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Utilization of artificial intelligence-assisted histopathological detection in surveillance of oral squamous cell carcinoma staging: A narrative review

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Abstract

Background: Oral squamous cell carcinoma (OSCC) is defined as an oral malignancy with worldwide prevalence of 90%. In 2018, the number of cases observed is 354.864 with 177.384 deaths globally. Early diagnosis for determining OSCC stage due to histopathological examination is required to sustain prognosis and minimize mortality. Determining the stage is mostly done manually and highly dependent on skill and experiences of the pathologist thus having a high tendency of misdiagnosis. Artificial intelligence (AI) is a technology that modifies machines with human-like intelligence thus making them able to solve the tasks. Utilization of AI in analyzing histopathological samples is known to give such a precision analysis then diagnosing the OSCC stage accurately

Purpose: This study describes utilization of AI-assisted histopathological detection in determining OSCC staging.

Review: Developmental process of OSCC begins with gene damage causing disruption of cell regulation, manifesting in impaired differentiation and proliferation of keratinocytes in the epithelium which is characterized by keratin pearl formation. AI-assisted histopathological detection is able to identify the percentage of keratinization and keratin pearls in histopathological images by convolutional neural network (CNN). CNN is a deep learning architecture specifically designed to recognize two-dimensional visual patterns with minimal preprocessing. CNN works by analyzing input in the form of visual images from histopathological images and producing output as keratinization percentage in related samples then being used to determine the staging of OSCC.

Conclusion: AI-assisted histopathological detection may potential to be used in determining OSCC staging.

Keywords: Artificial intelligence; Non-communicable disease; Oral squamous cell carcinoma; Dentistry; Medicine

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1. Introduction

Oral squamous cell carcinoma (OSCC) is a malignancy in the oral cavity with a prevalence of 90% of all oral cancer [1]. Globally, in 2018 there were 354,864 cases and 177,384 deaths due to OSCC [2]. OSCC survival rate is poor because the diagnosis is made at an advanced stage. Diagnosis of OSCC at an early stage can provide extensive treatment, so biomarkers can serve as a tool for diagnosis [3]. One of the frequently used diagnostic modalities is histopathological biomarkers [4]. In this process, the pathologist uses a biopsy sample taken from the patient, then examines the sample under a microscope, and then makes a subjective assessment. Assessment is done only by visual examination of cell structure, shape, tissue distribution, and cancer grade. Therefore, the results are purely qualitative and the specificity and sensitivity are uncertain. In addition, awareness of the dangers of oral cancer among patients as well as the general public increases the demand for sophisticated and accurate diagnostic techniques that can detect malignancy at an early stage [5].

Artificial intelligence (AI) is a technology that allows a machine to have human-like intelligence so that it can help complete certain tasks [6]. The use of AI in analyzing histopathological features can provide precise analysis results so as to be able to provide an accurate diagnosis of staging OSCC. The process of OSCC development begins with gene damage that causes cell regulation disorders, manifests in disorders of differentiation and proliferation of keratinocytes in the epithelium which is characterized by the formation of keratin pearls [7]. AI-assisted histopathological detection is able to identify the percentage of keratinization and keratin pearls on histopathological images using a *convolutional neural network* (CNN).

CNN is defined as deep learning architecture that is specially designed to detect visual pattern with minimal preprocessing [8]. The main components of CNN are *convolutional layer, pooling layer, fully connected layer* and *dropout* [9]. CNN is used to detect and identify objects in an image. This network has a special layer called the convolutional layer, where in this layer an input image will be processed based on predetermined filters. Each layer will create a pattern from several parts of the image which will later be easier to classify [10]. CNN works by analyzing input in the form of visual images from histopathological images and produces output in the form of the percentage of keratinization in related samples which can then be used to determine the staging of OSCC. Thus, this literature review is arranged in order to describe the potential of utilizing AI-assisted histopathological detection in determining OSCC staging.

