Risk stratification and prediction of locoregional recurrence in OSCC: the OraMod project up-dates and refines the NeoMark project results

NeoMark
FP7-ICT-2007-2.5.3-ICT-224483
ICT enabled prediction of cancer reoccurrence

OraMod
FP7-ICT-2013-10-VPH-611425
VPH based predictive model for oral cancer reoccurrence in the clinical practice
Collaborative project
36 months

Project coordinators
Prof. Enrico Sesenna
Prof. Tito Poli
IT-UNIPR
Dept. S.Bi.Bi.T.

Scientific coordinator
Prof. Tito Poli
IT-UNIPR
Dept. S.Bi.Bi.T.

Technical manager
Augusto Ruggieri
IT-OneToNet

Involved partners

- **Pilot clinics**
  - IT-NL-DE

- **Research Centres**
  - DE-FI

- **Technical Partners**
  - IT-EL
## The OraMod Consortium

<table>
<thead>
<tr>
<th>Partner</th>
<th>Role</th>
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<tbody>
<tr>
<td>Università degli Studi di Parma UNIPR (IT)</td>
<td><strong>Pilot Health Institution</strong>: Project and Scientific Coordination; responsible for IPRs and Dissemination strategy, Clinical and Impacts Assessment, Clinical Study Execution. Involved in all WPs.</td>
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<tr>
<td>Stichting VU - VUmc (NL)</td>
<td><strong>Pilot Health Institution</strong>: developer of the Model; responsible for Clinical Protocol, Study Design and Clinical Assessment; contributor to Clinical Study Execution and Impacts Assessment. Involved in all WPs.</td>
</tr>
<tr>
<td>Heinrich-Heine Universitaet Duesseldorf - UDUS (DE)</td>
<td><strong>Pilot Health Institution</strong>: responsible for Ethical aspects, contributor to Clinical Study Execution, Clinical and Impacts assessment. Involved in all WPs.</td>
</tr>
<tr>
<td>Teknologian Tutkimuskeskus - VTT (FI)</td>
<td>Research Institution; leader for the Clinical Impacts Assessment; contributor to evaluate usability aspects (WP2, WP5, WP7) and to WP8</td>
</tr>
<tr>
<td>Fraunhofer IGD (DE)</td>
<td>Technical R&amp;D partner; responsible for the Image Analysis Suite and Features Extraction Tool. Involved in WP1, WP2, WP4, WP6 and WP8</td>
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<tr>
<td>STMicroelectronics Srl (IT)</td>
<td>Technology Industry; developer of the qRT-PCR and lab-on-chip device; Exploitation Manager and responsible for products certification roadmap. Involved in WP6 and WP8</td>
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<td>Velti Kainotomes Epixeiriseis Anonimi Etaireia Kefalaioi Epixeirimatikon Simmetoxon kai Ependiseon - VCI (EL)</td>
<td>IT Company; developer of the Knowledge Assisted Visualization Tool, of the Simulation Environment and Virtual Tumour Board tools. Involved in WP2, WP5, WP7 and WP8</td>
</tr>
<tr>
<td>OneToNet Srl (IT)</td>
<td>Provider of the Platform infrastructure (ClinicalHub); Technical Manager, and responsible for the System Design; leader of the platform integration WP6. Involved in WP1, WP2, WP5 and WP8</td>
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To converge the technology and scientific breakthrough from research into clinical practice by developing a novel, modular and integrated ICT environment aimed to supporting key aspects of the clinical management of oral cavity cancer patients:

**Objective**

Pre-Surgery
Risk stratification

Improve the identification of high-risk patients at diagnosis

**PERSONALIZED TREATMENT**

Post-Surgery
Risk stratification

Re-assess individual patient’s recurrence risk prediction after treatment and remission
Head and neck cancer (HNSCC) is the seventh cancer for incidence worldwide (WHO): oral squamous cell carcinomas (OSCC) account for at least 25% of HNSCC.

