Clinical Study Protocol

Project Title: Preoperative Differentiation of Jaw Cystic Lesions Based on Radiomics from Computed Tomography Images: A Multicenter, Prospective Machine Learning Study

Sponsor: Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Version Number: V2

Version Date: June 9, 2024

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Protocol Signature Confirmation:

1. Study Protocol Summary

Objective: In previous studies, we have demonstrated the feasibility of developing an effective predictive diagnostic model using machine learning techniques combined with computed tomography (CT) radiomics for the preoperative differentiation of various jaw cystic lesions. This study aims to utilize the existing diagnostic predictive model to further conduct a multicenter, prospective study to construct a preoperative diagnostic predictive model, providing more reliable scientific references for clinical diagnosis and treatment.

Methods: In this multicenter, prospective study, we plan to enroll a total of 300 patients with jaw cystic lesions. We will collect all patient information and CT images, delineate the region of interest (ROI), extract radiomic features, and input them into the predictive diagnostic model after screening. We will verify the consistency between preoperative predictions and postoperative pathology to refine the model, aiming to provide scientific evidence for the precise selection of treatment plans for different lesions.

2. Study Background (including introduction of the disease, current treatment status at home and abroad, significance of the study, etc.)

Jaw cystic lesions include odontogenic tumors and non-tumorous cystic lesions occurring within the jawbone. Among these, ameloblastoma is the most common odontogenic tumor, while cystic lesions can be divided into odontogenic and non-odontogenic cysts. Currently, the treatment focus varies for different types of jaw cystic lesions. Ameloblastomas can recur and metastasize, often requiring surgical resection, whereas cystic lesions may be more amenable to curettage and marsupialization. Therefore, accurate preoperative differential diagnosis of various jaw lesions and the subsequent selection of appropriate treatment plans are crucial for achieving optimal treatment outcomes for patients. Inappropriate treatment choices may delay the disease or lead to overtreatment, affecting the patient's quality of life. At present, there is still a lack of an objective and accurate standard and differential diagnosis plan for the treatment of jaw cystic lesions. Establishing an objective and scientific preoperative diagnostic predictive model has important clinical significance. In previous research, we successfully developed an effective predictive diagnostic model by combining machine learning techniques with CT radiomics, achieving a maximum AUC value of >0.8, indicating good performance and clinical reference value in predictive diagnosis. In the current study, we aim to conduct a multicenter, prospective machine learning study to further enhance the predictive diagnostic performance of the model and assist clinical diagnosis and treatment.

3. Study Objectives

In previous studies, we have demonstrated the feasibility of developing an effective predictive diagnostic model using machine learning techniques combined with CT radiomics for the preoperative differentiation of various jaw cystic lesions. This study aims to utilize the existing diagnostic predictive model to further conduct a multicenter, prospective study to construct a preoperative diagnostic predictive model, providing more reliable scientific references for clinical diagnosis and treatment, while further optimizing and enhancing the performance of the predictive diagnostic model.

4. Study Design

This study is designed as a multicenter, prospective machine learning study, planned to be conducted across 12 centers, enrolling a total of 300 patients with jaw cystic lesions. Participating centers include: Sun Yat-sen Memorial Hospital of Sun Yat-sen University (25 cases), Xiangya Hospital Central South University (25 cases), Hospital of Stomatology, Sun Yat-sen University (25 cases), Stomatological Hospital, Southern Medical University (25 cases), Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine (25 cases), Hospital of Stomatology Wuhan University (25 cases), The Second Affiliated Hospital Zhejiang University School of Medicine (25 cases), The Fourth Military Medical University (25 cases), The People's Hospital Of QianNan (25 cases), The Second Xiangya Hospital of Central South University (25 cases), The First Affiliated Hospital of Xinjiang Medical University (25 cases), and Guangxi Medical University College of Stomatology (25 cases). Based on preliminary investigations of the actual diagnosis and treatment conditions at each research center, we plan to utilize different imaging data for grouping according to different imaging examinations conducted, and uniformly process the imaging data from different units and examination types for subsequent work. Sun Yat-sen Memorial Hospital of Sun Yat-sen University will serve as the primary center, with other units as sub-centers. Specific groupings are as follows: the spiral CT group includes Sun Yat-sen Memorial Hospital of Sun Yat-sen University, Second Affiliated Hospital of Zhejiang University School of Medicine, Xiangya Hospital of Central South University, Qiannan People's Hospital, Ninth People's Hospital Affiliated to Shanghai Jiao Tong University, and First Affiliated Hospital of Xinjiang Medical University; the cone beam CT (CBCT) group includes Wuhan University Stomatological Hospital, Stomatological Hospital of Southern Medical University, Third Affiliated Hospital of Air Force Medical University, Stomatological Hospital of Sun Yat-sen University, Xiangya Second Hospital of Central South University, and Stomatological Hospital Affiliated to Guangxi Medical University.