2. Oral Squamous Cell Carcinoma

Oral squamous cell carcinoma (OSCC) is the most common malignant neoplasm originating from stratified squamous epithelium of the oral mucosa, especially in Asia. This malignant neoplasm can occur in various places, the majority of which occur on the lips, lateral edges of the tongue, and the floor of the oral cavity [11]. The main risk factors that can trigger OSCC are consumption of tobacco (such as cigarettes) and alcohol which can have carcinogenic effects. Tobacco and alcohol can stimulate the body to endogenously produce many free radicals in various cellular metabolic activities. These free radicals can cause DNA damage by damaging strands, DNA-protein cross-linking, and base modification, can form lipid peroxides and react with fatty acids in cell membranes, and interfere with the antioxidant system. High oxidants and low antioxidants in the blood certainly trigger carcinogenesis [1]. In addition to tobacco and alcohol consumption, nutritional factors and genetic predisposition, as well as high-risk HPV types (especially HPV type 16) are also risk factors for OSCC [12]. Carcinogenesis that triggers OSCC can also originate from precancerous lesions, namely leukoplakia, erythroleukoplakia, erythroplakia, oral submucous fibrosis, and oral lichen planus [13]. However, not all of these precancerous lesions can develop into malignant neoplasms [11].

During the process of carcinogenesis, lesions present in the epithelium can be classified according to their reactive epithelial changes or preneoplastic changes (including mild, moderate, and severe dysplasia) prior to invasive carcinoma formation. OSCC originates from epithelial dysplasia which is characterized by changes in dysplastic squamous cell proliferation on the surface of the epithelial lining then degrades the subepithelial basement membrane. One form of epithelial changes in OSCC is hyperkeratosis [11]. Under normal circumstances, epithelial cells will experience periodic desquamation. In hyperkeratosis, this process is disrupted by excessive keratin formation and accumulation by a lack of adequate desquamation. Hyperkeratosis that occurs due to chronic irritation or the presence of malignancy is caused by a higher rate of epithelial cell proliferation. When there is lack of cohesion among the epithelial cells due to malignancy changes, the cells will be concentrically arranged. Because squamous cells are responsible for forming keratin, these cells lay out keratin concentrically and then appear as keratin pearl formations which can be seen on histopathological picture of OSCC [7].

OSCC can be diagnosed in several ways, namely examination of salivary biomarkers, exfoliative cytology, as well as biopsy and histopathological analysis. Of these various methods, biopsy and histopathological analysis are the gold standard in the diagnosis of OSCC [13]. In the histopathological picture of OSCC, there are a lot of specific features including keratin pearl formations, atypical cells, mitotic cells, and angiogenesis. From the histopathological picture, the staging of OSCC can be determined. Based on the classification according to the World Health Organization (WHO), at stages I and II, the tissue structure in histopathological picture can be differentiated well (well differentiated), at stage III, the tissue structure is still quite differentiated (medium differentiated), and at stage IV, tissue structure is difficult to differentiate (poor differentiated). In addition, an important structure that can differentiate between stages is the presence or absence of keratin pearls. In a well differentiated histopathological picture, keratin pearl formations can be found, whereas in medium and poor differentiated, keratin pearl formations are difficult or even absent [14]. OSCC needs to be diagnosed earlier in order to get a good prognosis, higher survival rate, and prevent death from OSCC.

3. Artificial Intelligence

Artificial intelligence (AI) is the development of a computer system that is capable of imitating human intelligence and behavior to perform certain tasks, such as visual perception, speech and image recognition, translation between languages, online search engines, and virtual assistants [15]. Deep learning (DL) is a part of AI that is able to learn various levels of representation and abstraction to help understand big data such as images, sound and text. DL is becoming very popular due to its various advantages. This method has dramatically increased the processing power of the chip, significantly increased the size of the data used for training, and made advances in information processing. These advances enable DL methods to exploit complex, compositional non-linear functions, and use labeled and unlabeled data effectively. This makes DL have a high chance of success because it requires little engineering, so it can take advantage of the increasing amount of computation and data available easily [16]. Convolutional Neural Network (CNN) is a type of DL architecture that aims to process two-dimensional data because its form of operation is a convolution operation. CNN is specifically designed to be able to recognize visual patterns directly from images with minimal pre-processing [17]. CNN works by receiving an input data in the form of two-dimensional data and propagating it on the network to get output.

