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INVITED COMMENTARY

Predicting cancer outcome: Artificial Intelligence vs Pathologists

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Determining cancer prognosis in patients is crucial to controlling the suffering and death due to cancer. In general, the diagnosis of cancer is based on the histology. Histology of cancer is determined by the tissue obtained from patients via several sampling approaches, including excision or biopsy, fine-needle aspiration, and cytologic smears. As the pathologic diagnosis of cancer is an essential initial step for the determination of the line of therapy, pathologists face a great responsibility in the diagnosis of cancer. The pathologists evaluate histology for characteristics, including nuclear atypia, mitotic activity, cellular density, and tissue architecture, incorporating cytologic details and higher-order patterns to classify and grade lesions. Therefore, the experience of a pathologist is necessary for accurate diagnosis. However, human assessments of histology are problematic, because they are highly subjective. Histological grading and staging based on the size of primary tumor, its extent of spread to regional lymph nodes, and the presence or absence of metastases are used for predicting a biologic behavior of cancer. Prediction of patient outcomes in cancer has been the subject of interest to clinicians, healthcare workers and patients. Survival is the most important outcome for patients to help them for planning their lives and provide them and their family for caring. Traditional methods of outcome prediction in cancer include the Kaplan–Meier non-parametric model and the Cox regression semi-parametric model. So far, numerous studies have been attempted for predicting the biologic behavior in various types of cancer. Prediction of patient outcomes has been applied with several tools including genomic biomarkers, gene expression, and epigenetic modifications as well as histology.

In glioma, treatment is dependent on many factors, including patient age and grade. However, gliomas assigned to WHO grades III and IV are typically treated very aggressively

with radiation and concomitant chemotherapy. Histologic diagnosis and grading of gliomas have been limited, but the emergence of molecular subtyping has resolved uncertainty related to lineage; criteria for grading need to be redefined in the context of molecular subtyping. Improving the accuracy and objectivity of grading will directly impact patient care by identifying patients who can benefit from more aggressive therapeutic regimens and by sparing those with less aggressive disease from unnecessary treatment. Mobadersany et al. recently published an elegant study of prediction of cancer outcome by using convolutional networks in Proc. Natl. Acad. Sci. USA (Mobadersany et al., 2018). In this study, they show a computational approach to predict the overall survival in patients with brain tumors by digital pathology images and genomic biomarkers. They examined the ability to predict overall survival in diffuse gliomas, a disease with wide variations in outcomes and an ideal test case where histologic grading and genomic classifications have independent prognostic power. Indeed, artificial intelligence (AI) software learned about survival from histologic images and created a unified framework that could integrate histology and genomic biomarkers for predicting time-to-event outcomes. Surprisingly, the ability of predicting patient outcomes by the AI was ultimately more accurate than that of surgical pathologists. Their study provides insights into applications of deep learning in medicine and the integration of histology and genomic data and provides methods for dealing with intratumoral heterogeneity and training data deficits when using deep learning algorithms to predict survival from histology images.

AI is attracting attention in many fields. Due to the breakthrough of deep learning, it rapidly developed in the 2010s. Along with the use of Internet of Things (IoT) and big data, AI realized by highly advanced computer processing power and software technology is expected

to greatly change our lives. Recently, a computer defeated a professional Japanese chess (shogi) player for the first time in a public match. Since captured pieces can be used by the opposing side, shogi presents a higher degree of complexity than many other strategy games and has been of interest to AI researchers. AI has entered the era of full-scale dissemination and will change our lives, industries and society including the medical field from now on. Recently, technology such as image recognition by deep learning has improved, and it is thought that it will bring about a change in the medical field. For detecting tumors, AI will be able to detect abnormal values from enormous examination results by X-ray, CT, and MRI as well as histopathology. Moreover, if it is done by humans, things that take 10 days can be done with AI instantly. Although AI may be responsible for some work, AI is ultimately an auxiliary tool to the last, and doctors are still required to be required. Even in the case of predicting a patient's outcome, the doctor's job is to define judgment criteria and make the final judgment on whether the results are correct or not. By introducing AI in the pathological field, I believe that standard medical treatment will be improved not only in developed countries but also in various less developed regions.