During the study, once patients meeting the inclusion criteria are enrolled, their maxillofacial CT examination images will be collected and imported into computer software (LIFEx version 6.30) for ROI delineation. Radiomic features within the ROI will be extracted using Pyradiomics software, screened, and used for preoperative diagnostic prediction with the existing model. After surgical treatment, the pathological results of the lesions will be tracked and recorded. If conditions permit, the model's predictive performance may be further optimized in phases during the study, or methodological adjustments and reconstructions of the predictive model may be attempted for all existing data, ultimately achieving a more ideal preoperative diagnostic prediction.

5. Study Protocol and Technical Route (including sample size calculation, inclusion, exclusion, and withdrawal criteria, evaluation indicators and methods of study results, statistical analysis plan, informed consent, ethics, etc.)

This project plans to include a total of 300 patients with jaw cystic lesions from Sun Yat-sen Memorial Hospital of Sun Yat-sen University and other sub-centers for validation, prediction, and optimization of the existing model. Inclusion criteria: 1) Patients who are visiting for the first time and have not received other treatment

interventions; 2) Patients with complete preoperative medical records, imaging examinations, and imaging data; 3) Patients who underwent maxillofacial CT examination preoperatively, with complete CT data, no artifact interference in the lesion area, and a lesion size with the longest diameter not less than 2 cm; 4) Patients who can tolerate surgical treatment, with specimens sent for routine pathological examination after surgery. Exclusion criteria: 1) Incomplete medical records, such as missing information on specialist examinations and therapeutic operations; 2) Patients who received therapeutic operations at an external hospital during the first visit, not completely cured or relapsed; 3) Patients who did not undergo CT examination preoperatively, with incomplete CT data, severe artifact interference in the lesion area, or lesion size not meeting requirements; 4) Patients whose lesions were not sent for pathological examination during surgery, with no routine pathological examination; 5) Patients with unclear postoperative pathological reports, or pathological diagnoses other than odontogenic cysts and non-solid ameloblastomas.

For different groups, the corresponding scan parameters for imaging examinations in this study are as follows:

① Spiral CT group: When conducting maxillofacial spiral CT examinations, units should use 64-slice or higher multi-slice spiral CT, with scan reconstruction layer thickness set between 0.75-1.25 mm, and the scan range must include from the skull base down to the submandibular area, fully covering the maxillary and mandibular regions; ② CBCT group: Axial scan reconstruction thickness set to 0.25-0.3 mm, with the scan area reaching the maximum field of vision (FOV) as much as possible and fully covering the lesion area.

The evaluation indicators of the study results mainly refer to statistical analysis indicators (such as model prediction AUC value and ACC value, etc.). Statistical analysis will be conducted using SPSS software and R language, with results analyzed using chi-square tests, lasso regression, and other statistical methods. Regarding informed consent, all enrolled patients will sign informed consent forms. In terms of ethics, the relevant examinations and treatment plans conform to the treatment process for maxillofacial jaw cystic lesions, will not increase the financial burden or life safety risk for patients, and pose no major ethical risks. It should be noted that to ensure the smooth progress of the project, adaptive adjustments to the grouping and actual number of cases collected by each unit may be made if necessary during the actual progress.

6. Safety Evaluation (including definitions and assessments of adverse events and serious adverse events, etc.)

This study is a low-risk medical data machine learning project. Adverse events mainly include data leakage, with no additional interventions or potential harm to patients. All image processing for patients in this study will strictly adhere to confidentiality clauses and relevant regulations, with no major adverse events expected.

