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Would Artificial Intelligence Methods Improve Early Diagnosis and Progress of Ovarian Cancer?

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ABSTRACT

Ovarian cancer is one of the most common cancers in women, characterized by advanced-stage diagnosis, poor prognosis, and high mortality rate. The predominant screening methods rely on ultrasound images and carbohydrate antigen 125, which has limitations such as a lack of specificity. More insight is needed to understand the etiology of ovarian cancer. Machine learning offers a solution to some of these issues and can be applied in diagnosing and prognosing ovarian cancer. This review article collects information on how machine learning models can be trained on a variety of data types, such as biomarkers, clinical factors, and medical imaging, and how these models can be used to classify benign and malignant tumors, predict survival rates, and determine response to drugs and treatment. Overall, we found that machine learning methods have shown great potential in applications in ovarian cancer, but more research needs to be conducted to further advance machine learning technologies in clinical practices.

Introduction

Ovarian Cancer

Ovarian cancer is one of the most common cancers among all women. This cancer is marked by poor prognosis, late diagnosis, and high mortality rates. Roughly 80% of women are diagnosed at an advanced stage of ovarian cancer, [1] where the survival rate is at its lowest. Ovarian cancer is the fifth highest cause of cancer-related deaths in women and the highest for all gynecological cancers, [2] with the American Cancer Society estimating 12,740 deaths will be caused by ovarian cancer by the end of 2024. [3] Late-stage diagnoses are caused in part by a lack of routine screening. The United States Preventive Services Task Force (USPSTF) recommends against screening for ovarian cancer in asymptomatic women due to the associated risks and low reward with current screening methods of transvaginal ultrasound and testing for the serum tumor marker carbohydrate antigen 125 (CA-125). [4] Some of the associated challenges with current testing methods are an incomplete understanding of the etiology of the cancer, high false-positive rates, and lack of evidence of a lowered mortality rate after screening at the population level. [5] With the prevalence of late-stage diagnosis and imperfect screening approach, it would be of great benefit to modify screening methods.

Ovarian cancer typically refers to a tumor present in the ovary; however, these types of cancers consist of several distinct histological subtypes. [6] The fifth edition of the WHO Classification of Female Genital Tumours lists six different subtypes: high-grade serous, low-grade serous, mucinous, endometrioid, clear cell, and Brenner. [7] The low-grade serous, mucinous, endometrioid, and clear cells fall under the Type I category, characterized by slow growth and well-defined precursor lesions. However, high-grade serous ovarian cancer is a Type II carcinoma, where Type 2 is characterized by aggressive growth and lesions that develop from tubal or ovarian surface epithelium. [8] The lack of specificity in ovarian cancer symptoms hampers early-stage detection. [9]

Furthermore, the progression of ovarian cancer is not fully understood due to challenges like the lack of early-stage data, [10] heterogeneity of cancer subtypes, and weak prognostic factors. The standard for ovarian cancer treatment is an aggressive cytoreductive surgery combined with platinum-based chemotherapy. This treatment is challenged by platinum-resistant diseases, high rates of relapse, and chemotherapy side effects. [11] With these downsides, the rate of survival remains low and recurrence is common. [12] A possible solution is the development of targeted treatments based on precision medicine.

Machine Learning

Machine learning is trained on a set of inputs, also called features, in big data and outputs to produce a model. The model can identify patterns and relationships in the original data and predict an output with completely new inputs. [13] In the medical setting, machine learning differs from traditional methods that rely on a set of rules to produce a prediction. Some common machine learning models, that will be discussed in this review, include decision tree (DT), logistic regression (LR), random forest (RF), GA-XGBoost (XGB), gradient boosting machine (GBM), support vector machine (SVM), neural network (NN), convolutional neural network (CNN), and k-nearest neighbors (KNN).