In head and neck locale, squamous cell carcinoma is the most common type of cancer. Head and neck squamous cell carcinomas (HNSCCs) affect, 600,000 patients per year worldwide (Ferlay et al., 2010). Smoking is implicated in the rise of HNSCC in developing countries, and the role of human papillomavirus (HPV) is emerging as an important factor in the rise of oropharyngeal tumors affecting non-smokers in developed countries (Ang et al., 2010). Similar to other types of cancer, risk stratification for HNSCC is by anatomic site, stage and histological characteristics of the tumor. The prognosis for patients with HPV-positive

HNSCC is substantially better than that for patients with HPV-negative tobacco-related cancers treated similarly (Fakhry et al., 2008). With the recognition of high-risk HPV infection as a risk factor for HNSCC and its prognostic importance, HNSCC can be divided for two distinct types, HPV-positive and HPV-negative disease. In contrast to HPV-positive HNSCC, HNSCC caused by exposure to smoking and alcohol is more likely to be associated with mutations in tumor suppressor genes and specifically *TP53*, making these cancers less sensitive to chemoradiation. An inverse correlation between HPV status and *TP53* mutation was observed (Westra et al., 2008). The HPV-positive HNSCCs show unique gene expression and DNA methylation profiles (Lechner et al., 2013a). In addition to *TP53* mutation, whole-genome sequencing has identified additional mutations, such as in the pathways involved in tumor survival (PIK3CA-AKT1-MTOR-PTEN, EGFR and MET pathways), tumor proliferation (p16, RB, MET, CCND1, CDKN2A/CDKN2B), and tumor differentiation (NOTCH1) (Lechner et al., 2013b; Agrawal et al., 2011). Moreover, the Cancer Genome Atlas Network reported the results of whole-genome sequencing on HNSCC (Cancer Genome Atlas Network, 2015). This report shows that HPV-positive HNSCCs are dominated by helical domain mutations of the oncogene *PIK3CA*, novel alterations involving loss of *TRAF3*, and amplification of the cell cycle gene *E2F1* (Cancer Genome Atlas Network, 2015). Moreover, smoking-related HNSCCs demonstrate near universal loss-of-function *TP53* mutations and *CDKN2A* inactivation with frequent copy number alterations including amplification of 3q26/28 and 11q13/22 (Cancer Genome Atlas Network, 2015). Recently, single cell analysis of HNSCC including five matched pairs of primary tumors and lymph node metastases has revealed that cancer cells varied within and between tumors in their expression of signatures related to cell cycle, stress, hypoxia, epithelial differentiation, and partial epithelial-to-mesenchymal transition (p-EMT) (Puram et al., 2017).

Importantly, the p-EMT is an independent predictor of nodal metastasis, grade, and adverse pathologic features. Based on these comprehensive analyses, to predict HNSCC patient outcomes by using AI, the status of HPV infection, mutation of several genes, and gene expression of p-EMT program will be required in addition to histological findings. To apply AI in the field of head and neck pathology, the above parameters should be considered for predicting patient's outcome.

In the near future, cancer prediction by using AI will provide an important approach to assessing risk and prognosis by identifying individuals at high risk, facilitating the design and planning of clinical cancer trials, fostering the development of benefit-risk indices, and enabling estimates of the population burden and cost of cancer. It is the task of the pathologist to provide an accurate, specific, and sufficiently comprehensive diagnosis to enable the clinician to develop an optimal plan of treatment and estimate of prognosis. There are large opportunities for more systematic and clinically meaningful data extraction using computational approaches. AI may help pathologists to make an accurate diagnosis in the combination with molecular pathology to detect the expression of specific genes or gene mutations. Diagnosis by pathologists using AI has not yet reached standard practice but may be a golden age in the next decade.

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Conflict of interests

None to declare.

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