In recent years, AI, especially CNN has developed rapidly in the medical world. AI has been proven to be able to detect disease, analyze treatment results, analyze radiographic images, analyze histopathological images, and so on so that AI can improve patient care and reduce misdiagnosis in daily practice [18]. In the field of oncology, many studies have been carried out regarding the CNN application to help make a diagnosis quickly and accurately. Bejnordi et al. (2017) used CNN to diagnose breast cancer in 646 breast tissue samples and achieved an area under characteristic curve (AUC) of 0.92 at the whole slide image (WSI) level to differentiate breast cancer from benign breast tissue [19]. A later study by Bejnordi et al. (2017) used CNN to classify breast pathology from WSI into three categories. Their system achieved an AUC of 0.96 for binary classification (non-malignant and malignant) and a three-class accuracy of 81% for classification of WSI into normal/benign, DCIS (ductal carcinoma in situ), or invasive ductal carcinoma [20]. Not only that, various studies have also been conducted to detect and diagnose oral cancer, including OSCC, as was done by Das et al. (2018) using 42 samples of OSCC histopathological features and obtaining an accuracy of 98.04% [21]. Jeyaraj & Nadar (2019) also used CNN in classifying OSCC and benign tumor tissue as well as OSCC and normal tissue. The results of their research showed an accuracy value of 91% and 95% [22]. From the results of these studies, AI, especially using the CNN architecture, has the potential to be used to determine the staging of OSCC through its histopathological picture.

4. Discussion

Disorders of cell proliferation and differentiation in OSCC can be caused by mutations in genes so that the regulation of cell activity is disrupted. This condition is caused by the process of epithelial-mesenchymal transition (EMT), namely the change in the properties of epithelial cells to mesenchymal cells which causes cells to change towards malignancy. The EMT process begins with exposure to persistent injury which induces an increase in ROS levels which manifests in the appearance of double strand breaks (DSB) in DNA resulting in mutations in the p53 gene so that the function of cell regulators is disrupted. Mutation of p53 resulted in decreased expression of p53 upregulated modulator of apoptosis (Puma) and Noxa as pro-apoptotic proteins, so that the expression of B-cell lymphoma 2 (Bcl-2), B-cell lymphoma extra large (Bcl-XL), and myeloid cells lymphoma (Mcl-1) as anti-apoptotic protein are upregulated. This condition manifests in impaired activation of the pro-apoptotic protein Bcl-2-like protein 4 (Bax) and Bcl-2 homologous antagonist/killer (Bak) so that the pore on the mitochondrial outer membrane cannot open and manifests in inhibition of the formation of the apoptosome as the initiator of apoptosis [23-27].

Keratin is a protein produced by keratinocytes in the epithelium and plays an important role in the protective function of epithelial tissue. Keratin interacts with integrins to maintain hemidesmosome stability so that cell adhesion is maintained and prevents cells from migrating [28,7]. In OSCC, the process of keratin formation is disrupted due to an increase in the keratin 8 (K8) and keratin 7 (K7) families resulting in excess keratinization activity. These conditions lead to disruption of α6β4-integrin resulting in damage to the extracellular matrix (ECM) which manifests in loss of cell attachment to the basement membrane. These conditions cause OSCC cells to easily experience disorientation which has the potential to migrate and extravasate to the nearest blood vessels or even to the lymphatic drainase for metastasis [29-30].

On the other hand, increased ROS in OSCC results in activation of the transmembrane epidermal growth factor receptor (EGFR) protein which induces PIP2 phosphorylation towards PIP3 so that protein kinase B (Akt) is activated. Akt is a protein that plays an important role in survival and induction of cell proliferation. Akt activation results in mammalian target of rapamycin C1 (MTORC1) increases so that the cell cycle regulatory protein namely Cyclin D/E is activated and manifests in the G1/S phase transition to the G2 phase in the cell cycle, causing cell mitosis to undergo [23, 31-32].

