Official Title of the Study: ITHACA: Development and Validation of a Multivariate Predictive Model for Prognosis in Head and Neck Cancer Patients Undergoing Radiotherapy - Ambispective Study.

NCT Number: Not yet assigned

Date of the Document: 17/10/2024

Background and Rationale

The importance of targeted and personalized treatment in head and neck cancers is underscored by the variability of tumor locations in this region and the necessity of preserving critical functions such as chewing, swallowing, speaking, and breathing. A personalized treatment approach that integrates clinical, laboratory, and instrumental data into an advanced predictive model for assessing survival and toxicity represents a significant advancement in managing head and neck cancers.

Radiomics plays a crucial role in this approach by extracting detailed morphological and biological information from radiological images, allowing for a more in-depth understanding of tumor pathology. Similarly, dosiomics provides valuable data on radiation dose distribution, aiding in treatment optimization and predicting potential side effects. By integrating radiomics and dosiomics, this study aims to enhance treatment outcome predictions while improving the management of associated toxicities, particularly those that impact patients' quality of life.

The ITHACA model seeks to incorporate a comprehensive range of data, including clinical parameters such as tumor stage, risk factors, and previous treatment responses, alongside radiological and dosimetric data. This holistic approach enables more precise predictions and facilitates more effective treatments tailored to individual patients.

Objectives

The study aims to develop and validate a multivariate predictive model for predicting:

1. Cancer recurrence
2. Survival
3. Treatment-related toxicity in patients with head and neck cancer

---

Materials and Methods

Study Design

- Type: Multicenter ambispective observational study utilizing clinical, laboratory, and instrumental data.

Study Population

- Inclusion: Consecutive patients with a histologically confirmed diagnosis of head and neck cancer.

Study Duration

The study is expected to last 10 years, beginning after ethics committee approval, with:

- Retrospective recruitment period: 2013–2023
- Prospective recruitment period: 2024–2034

Eligibility Criteria

Inclusion Criteria

Participants must meet all of the following criteria:

- Confirmed Diagnosis: Histologically confirmed head and neck cancer.
- Age: ≥ 18 years (adult patients).
- Complete Data Availability: Clinical data must include treatment details, follow-up information, and outcomes.
- Medical History: A comprehensive record of comorbidities and relevant medical background.

Exclusion Criteria

- Incomplete Data: Patients lacking essential clinical data for analysis.

Endpoints

Primary Endpoint

- Cancer Recurrence: Probability of recurrence after completing radiotherapy.

Outcome Evaluation Methods

- Evaluation Timing: 3, 6, 12, 24, and 36 months post-treatment.
- Methods: PET-CT, MRI, and CT scans to detect signs of recurrence.
- Clinical Documentation: Review of medical records to confirm recurrence episodes.
- Event Reporting: Inclusion of events identified during follow-up or reported by clinicians.

Secondary Endpoints

1. Overall Survival: Duration from the start of radiotherapy until death.
2. Disease-Free Survival: Time from completion of radiotherapy to cancer recurrence or death.

3. Treatment Toxicity: Incidence, type, and severity of acute and late radiotherapy-related toxicities.

Secondary Outcome Evaluation Methods

1. Regular Follow-up: Clinical assessments and radiological investigations to track health status and toxicities.
2. Data Recording: Use of clinical databases to monitor survival, disease progression, and toxicities.

Variables and Procedures

Clinical Variables

- Tumor Stage: Classified using the TNM system.
- Treatment Details: Radiotherapy, chemotherapy, and/or surgery specifics.
- Demographics: Age, sex, ethnicity.
- General Health & Comorbidities: Charlson Comorbidity Index or similar assessment tools.
- Risk Factors: Tobacco use, alcohol consumption, HPV exposure.
- Oncological History: Previous cancer diagnoses and prior oncological treatments.

Radiological Variables

- Pre-Treatment Imaging: Tumor size, adjacent tissue involvement, presence of lymph node metastases.
- Treatment Response: Tumor and lymph node changes, metabolic response in PET-CT.
- Recurrence Indicators: New lesions or changes in existing lesions.
- Post-Treatment Effects: Anatomical and tissue alterations caused by radiotherapy or surgery.

Radiomics Analysis

Radiomics analysis involves extracting quantifiable characteristics from radiological images to identify patterns associated with recurrence, survival, and toxicity.

Timing of Measurements

- Baseline: Collection of clinical, radiological, and radiomics variables before treatment.
- During Treatment: Monitoring tumor response and toxicities.
- Follow-Up: Evaluations at 3, 6, 12, 24, and 36 months post-treatment.

Dosiomics Variables

Dosiomics variables provide quantitative insights into the radiation dose delivered during treatment. These parameters help optimize planning and assess side effect risks.

Key Aspects of Dosiomics Variables

1. Dose Distribution: Measurement of spatial radiation dose distribution.
2. Dose-Volumetric Parameters: Correlation of radiation dose with tissue volume.
3. Heterogeneity Indices: Quantification of dose heterogeneity within the target area.
4. Toxicity Risk Assessment: Evaluating potential side effects based on radiation dose and tissue sensitivity.

References

1. Miccichè F, Chiloiro G, Longo S, Autorino R, Massaccesi M, et al. Development of a prognostic model of overall survival in oropharyngeal cancer from real-world data: PRO.M.E.THE.O. *Acta Otorhinolaryngol Ital*. 2022;42(3):205-214. doi: 10.14639/0392-100X-N1672.
2. Yu H, Ma SJ, Farrugia M, Iovoli AJ, Wooten KE, et al. Machine Learning Incorporating Host Factors for Predicting Survival in Head and Neck Squamous Cell Carcinoma Patients. *Cancers (Basel)*. 2021;13(18):4559. doi: 10.3390/cancers13184559.
3. Marcu DC, Grava C, Marcu LG. Current Role of Delta Radiomics in Head and Neck Oncology. *Int J Mol Sci*. 2023;24(3):2214. doi: 10.3390/ijms24032214.
4. Placidi L, Gioscio E, Garibaldi C, Rancati T, Fanizzi A, et al. A Multicentre Evaluation of Dosiomics Features Reproducibility, Stability and Sensitivity. *Cancers (Basel)*. 2021;13(15):3835. doi: 10.3390/cancers13153835.
5. Ghanati H, Madathil S, Al-Tamimi M, Al Asmar Z, et al. Methodological Issues with Head and Neck Cancer Prognostic Risk Prediction Models. *Community Dent Health*. 2023;40(4):252-260. doi: 10.1922/CDH_00015Ghanati09.