LGSC by IHC integrated histotype.

Given that 403 cases were deemed ‘other epithelial’ by the historic histotype approach, many of which were reassigned as a principal histotype after standardized pathologic review, we assessed the impact of including these cases on the concordance between approaches. Not surprisingly, the kappa changed from 0.892 to 0.717 for the comparison of historic histotype to standardized pathologic review and 0.849 to 0.823 for the comparison of standardized pathologic review to IHC integrated histotype (data not shown).

Kaplan-Meier survival curves and adjusted HRs for women with localized/regional stage disease are shown in Figure 2A-C and Table 2, respectively. The survival of women diagnosed with localized/regional HGSC appeared to be similar across histotype assignment approaches. In comparison to the other histotypes, women with localized/regional EC and CCC had consistently better survival irrespective of histotype assignment approach. Survival estimates and HRs for LGSC and MC tumors should be interpreted with caution due to the low prevalence of these tumors.

Survival patterns by histotype for women with distant stage ovarian carcinoma are also fairly consistent across histotype assignment approaches (Figure 2D-F). Again, the absolute mortality for distant stage HGSC is similar irrespective of approach. In comparison to HGSC, women diagnosed with MC and CCC had a statistically significant greater risk of mortality within the first two years after diagnosis (Table 3). In subsequent years of follow-up, there were no clear differences in the survival patterns of MC and CCC compared to HGSC. For LGSC, survival appeared to be somewhat favorable (though the difference was not statistically significant) relative to HGSC using the historic histotype, while the HGSC and LGSC curves were similar to one another for both the standardized pathology review and integrated IHC approaches.

The analyses evaluating risk of mortality included cases with a histotype diagnosis of one of the five principal histotypes for each approach. As a sensitivity analysis, we repeated the survival analyses restricted to women who had a principal histotype assignment for both the original and standardized pathologic review approaches in order to compare risk of mortality for the same subset of women (N=1,600) (Supplementary Tables 4 and 5). In general, the HRs were similar to, although less precise, than those in Tables 2 and 3, and the overall conclusions remained the same.

Discussion

Our ability to utilize data from historic epidemiologic studies of ovarian carcinoma to answer histotype-specific questions hinges on whether there is a reliable approach to re-classify historic histotype diagnoses to approximate the 2014 WHO criteria, which better reflect the current knowledge of ovarian carcinoma pathogenesis. The comparison of three classification approaches showed overall high agreement for the five principal histotypes, with the largest discrepancies in histotype assignment affecting EC and LGSC. The results

from the present study suggest a simple, practical strategy for re-classification of historic data that can be used to retain the utility of these data for future research: 1. Collapse some outdated histologic categories into contemporary categories (e.g., undifferentiated and transitional cell carcinomas into HGSC); and 2. use tumor grade to re-classify historic serous tumors into HGSC (grades 2–4) and LGSC (grade 1).

LGSC is a new histotype category under the 2014 WHO criteria, which we defined in our study as cases of serous histology with tumor grade 1. However, some grade 2 LGSC may be missed using this strategy. Our data indicate that a new pathologic review using the 2014 criteria, with or without additional integration of IHC, could be utilized to better distinguish grade 2 serous carcinomas as either HGSC or LGSC. Standardized pathologic review identified an additional 10 LGSC cases and IHC integrated histotype identified another 18 LGSC cases that had been classified previously as HGSC. Recent advances in p53 IHC help to assign serous carcinomas with morphological borderline features such as mild to moderate nuclear atypia and slightly increased mitotic activity to either HGSC or LGSC [27]. Though we observed that late stage LGSC had more favorable survival than HGSC in analyses using historic histotype assignment, survival of late stage LGSC and HGSC were similar to one another in analyses of the standardized pathologic and IHC integrated approaches (though there were only a small number of LGSC in these analyses). In our recent analysis of SEER data which included much larger numbers of LGSC (n=708), we also observed that late stage LGSC had favorable survival compared to HGSC [21]. However, in that analysis, we attempted to define histotype according to the 2014 WHO criteria but had no IHC available. A recent Canadian study that included IHC markers for classification also observed favorable survival of late stage LGSC (n=102) compared to HGSC (n=1,246) [28]. Larger comparative studies on rigorously classified LGSC using standardized current histopathologic classification alone or in combination with IHC markers are needed to determine whether late stage LGSC and HGSC have similar outcomes.