In the histopathology picture, this condition can be characterized by a change towards dysplastic cells with several distinctive characteristics, namely loss of adhesion and cell orientation, irregular epithelial stratification processes, increased nuclear-cytoplasmic ratio, and atypical cell nuclei [23]. OSCC staging is very important because it can determine the patient's prognosis. Staging can be done using Broder's grade. The use of AI in the health sector can be in the form of analysis capabilities on samples in the form of images, for example images of histopathology results. Machine capabilities resembling human intelligence can be formed through the concept of deep learning (DL). In general, DL is part of machine learning based on artificial neural network (ANN) or technology that resembles the formation of complex neural networks in the human brain, so it is expected to have human-like abilities in processing data and recognizing certain patterns that play an important role in the decision-making process [34-36]

Convolutional neural network (CNN) is one part of ANN that can be used to analyze images. CNN is composed of 3 parts of an artificial network or called nodes, namely the input layer, multiple hidden layers, and the output layer. In the use of AI in the field of pathology, the histopathology image is recognized as part of the input. The input layer receives histopathology image which will then be pooled or divided into several small symmetrical matrices. Each matrix will be adjusted according to the size of the image so that keratinization and anomalies in cells can be observed to the fullest. This process occurs in multiple hidden layers, where each matrix will be clarified by the CNN system including branching, matching, and skipping based on the numerical activation function (AF), a basic program of AI based on statistical methods (such as linear regression and others) that underlies CNN's ability to be able to consider and make decisions on a task being carried out. If the AF analysis results show that it can exceed the threshold value based on big data repositories, then the signal will be forwarded to other parts of the hidden layer so that the formation of keratin pearls and cell anomalies in each matrix can be identified. The results are sent to the output layer and analyzed as a whole so that the percentage of keratinized and dysplastic cells in histopathology image can be known which are generally marked by marking the corresponding histopathology image in specific color [34,35]. The results of the analysis at the output layer are then interpreted accordingly with a staging system by a pathologist so that it can provide an accurate and precise diagnosis of OSCC staging in patients [37-39].

5. Conclusion

Based on the review, the AI-assisted histopathological detection may potential to be used in determining OSCC staging. However, further study is still needed to examine the use of AI-assisted histopathological detection of OSCC staging in the clinical setting.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare there is no conflict of interest in this study.

References

[1] Jiang, X., Wu, J., Wang, J., & Huang, R. (2019). Tobacco and oral squamous cell carcinoma: A review of carcinogenic pathways. Tobacco induced diseases, 17.

[2] Almangush, A., Mäkitie, A. A., Triantafyllou, A., de Bree, R., Strojan, P., Rinaldo, A., & Leivo, I. (2020). Staging and grading of oral squamous cell carcinoma: An update. Oral oncology, 107, 104799.

[3] Hema Shree, K., Ramani, P., Sherlin, H., Sukumaran, G., Jeyaraj, G., Don, K. R., & Sundar, R. (2019). Saliva as a diagnostic tool in oral squamous cell carcinoma–a systematic review with meta analysis. Pathology & Oncology Research, 25(2), 447-453.

[4] Musulin, J., Štifanić, D., Zulijani, A., Ćabov, T., Dekanić, A., & Car, Z. (2021). An enhanced histopathology analysis: An ai-based system for multiclass grading of oral squamous cell carcinoma and segmenting of epithelial and stromal tissue. Cancers, 13(8), 1784.

[5] Ulaganathan, G., Niazi, K. T. M., Srinivasan, S., Balaji, V. R., Manikandan, D., Hameed, K. S., & Banumathi, A. (2017). A clinicopathological study of various oral cancer diagnostic techniques. Journal of pharmacy & bioallied sciences, 9(Suppl 1), S4

[6] Lubis, M. S. Y. (2021, August). Implementasi Artificial Intelligence Pada System Manufaktur Terpadu. In Seminar Nasional Teknik (SEMNASTEK) UISU (Vol. 4, No. 1, pp. 1-7).

[7] Deo, P. N., & Deshmukh, R. (2018). Pathophysiology of keratinization. Journal of oral and maxillofacial pathology: JOMFP, 22(1), 86.