The DT utilizes a tree structure with a root node and decision nodes that determine the terminal node based on the inputs. LR and RF are both regression techniques with RF combining the strengths of DT with the ability to model numeric data. XGB and GBM also build off of DT, combining several "weaker" DT's to create a "stronger" model. SVM, NN, CNN are all black box processes due to the obfuscated process that takes an input to an output. NN and CNN mimic the structure of animal brains with several layers of nodes mimicking neurons. The KNN learning model measures the euclidean distance between an input and known points. It can then group different points based on its neighbors. [14]

The value of machine learning in analyzing complex relationships within large datasets has led to its growth in medicine and research. Some successful applications of machine learning include identifying high-risk patients in modern intensive care units, [15] identifying various risks from imaging data in vascular surgery, [16] and predicting drug synergy in cancer treatments. [17]

Since ovarian cancer is a highly lethal disease in women and there is still a lack of effective early diagnosis tools in clinical practice, a study question comes up: can we employ novel artificial intelligence, such as prediction models based on machine learning algorithms, to forecast the occurrence of ovarian cancer at earlier stages and improve its prognosis and patient survival? With this question in mind, my review article aims to discuss the role of machine learning in identifying biomarkers to help guide the diagnosis and treatment of ovarian cancer.

Biomarkers, Imaging Data, and Clinical Factors

Current biomarkers for ovarian cancer diagnosis, prognosis and therapy include CA-125, Osteopontin (OPN, a matricellular protein that mediates diverse biological functions), Kallikreins (KLKs, a subgroup of serine proteases, enzymes capable of cleaving peptide bonds in proteins), Bikunin (a plasma proteinase inhibitor), Human Epididymis Protein 4 (HE4), Vascular Endothelial Growth Factor (VEGF). [18]

CA-125 has been the most crucial biomarker in screening, detecting, and managing ovarian cancer for the last four decades. The antigen is found in the patient's serum, and its levels are elevated in 50% of early-stage tumors and 92% of advanced-stage tumors. [19] However, the low rate of altered expression in early-stage tumors poses a problem for detecting ovarian cancer early. Furthermore, the low incidence of cancer leads to a considerable number of false positives when screening average-risk women. [20]

Research for other useful biomarkers has been conducted to address these limitations in CA-125. OPN used with CA-125 helped improve sensitivity in ovarian cancer detection; however, it also decreased specificity.

[21] Human kallikrein 6 concentration in a patient's serum has been promising in ovarian cancer diagnosis and prognosis. [22] Bikunin levels in patient plasma is associated with the efficacy of debulking surgery and survival time. [23] HE4 has increased expression in several cancers but still has high specificity for ovarian cancer diagnosis. [24] VEGF, due to its role in angiogenesis (formation of new blood vessels), could predict survival and disease progression. [25]

The use of medical imaging techniques–ultrasound (US), magnetic resonance imaging (MRI), and computed tomography (CT)–can help aid in diagnosing and prognosing ovarian cancer. The use of a transvaginal ultrasound combined with Doppler techniques is often a first-line tool used to diagnose ovarian cancer. [26] Even with US paired with other clinical factors and biomarkers (age, CA-125 levels), roughly 5-20% of adnexal masses will remain difficult to classify. [27] The European Society of Urogenital Radiology guidelines suggest that MRI can be used as a complementary tool in these indeterminate cases. [28] CT remains an important determinant for ovarian cancer, for example, in predicting successful cytoreduction and staging ovarian cancer. [29-30] Additionally, radiomics can be paired with these medical imaging techniques to extract quantitative features from an image. Radiomics uses features such as pixel intensity, pixel arrangement, pixel color, and texture[31]. These features can then be used as inputs for a machine-learning model.

A number of clinical factors are also associated with developing ovarian cancer. These risk factors include: older age, [32] postponed menopausal status, [33] family history, [34] fewer pregnancies, [35] chronic inflammation, and non-steroidal anti-inflammatory drug use, [36] being racial or ethnic minority, [37] use of estrogen-only hormone replacement therapy [38]. The protective factors include undergoing hysterectomy and the use of oral contraceptives [39-40]. Other factors are more complicated, such as smoking, which can increase the risk in developing mucinous ovarian cancer, [41-42] while reducing the risk of endometrioid and clear-cell ovarian cancers [42]. Certain genes or genetic mutations such as the BRCA1 and BRCA2 are also associated with increased risks of ovarian cancer [43].