EC were also affected by shifts across different histotype assessments. While standardized pathologic review reclassified 37 historic EC to HGSC in the DOVE study, IHC integrated histotype re-classified 25 standardized pathology review HGSC cases to EC (of which, 4 were initially EC by historic histotype). There are suggestions to reclassify historical high-grade EC to HGSC [29]. In the present study, the majority of EC cases reclassified to HGSC by standardized pathology review were originally grade 3 or 4 EC (29 of 37, 78%). Yet, in the full dataset of DOVE and NCOCS, 45% (44 of 98) of all historic high-grade EC cases remained as EC upon standardized pathology review. These data show that historical high-grade EC is contaminated by HGSC but grade alone may not be sufficient to reclassify all high-grade EC as HGSC. Of the 41 historic high-grade EC in DOVE, 16 (39%) were high-grade EC according to the IHC integrated histotype and 20 (49%) were HGSC. In another population-based study incorporating IHC markers, the interobserver agreement for the distinction of high-grade EC from HGSC increased from 69% to 96% [30]. Nevertheless, outcome for EC in our study was fairly consistent across approaches, with the Kaplan-Meier curves showing increased separation of EC from HGSC at late stage.

Minor, but notable, differences were seen between standardized pathologic review and IHC integrated histotype for MC, where 17% of MC at standardized pathologic review were re-classified to EC using the IHC integrated histotype approach, and for CCC, where 12% of IHC integrated histotype designated CCC were HGSC at standardized pathologic review. With respect to outcome, we also observed increased overlap of survival patterns of MC and HGSC at early stage in analyses using the historic histotype versus standardized pathologic review and IHC integrated histotype.

In the present study, 17% of cases were historically designated as other epithelial tumors using ICD-O morphology codes. Many of these histotype designations were once a catch-all category when the principal histotypes could not be definitively determined (e.g., carcinoma, NOS; mixed carcinoma). However, these historic non-principal histotype categories are no longer represented in the 2014 WHO criteria, and are thus more challenging to re-classify using simple assumptions such as using tumor grade to re-classify serous carcinomas. As an example, there were 148 tumors designated as 'Carcinoma, NOS' for historic histotype that had tumor blocks. Of these, the large majority were re-classified as HGSC by standardized pathologic review (113 of 148; 76%), with a continued designation of 'Carcinoma, NOS' for 18 tumors. Likewise, there were 55 tumors historically classified as 'mixed' with tumor tissue. Upon standardized pathology review, 31 of the 55 (56%) were reclassified as HGSC (majority high-grade and distant stage), and 12 of the 55 (22%) were reclassified as EC (all were localized/regional stage and majority low-grade). These historic cases are ideal candidates for a subsequent pathologic review and/or IHC assessment of a few key biomarkers (e.g., WT1, p53). However, given that the majority of these groups are reclassified as HGSC, results of prior or future epidemiologic studies that group these as HGSC are likely to be unchanged.

We observed modest differences in survival outcomes by histotype assignment approach. Most HRs mimic the patterns observed in the Kaplan-Meier curves; however, due to small numbers, some estimates were unstable and there was inadequate power to detect an association for early stage LGSC and distant stage MC for the IHC integrated histotype approach. Some of these patterns have been reported previously [21,31–34], supporting the reclassification; however, the overall modest outcome changes indicate that the historical histotype is a reasonable assessment, provided that serous carcinomas are separated into low- and high-grade using tumor grade. The histotype-specific differences in risk of mortality are likely due to the biology of the disease and therapeutic efficacy. For late stage disease, we observed the highest mortality for women with MC and CCC, especially within the first two years after diagnosis. This is a similar finding to other studies [21,35–37] and may be due to the poor response of MC and CCC to platinum and taxane-based chemotherapy [38,39]. We also observed the best outcomes for EC, which likely reflects the less aggressive nature of this histotype.

This study has a few limitations. DOVE and NCOCS used different procedures to define historic histotype, i.e., review by a single expert pathologist for NCOCS versus community pathologists for DOVE. Additionally, during our standardized pathology review, only one H&E slide per case in NCOCS was reviewed, compared to a few slides for DOVE. To assess whether this had an impact on our findings, we evaluated the concordance of historic

histotype and standardized pathologic review by study. While the kappa statistic for NCOCS was higher than for DOVE (0.938 and 0.854, respectively), both indicate a high level of agreement, suggesting that these between-study differences likely had a minor impact. We did not design our study to assess concordance between pathologists; rather, we sought to evaluate concordance between past histotype assignment and histotype assignment based on the 2014 WHO criteria. Thus, we were unable to assess interrater agreement between pathologists, and no validation was conducted in the IHC integrated approach. Although DOVE included all women diagnosed with ovarian carcinoma regardless of whether they were interviewed, there is a possibility of immortal time bias for NCOCS. Utilizing the date of interview as the date of entry for follow-up time (left truncation) resulted in similar HRs and the conclusions remained the same. There is also a potential for selection bias, given that subjects were excluded from different portions of the analyses due to unavailable tissue, assay failures, etc. [40] However, the characteristics of the study participants across each analytic subset were fairly similar, suggesting minimal bias. Our study is also limited by the inability to define histotype using the IHC integrated histotype approach for NCOCS cases due to the lack of TMAs, and we were unable to separately assess localized and regional disease owing to small numbers of these tumors. Lastly, it is possible that limited availability of treatment data led to residual confounding in the multivariable models assessing risk of mortality.