7. Data Collection and Management

Patient case data, imaging data, and pathology reports will be collected by corresponding groups from different research centers, filled in according to a predetermined form template, and uploaded to a unified EDC system, then collected and summarized by our unit. Our unit has a dedicated computer for collecting and

storing data for this study (registered with the Equipment Department and Research Department), and related work will be handled by this equipment to ensure the confidentiality of patient data.

8. Quality Management Plan (please introduce measures to ensure project quality and progress)

(1) After ethical approval and project establishment, before officially starting, the research team will draft a cooperation agreement for signing with sub-center cooperation units when conducting the study (if necessary, if sub-center units do not require it, it will not be submitted for review). After formal project establishment, online discussion meetings or offline surveys will be conducted with the heads of each sub-center to understand the actual diagnosis and treatment conditions at different centers, determine whether different centers can admit enough eligible cases within the study period, and make adaptive adjustments to the planned enrollment numbers based on the results. Subsequently, personnel responsible for actual project advancement at different centers will be trained to ensure that enrolled patients meet the inclusion and exclusion criteria and that clinical and imaging data quality is controllable.

(2) Determine the inclusion and exclusion criteria for jaw cystic lesions, screen patients with jaw cystic lesions visiting for consultation according to the inclusion criteria, collect case data for those meeting the criteria, and exclude those not meeting the criteria.

(3) Collect clinical and imaging data for patients, fill in clinical data according to the predetermined template form, upload it to the electronic data capture system (EDC), transfer imaging data DICOM files to our center, where researchers will extract imaging features using software, input them into the predictive diagnostic model, and obtain preoperative diagnostic predictions.

(4) During the mid-term phase, statistical analysis of data will be conducted at different time points, observing the model's predictive results. If necessary, phase optimization of the model may be conducted through discussion to further enhance clinical application value.

(5) Submit the independent validation set for final model prediction, then complete the writing of the article and publish academic results.

9. Preliminary Assessment of Project Risks and Benefits and Risk Control Plan (please describe the potential risks and benefits for researchers, subjects, and the medical institution when conducting this project; if there are risks, please introduce risk control measures and feasibility)

The main research outcome of this project is the establishment of a preoperative predictive model for jaw cystic lesions. The existing model has been validated, and statistical indicators prove its predictive efficacy is practically feasible and applicable in clinical settings. It can be considered for assisting differential diagnosis in difficult cases. Benefits mainly include patients achieving ideal survival outcomes, avoiding overtreatment, misdiagnosis, and missed diagnosis. In terms of risks, this project is a multicenter, prospective study, with the main risk being data leakage. The project team will strictly maintain confidentiality for all data used, ensuring that all data and related materials are not used for any other projects or purposes, and all data will not be

disseminated externally in any form before desensitization. Researchers commit to taking effective confidentiality measures in accordance with national laws, regulations, and relevant policies, and will not disclose data. If the contents of the commitment are violated, they will bear full responsibility for all consequences arising from it.

10. References

[1] Baumhoer D, Höller S. Zystische Kieferläsionen [Cystic lesions of the jaws]. Pathologe. 2018 Feb;39(1):71-84. German. doi: 10.1007/s00292-017-0402-x. PMID: 29322252.

[2] Effiom OA, Ogundana OM, Akinshipo AO, Akintoye SO. Ameloblastoma: current etiopathological concepts and management. Oral Dis. 2018 Apr;24(3):307-316. doi: 10.1111/odi.12646. Epub 2017 Mar 9. PMID: 28142213.

[3] Al-Moraissi EA, Kaur A, Gomez RS, Ellis E 3rd. Effectiveness of different treatments for odontogenic keratocyst: a network meta-analysis. Int J Oral Maxillofac Surg. 2023 Jan;52(1):32-43. doi: 10.1016/j.ijom.2022.09.004. Epub 2022 Sep 21. PMID: 36150944..

[4] Yoshiura K, Higuchi Y, Araki K, Shinohara M, Kawazu T, Yuasa K, Tabata O, Kanda S. Morphologic analysis of odontogenic cysts with computed tomography. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997 Jun;83(6):712-8. doi: 10.1016/s1079-2104(97)90325-5. PMID: 9195629.

[5] Neagu D, Escuder-de la Torre O, Vázquez-Mahía I, Carral-Roura N, Rubín-Roger G, Penedo-Vázquez Á, Luaces-Rey R, López-Cedrún JL. Surgical management of ameloblastoma. Review of literature. J Clin Exp Dent. 2019 Jan 1;11(1):e70-e75. doi: 10.4317/jced.55452. PMID: 30697397; PMCID: PMC6343988.