Diagnosis

The most widespread tools in risk assessment of ovarian tumors are measuring CA-125 and HE4 levels, risk of malignancy algorithm (ROMA) proposed in 2009 by Moore et al., [44] and a risk of malignancy index (RMI) proposed in 1990 by Jacobs et al. [45] A review conducted by Dochez et al. found an area under the receiver operating characteristic curve (AUC) for RMI (0.86) and a specificity for ROMA (84%), leaving both algorithms with some room for improvement as diagnostic tools. [46]

In a study conducted by Lu et al., [47] a simple DT model and a LR model were both developed from eight features. The models identified HE4 and carcinoembryonic antigen (CEA) as valuable biomarkers in classifying ovarian tumors. The tree also pointed to the value of CEA levels when the level of HE4 in patients was low. Both the tree and LR model achieved a statistically insignificant AUC when compared with ROMA. In a study conducted by Hamidi et al., [48] LR, RF, ANN, and XGB models identified ten potential microRNA in patient classification into cancerous and non-cancerous groups. Kawakami et al. used preoperative blood biomarkers with GBM and RF models to classify tumors as cancerous as well as classify the histological subtype and stage of malignancies. [49] In a study conducted by Ahamad, RF and GBM models showed high accuracy in detecting early-stage ovarian cancer. [50] The most important biomarkers found in this study were CA125, carbohydrate antigen 19-9, carcinoembryonic antigen, and HE4.

Machine learning can also be applied in analyzing medical imaging data from US, MRI, and CT. [51] Machine learning has found success in diagnosing ovarian cancer from MRI data. [52] In a study conducted by Saida et al., a CNN performed similarly in identifying malignant and benign tumors compared to human readers. [53] Notably, the CNN had a significantly better AUC (0.88 versus 0.81, 0.74, and 0.82 among three radiologists) when interpreting diffusion-weighted images. However, the CNN technique makes it unclear which features were important in diagnosing ovarian cancer. Li et al. developed a machine learning model based on MRI

imaging to differentiate borderline and malignant epithelial ovarian cancers. [54] Chen et al. developed a CT-based radiomics model to classify benign, borderline, and malignant ovarian tumors. [55] Distinguishing these masses is critical for therapeutic outcomes and prolonging survival. The RF model outperformed the LR, NN, KNN, and DT models.

A multi-modal approach, using both genetic data and imaging data, was described by Ghoniem et al. [56] A long-short-term-memory model (LSTM) was used to process genetic data, and a CNN was used on pathology images. The resulting model combining the LSTM and CNN displayed high accuracy in classifying ovarian cancer. However, this study failed to conclude which features were important in the model's diagnosis.

Prognosis and Treatment

Ovarian cancer is associated with poor prognosis. The cancer primarily develops in older women. In the United States, between 1975 and 2017, the incidence rate in women older than 65 was 49.67 per 100,000, whereas the incidence rate in women younger than 65 was 8.76 per 100,000. This is pertinent as the five-year relative survival, in 2016, of women older than 65 was just 33.3%, while that of women younger than 65 was 61.0%. [1] Ten-year survival rates are even worse, with less than 20% of women with advanced-stage ovarian cancer living for ten years. [57]

Due to ovarian cancer's poor prognosis and high mortality, improvements in treating advanced-stage ovarian cancers would have great merit. Personalized medicine in treating cancer has grown with targeted therapies based on the patient's genetics, tumor environment, and lifestyle. [58] In ovarian cancer, the heterogeneity of patients results in vastly different responses to specific immunotherapies. [59] Therefore, it is important to analyze different biomarkers and identify those most likely to benefit from various treatments.