Overall, our data suggest that ovarian carcinoma histotype is generally concordant, with similar mortality patterns, across the three histotype assignment approaches that we assessed. Contrary to Kommoss, et al. [14], we suggest that historic histotype data can be used, provided some outdated categories are collapsed into contemporary categories using a few histology/grade assumptions. Additional studies, specifically those with historic histotype data, are needed to further corroborate the findings of the present study. IHC assessment as a supplement to pathologic review may enhance histotype classification overall, and for cases with a historic histotype designation that is no longer represented in the 2014 criteria. In the current study, such an assessment identified substantially more non-HGSC cases, possibly suggesting that the findings of studies on LGSC, EC, MC, and, CCC might be made more representative if pathologic review is supplemented by IHC testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

Figure 1.

Sankey diagrams of histotype assignment across the different classification approaches.

Panel A: Comparison of histotype assignment for Historic Histotype (Column 1) and Standardized Pathologic Review (Column 2) for all DOVE and NCOCS cases (N=2,361).

‘Other Histology’ refers to tumors that were designated as an invasive epithelial histology other than the five principal histotypes (e.g., carcinoma NOS, adenocarcinoma NOS, mixed carcinoma). ‘Excluded After Review’ refers to tumors that were reviewed by expert pathologists at UBC but excluded due to various reasons, including insufficient tissue for histotyping, tissue in block received was not ovarian primary, etc., and ‘Unavailable Tissue’ refers to tumors that could not be obtained and were unable to be reviewed by the second approach, standardized pathologic review.

Panel B: Because NCOCS cases were not evaluated for IHC Integrated Histotype, the comparison of histotype assignment for Historic Histotype (Column 1), Standardized Pathologic Review (Column 2), and IHC Integrated Histotype (Column 3) was restricted to DOVE cases assigned one of the five principal histotypes by Standardized Pathologic Review (N=1,106). ‘Insufficient Tissue/Assay Failure’ refers to tumors that either did not have enough tissue for IHC staining or had an IHC assay failure. HGSC: high-grade serous carcinoma; LGSC: low-grade serous carcinoma; EC: endometrioid carcinoma; MC: mucinous carcinoma; CCC: clear cell carcinoma; DOVE: Diseases of the Ovary and their Evaluation; NCOCS: North Carolina Ovarian Cancer Study; NOS: not otherwise specified; IHC: immunohistochemistry.

Figure 2.

Kaplan-Meier survival curves for the association between histotype and ovarian carcinoma survival by stage and histotype assignment approach. (A-C) Localized and regional stage disease. (A) Historic histotype. (B) Standardized pathologic review approach. (C) IHC integrated histotype. (D-F) Distant stage disease. (D) Historic histotype. (E) Standardized pathologic review approach. (F) IHC integrated histotype. HGSC: high-grade serous carcinoma; LGSC: low-grade serous carcinoma; EC: endometrioid carcinoma; MC: mucinous carcinoma; CCC: clear cell carcinoma; IHC: immunohistochemistry.

Table 1.

Pair-wise agreement of historic histotype and IHC integrated histotype to the standardized pathologic review

	Standardized Pathologic Review						
	HGSC	LGSC	MC	EC	CCC	Total	Kappa
Historic Histotype							
HGSC	1056	10	1	5	8	1080	98
LGSC	5	25	0	2	1	33	76
MC	1	1	58	1	0	61	95
EC	37	1	3	223	2	266	84
CCC	7	1	0	0	152	160	95
Total	1106	38	62	231	163	1600	
Concordance (%)	95	66	94	97	93		95
IHC Integrated Histotype							
HGSC	693	2	0	4	1	700	99
LGSC	18	12	0	0	0	30	40
MC	0	0	25	0	0	25	100
EC	25	1	5	131	2	164	80
CCC	12	1	0	0	84	97	87
Total	748	16	30	135	87	1016	
Concordance (%)	93	75	83	97	97		93

HGSC: high-grade serous carcinoma; LGSC: low-grade serous carcinoma; MC: mucinous carcinoma; EC: endometrioid carcinoma; CCC: clear cell carcinoma; IHC: immunohistochemistry.

Bold typeface indicates cases with agreement.

Estimated hazard ratios and 95% confidence intervals for the association between histotype and ovarian carcinoma survival among localized and regional stage disease for three histotype classification approaches

Table 2.