[6] Kreppel M, Zöller J. Ameloblastoma-Clinical, radiological, and therapeutic findings. Oral Dis. 2018 Mar;24(1-2):63-66. doi: 10.1111/odi.12702. PMID: 29480593.

[7] Yip SS, Aerts HJ. Applications and limitations of radiomics. Phys Med Biol. 2016 Jul 7;61(13):R150-66. doi: 10.1088/0031-9155/61/13/R150. Epub 2016 Jun 8. PMID: 27269645; PMCID: PMC4927328..

[8] Mayerhoefer ME, Materka A, Langs G, Häggström I, Szczypiński P, Gibbs P, Cook G. Introduction to Radiomics. J Nucl Med. 2020 Apr;61(4):488-495. doi: 10.2967/jnumed.118.222893. Epub 2020 Feb 14. PMID: 32060219; PMCID: PMC9374044.

[9] Avanzo M, Wei L, Stancanello J, Vallières M, Rao A, Morin O, Mattonen SA, El Naqa I. Machine and deep learning methods for radiomics. Med Phys. 2020 Jun;47(5):e185-e202. doi: 10.1002/mp.13678. PMID: 32418336; PMCID: PMC8965689.

[10] Binczyk F, Prazuch W, Bozek P, Polanska J. Radiomics and artificial intelligence in lung cancer screening. Transl Lung Cancer Res. 2021 Feb;10(2):1186-1199. doi: 10.21037/tlcr-20-708. PMID: 33718055; PMCID: PMC7947422.

[11] Alves DBM, Tuji FM, Alves FA, Rocha AC, Santos-Silva ARD, Vargas PA, Lopes MA. Evaluation of mandibular odontogenic keratocyst and ameloblastoma by panoramic radiograph and computed tomography. Dentomaxillofac Radiol. 2018 Oct;47(7):20170288. doi: 10.1259/dmfr.20170288. Epub 2018 Jun 5. PMID: 29791200; PMCID: PMC6196060.

[12] Meng Y, Zhang YQ, Ye X, Zhao YN, Chen Y, Liu DG. [Imaging analysis of ameloblastoma, odontogenic keratocyst and dentigerous cyst in the maxilla using spiral CT and cone beam CT]. Zhonghua Kou Qiang Yi Xue Za Zhi. 2018 Oct 9;53(10):659-664. Chinese. doi: 10.3760/cma.j.issn.1002-0098.2018.10.003. PMID: 30392221
[13] Valdivia ADCM, Ramos-Ibarra ML, Franco-Barrera MJ, Arias-Ruiz LF, García-Cruz JM, Torres-Bugarín O. What is Currently Known about Odontogenic Keratocysts? Oral Health Prev Dent. 2022 Jun 28;20(1):321-330. doi: 10.3290/j.ohpd.b3240829. PMID: 35866678.
[14]Huang CB, Hu JS, Tan K, Zhang W, Xu TH, Yang L. Application of machine learning model to predict osteoporosis based on abdominal computed tomography images of the psoas muscle: a retrospective study. BMC Geriatr. 2022 Oct 13;22(1):796. doi: 10.1186/s12877-022-03502-9. PMID: 36229793; PMCID: PMC9563158.
[15] Zhu Y, Yao W, Xu BC, Lei YY, Guo QK, Liu LZ, Li HJ, Xu M, Yan J, Chang DD, Feng ST, Zhu ZH. Predicting response to immunotherapy plus chemotherapy in patients with esophageal squamous cell carcinoma using non-invasive Radiomic biomarkers. BMC Cancer. 2021 Oct 30;21(1):1167. doi: 10.1186/s12885-021-08899-x. PMID: 34717582; PMCID: PMC8557514.
[16] Fang S, Wang Y, He Y, Yu T, Xie Y, Cai Y, Li W, Wang Y, Huang Z. Machine Learning Model Based on Radiomics for Preoperative Differentiation of Jaw Cystic Lesions. Otolaryngol Head Neck Surg. 2024 Apr 1. doi: 10.1002/ohn.744. Epub ahead of print. PMID: 38557958.