[8] Paliwang, A. A. A., Septian, M. R. D., Cahyanti, M., & Swedia, E. R. (2020). Klasifikasi Penyakit Tanaman Apel Dari Citra Daun Dengan Convolutional Neural Network. Sebatik, 24(2), 207-212.

[9] Skourt, B. A., El Hassani, A., & Majda, A. (2022). Mixed-pooling-dropout for convolutional neural network regularization. Journal of King Saud University-Computer and Information Sciences, 34(8), 4756-4762.

[10] Thohari, A. N. A., & Hertantyo, G. B. (2018). Implementasi Convolutional Neural Network untuk Klasifikasi Pembalap MotoGP Berbasis GPU. In Conference on Electrical Engineering, Telematics, Industrial technology, and Creative Media (CENTIVE) (pp. 50-55).

[11] Rivera, C., & Venegas, B. (2014). Histological and molecular aspects of oral squamous cell carcinoma. Oncology letters, 8(1), 7-11.

[12] Pires, F. R., Ramos, A. B., Oliveira, J. B. C. D., Tavares, A. S., Luz, P. S. R. D., & Santos, T. C. R. B. D. (2013). Oral squamous cell carcinoma: clinicopathological features from 346 cases from a single oral pathology service during an 8-year period. Journal of Applied Oral Science, 21, 460-467.

[13] Bugshan, A., & Farooq, I. (2020). Oral squamous cell carcinoma: metastasis, potentially associated malignant disorders, etiology and recent advancements in diagnosis. F1000Research, 9.

[14] Budhy, T. I. (2015). Penentuan Grading Tumor Ganas Oral Squamous Cell Carcinoma Berdasarkan Gambaran Histopatologi. Jurnal Biosains Pascasarjana, 17(1), 46-51.

[15] Jiang, L., Chen, D., Cao, Z., Wu, F., Zhu, H., & Zhu, F. (2021). A Two-Stage Deep Learning Architecture for Radiographic Assessment of Periodontal Bone Loss.

[16] Soffer, S., Ben-Cohen, A., Shimon, O., Amitai, M. M., Greenspan, H., & Klang, E. (2019). Convolutional neural networks for radiologic images: a radiologist's guide. Radiology, 290(3), 590-606.

[17] Putra, R. H., Doi, C., Yoda, N., Astuti, E. R., & Sasaki, K. (2022). Current applications and development of artificial intelligence for digital dental radiography. Dentomaxillofacial Radiology, 51(1), 20210197.

[18] Malamateniou, C., Knapp, K. M., Pergola, M., Woznitza, N., & Hardy, M. (2021). Artificial intelligence in radiography: Where are we now and what does the future hold?. Radiography, 27, S58-S62.

[19] Bejnordi, B. E., Lin, J., Glass, B., Mullooly, M., Gierach, G. L., Sherman, M. E., & Beck, A. H. (2017, April). Deep learning-based assessment of tumor-associated stroma for diagnosing breast cancer in histopathology images. In 2017 IEEE 14th international symposium on biomedical imaging (ISBI 2017) (pp. 929-932). IEEE.

[20] Bejnordi, B. E., Zuidhof, G., Balkenhol, M., Hermsen, M., Bult, P., van Ginneken, B., & van der Laak, J. (2017). Context-aware stacked convolutional neural networks for classification of breast carcinomas in whole-slide histopathology images. Journal of Medical Imaging, 4(4), 044504.

[21] Das, D. K., Bose, S., Maiti, A. K., Mitra, B., Mukherjee, G., & Dutta, P. K. (2018). Automatic identification of clinically relevant regions from oral tissue histological images for oral squamous cell carcinoma diagnosis. Tissue and Cell, 53, 111-119.

[22] Jeyaraj, P. R., & Samuel Nadar, E. R. (2019). Computer-assisted medical image classification for early diagnosis of oral cancer employing deep learning algorithm. Journal of cancer research and clinical oncology, 145(4), 829-837.

[23] Bai, Y., Boath, J., White, G. R., Kariyawasam, U. G., Farah, C. S., & Darido, C. (2021). The Balance between Differentiation and Terminal Differentiation Maintains Oral Epithelial Homeostasis. Cancers, 13(20), 5123.