Histotype	Total		Deceased		HR (95% CI) ^a
	n	%	n	%	
Historic Histotype (N=663)					
HGSC	193	29.1	58	38.9	1.00 (Referent)
LGSC	13	2.0	7	4.7	1.41 (0.57–3.44)
MC	75	11.3	12	8.1	0.61 (0.31–1.20)
EC	237	35.8	41	27.5	0.57 (0.36–0.89)
CCC	145	21.9	31	20.8	0.68 (0.42–1.10)
Standardized Pathologic Review (N=575)					
HGSC	207	36.0	71	49.0	1.00 (Referent)
LGSC	6	1.0	1	0.7	0.86 (0.11–6.66)
MC	57	9.9	14	9.7	0.83 (0.44–1.56)
EC	184	32.0	33	22.8	0.60 (0.38–0.95)
CCC	121	21.0	26	17.9	0.78 (0.47–1.28)
IHC Integrated Histotype (N=333)					
HGSC	109	32.7	38	45.2	1.00 (Referent)
LGSC	1	0.3	1	1.2	N/A
MC	20	6.0	9	10.7	1.62 (0.70–3.75)
EC	139	41.7	27	32.1	0.66 (0.38–1.16)
CCC	64	19.2	9	10.7	0.63 (0.28–1.42)

HR: hazard ratio; CI: confidence interval; HGSC: high-grade serous carcinoma; LGSC: low-grade serous carcinoma; MC: mucinous carcinoma; EC: endometrioid carcinoma; CCC: clear cell carcinoma; IHC: immunohistochemistry.

^aModels are adjusted for age, race, study and stage.

Table 3.

Estimated hazard ratios and 95% confidence intervals for the association between histotype and ovarian carcinoma survival among distant stage disease for three histotype classification approaches, stratified by time since diagnosis

Histotype	0–2 years after diagnosis						>2 years after diagnosis					
	Total			Deceased			Deceased			Deceased		
	n	%	n	%	HR (95% CI) ^a	n	%	HR (95% CI) ^a	n	%	HR (95% CI) ^a	
Historic Histotype (N=1295)												
HGSC	1,080	83.4	282	82.5	1.00 (Referent)	613	85.9	1.00 (Referent)			1.00 (Referent)	
LGSC	53	4.1	6	1.8	0.48 (0.21–1.11)	36	5.0	0.95 (0.66–1.36)			0.95 (0.66–1.36)	
MC	17	1.3	12	3.5	4.92 (2.66–9.10)	4	0.6	1.12 (0.39–3.24)			1.12 (0.39–3.24)	
EC	97	7.5	14	4.1	0.64 (0.37–1.10)	47	6.6	0.60 (0.44–0.82)			0.60 (0.44–0.82)	
CCC	48	3.7	28	8.2	4.05 (2.70–6.06)	14	2.0	0.84 (0.49–1.45)			0.84 (0.49–1.45)	
Standardized Pathologic Review (N=1214)												
HGSC	1,057	87.1	256	82.6	1.00 (Referent)	632	89.6	1.00 (Referent)			1.00 (Referent)	
LGSC	32	2.6	6	1.9	0.85 (0.37–1.94)	25	3.5	1.30 (0.86–1.97)			1.30 (0.86–1.97)	
MC	12	1.0	9	2.9	5.03 (2.52–10.04)	2	0.3	0.80 (0.18–3.65)			0.80 (0.18–3.65)	
EC	66	5.4	11	3.6	0.79 (0.43–1.47)	33	4.7	0.62 (0.43–0.90)			0.62 (0.43–0.90)	
CCC	47	3.9	28	9.0	4.46 (2.98–6.68)	13	1.8	0.78 (0.45–1.37)			0.78 (0.45–1.37)	
IHC Integrated Histotype (N=683)												
HGSC	591	86.5	169	79.7	1.00 (Referent)	332	90.2	1.00 (Referent)			1.00 (Referent)	
LGSC	29	4.3	8	3.8	1.32 (0.64–2.72)	20	5.4	1.45 (0.90–2.34)			1.45 (0.90–2.34)	
MC	5	0.7	4	1.9	3.78 (1.37–10.46)	1	0.3	N/A			N/A	
EC	25	3.7	6	2.8	0.97 (0.43–2.21)	8	2.2	0.33 (0.16–0.68)			0.33 (0.16–0.68)	
CCC	33	4.8	25	11.8	5.36 (3.47–8.28)	7	1.9	1.63 (0.76–3.49)			1.63 (0.76–3.49)	

HR: hazard ratio; CI: confidence interval; HGSC: high-grade serous carcinoma; LGSC: low-grade serous carcinoma; MC: mucinous carcinoma; EC: endometrioid carcinoma; CCC: clear cell carcinoma; IHC: immunohistochemistry.

^aModels are adjusted for age, race, and study.