Huan et al. developed a machine learning-derived prognostic signature (MLDPS) from mRNA expression data. [60] The researchers identified 11 candidate prognostic genes in ovarian cancer using a univariate Cox analysis. For example, the chimera of EpCAM aptamer and FAP siRNA are involved in slowing the development of ovarian cancer. [61] The MLDPS scored each patient and found that patients with a high score demonstrated lower survival rates. The group also found that patients with low MLDPS were more responsive to nineteen different drugs. The MLDPS score was correlated to the half maximal inhibitory concentration (IC50), or the amount of drug needed to inhibit half of a biological process. A similar macrophage-related signature (MRS) was developed by Zhao and Pei. [62] A univariate Cox analysis was used to identify thirty-seven potential prognostic genes, and MRS included twenty-seven of these macrophage-related genes MRS had relatively strong predictive values in 1-, 3-, and 5-year overall survival rates. Their score could similarly predict response to treatment options (immunotherapy, chemotherapy, hormonal therapy, target therapy) and IC50 levels for various drugs.

Wang et al. developed a deep-learning method to extract prognostic biomarkers for HGSOC from CT images. [63] The convolutional layers of the deep-learning model each contained different filters that extracted certain tumor characteristics. While the first and second layers extracted simpler characteristics, such as the intensities of the tumor and tumor edges, the deeper layers became more abstract and difficult to interpret. The model demonstrated strong performance when predicting 3-year recurrence, achieving an AUC of 0.833. Lei et al. developed two deep-learning models to predict platinum sensitivity from MRI. [64] The model that used images of the whole abdomen predicted platinum sensitivity with high sensitivity and specificity.

Wei et al. developed an ensemble model to predict peritoneal metastasis in ovarian cancer patients using MRI images and clinical factors. [65] The ensemble model combined three different machine-learning models: a deep-learning model trained on the MRI images, a radiomics model using a SVM with LASSO, and a clinical model using LR based on age, menopausal status, abdominal symptoms, CA125, carbohydrate antigen 199, CEA, and HE4. The final ensemble model had an AUC of 0.857 and outperformed senior radiologists. The study also found that using artificial intelligence helped radiologists diagnose peritoneal metastasis.

Discussion

Principal Findings

Machine learning has demonstrated strong potential in ovarian cancer diagnosis and prognosis. Machine learning models may help amend the issue of late-stage diagnoses and static treatment for highly complex and heterogeneous cancer. Not only can machine learning models accurately diagnose cancers and predict the progression of the disease, but they can also assist in an expert's diagnosis. These models can also point towards potential new biomarkers and reinforce the value of other factors in ovarian cancer.

Limitation of Machine Learning Models

Machine-learning models are susceptible to biases such as overfitting. For instance, Hamidi et al achieved 100% AUC on several models, a sign of clear overfitting to the data. Furthermore, black-box models such as SVM and CNN have limited interpretability. Another limitation is the quantity of data needed to train an accurate model. Ovarian cancer has relatively low incidence rates, limiting the amount of data that can be collected. Most of the studies discussed were done retrospectively, and prospective validation is needed to confirm their results.

Conclusion

Ovarian cancer poses significant challenges in terms of late-stage diagnosis, high mortality rates, and limited effective screening methods. The disease's complexity, diverse histological subtypes, and lack of clear prognostic factors further complicate early detection and treatment. Common screening methods–transvaginal ultrasound and CA-125 testing–have major limitations, leading to late-stage diagnoses.

Machine learning has demonstrated strong potential with its ability to analyze complex relationships within large datasets.

The prognosis and treatment of ovarian cancer, particularly in advanced stages, remain challenging. Machine learning-driven prognostic signatures, derived from mRNA expression data and deep learning models analyzing CT or MRI images, show promise in predicting survival rates and treatment responses. Personalized medicine approaches, guided by machine learning, aim to identify biomarkers that can guide targeted therapies based on individual patient characteristics.

Overall, the integration of machine learning in ovarian cancer research holds significant potential to revolutionize early detection, diagnosis, prognosis, and treatment strategies. As advancements in machine learning continue, there is optimism that these technologies will contribute to
improved outcomes for individuals affected by ovarian cancer.

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