[24] Usman, S., Jamal, A., Teh, M. T., & Waseem, A. (2021). Major molecular signaling pathways in oral cancer associated with therapeutic resistance. Frontiers in Oral Health, 1, 603160.

[25] Peña-Blanco, A., & García-Sáez, A. J. (2018). Bax, Bak and beyond—mitochondrial performance in apoptosis. The FEBS journal, 285(3), 416-431.

[26] Cosentino, K., Hertlein, V., Jenner, A., Dellmann, T., Gojkovic, M., Peña-Blanco, A., & Garcia-Saez, A. J. (2022). The interplay between BAX and BAK tunes apoptotic pore growth to control mitochondrial-DNA-mediated inflammation. Molecular cell, 82(5), 933-949.

[27] Dorstyn, L., Akey, C. W., & Kumar, S. (2018). New insights into apoptosome structure and function. Cell Death & Differentiation, 25(7), 1194-1208.

[28] Jang, T. H., Huang, W. C., Tung, S. L., Lin, S. C., Chen, P. M., Cho, C. Y., & Wang, L. H. (2022). MicroRNA-485-5p targets keratin 17 to regulate oral cancer stemness and chemoresistance via the integrin/FAK/Src/ERK/β-catenin pathway. Journal of biomedical science, 29(1), 1-20.

[29] Vaidya, M., Dmello, C., & Mogre, S. (2022). Utility of keratins as biomarkers for human oral precancer and cancer. Life, 12(3), 343.

[30] Huang, W. C., Jang, T. H., Tung, S. L., Yen, T. C., Chan, S. H., & Wang, L. H. (2019). A novel miR-365-3p/EHF/keratin 16 axis promotes oral squamous cell carcinoma metastasis, cancer stemness and drug resistance via enhancing β5-integrin/c-met signaling pathway. Journal of Experimental & Clinical Cancer Research, 38(1), 1-17.

[31] He, S., Chakraborty, R., & Ranganathan, S. (2022). Proliferation and apoptosis pathways and factors in oral squamous cell carcinoma. International Journal of Molecular Sciences, 23(3), 1562.

[32] Harsha, C., Banik, K., Ang, H. L., Girisa, S., Vikkurthi, R., Parama, D., & Kunnumakkara, A. B. (2020). Targeting AKT/mTOR in oral cancer: mechanisms and advances in clinical trials. International journal of molecular sciences, 21(9), 3285.

[33] Vijayakumar G, Sharma G, Narwal A, Kamboj M. Broder versus Bryne's histologic grading parameters on incision biopsy specimens: A comparative study with P53 and KI67 expression. Journal of Oral and Maxillofacial Pathology. 2021;25(1):55.

[34] Cui, M., & Zhang, D. Y. (2021). Artificial intelligence and computational pathology. Laboratory Investigation, 101(4), 412-422.

[35] Försch, S., Klauschen, F., Hufnagl, P., & Roth, W. (2021). Artificial intelligence in pathology. Deutsches Ärzteblatt International, 118(12), 199.

[36] Stenzinger, A., Alber, M., Allgäuer, M., Jurmeister, P., Bockmayr, M., Budczies, J., & Klauschen, F. (2021, February). Artificial intelligence and pathology: From principles to practice and future applications in histomorphology and molecular profiling. In Seminars in cancer biology. Academic Press.

[37] Ahmad, Z., Rahim, S., Zubair, M., & Abdul-Ghafar, J. (2021). Artificial intelligence (AI) in medicine, current applications and future role with special emphasis on its potential and promise in pathology: present and future impact, obstacles including costs and acceptance among pathologists, practical and philosophical considerations. A comprehensive review. Diagnostic Pathology, 16(1), 1-16.

[38] Moxley-Wyles, B., Colling, R., & Verrill, C. (2020). Artificial intelligence in pathology: an overview. Diagnostic Histopathology, 26(11), 513-520.

[39] Wang, Y., Li, Y., Song, Y., & Rong, X. (2020). The influence of the activation function in a convolution neural network model of facial expression recognition. Applied Sciences, 10(5), 1897.