- Low survival rate: 50% of patients die within five years from diagnosis.
- Increasing number of patients who seem reach complete remission after treatment, present a poor outcome within 5 years.
- The incidence trend is growing especially in the younger population.
- The biological behaviour of such cancers is often un-predictable and current risk stratification models may neglect high-risk cases.
- Disease relapses are frequent (ranging 10-25% of cases).
- The treatment of OSCC is extremely invasive.
Healthcare Problem #2

Clinicians’ needs

- Tools to allow a more precise stratification of patients at diagnosis aiming to personalized therapy
- Objective evaluation of parameters and risk factors bypassing the human bias
- Availability of point-of-care diagnostic instruments (RT-PCR) and predictive tools (mobile device support)
- Integration of genomic factors in the predictive model (at affordable costs)
- Availability of all data for case study to the multidisciplinary team of clinicians-researchers involved in OSCC treatment
- Possibility to include new research findings to model risk prediction and perform risk stratification simulations
Healthcare Problem #2bis
Clinicians need answers

- Locoregional reoccurrence and survival
  - TN staging and histopathology inappropriate for risk assessment
  - Which patient needs post-operative radiotherapy?
  - Which patient needs post-operative chemoradiation?
  - Which patient requires more frequent follow-up?

- Overtreatment should be prevented
  - Toxicity and reduced quality of life
  - To save treatment options for recurrent and second primary tumors
Significant progress on cancer predictive models, (breast, lung, prostate, colon, etc.), BUT OSCC remains less investigated due to relatively low incidence and high-variability of disease presentation

- Literature data propose several biomarkers to predict reoccurrence, survival and N stage in OSCC patients.
- Since 2000, single center prognostic model prototypes have been proposed, encouraging in perspective but not yet actively applied in the treatment of oral cancer.

However, these studies have NOT YET BEEN ABLE to produce an accurate model to predict OSCC reoccurrence.
Tumor recurrence prediction

Online: Leiden Prognostic HNSCC Model Version 2.0

Chart

Leiden prognostic HNSCC model version 2.0

Variables

- Age
- N
- M

Information

Software by: LUMC - Medical Statistics and Bioinformatics - H. J. van der Wijk
Tumor recurrence prediction

Online: Leiden Prognostic HNSCC Model Version 2.0
Today scenario

Current decision making approach for OSCC treatment (NCCN Guidelines)
OraMod scenario

OraMod future clinical decision scheme
The OraMod progress beyond State of Art

- Introduction of innovative techniques for:
  - genomic data collection (RNA sequencing, RNA extraction from paraffin-embedded biologic specimens, genomic data analysis using the portable qRT-PCR device)
  - automatic features extraction from imaging (lymph-node segmentation, image fusion) and research findings (i.e. genomic markers) included into the decision-making process

- Fostering a collaborative case management approach, in line with the new trends of multidisciplinary treatment (the Virtual Tumour Board).

- Reduction of the intra-observer variability of data interpretation by introducing "objective" data analysis mechanisms able to present the individual patient's predictive factors in an unbiased way
How OraMod builds up on existing knowledge

- Known biomarkers (i.e. genomics)
- Current clinical prognostic factors
- Front-edge VPH models (NeoMark)
- OraMod model
The OraMod Platform

Pre-surgical risk assessment

Post-surgical risk assessment

Features Extraction

Image Processing

Image data

Genomic data

Clinical Data

Reoccurrence Risk

OraMod Predictive Model

Interactive Simulation Environment

Optimal Treatment Plan

Virtual Tumor Board

Optimal Follow-up Plan

Multi-layer Data Visualisation

Multi-layer Data Visualisation

Multi-layer Data Analysis

OraMod Predictive Model

Interactive Simulation Environment

Multidisciplinary medical team

qRT-PRC

Surgery outcome

Multi-layer Data Analysis
Multidisciplinary approach

Treatment of patients affected by OSCC is conducted with a multi-modal approach decided within a multidisciplinary team.

- Maxillofacial Surgeons
- Radiation Oncologists
- Medical Oncologists
- Pathologists
- Molecular Biologists
- Nuclear Medicine Physicians
- Clinical Internists
- Radiologists
Gene selection

**Phase I**
- Microarray data
  - NeoMark + VUmc data
  - Selection of 60 genes for outcomes variables:
    - Overall Survival (20 genes)
    - Local and/or Regional Recurrence (20 genes)
    - N-Stage (20 genes)

**Phase II**
- TaqMan RT-qPCR
  - 60 genes from Phase I
  - Platform transition: Technical validation
    - Model training
      - Including other predictive parameters (independent cases, >2 yrs follow-up)
    - Further selection predictive geneset (12 genes)

**Phase III**
- Lab-on-chip RT-qPCR
  - Final model: geneset from Phase II + other predictive variables
  - Prospective enrolled cases
  - Assessment predictive value in independent cohort
Gene selection

Two independent DNA Microarray studies of HPV-negative oral cancer patients (total n=249) were used for gene selection.

Univariate and multivariate tests were performed to select genes related to Overall Survival, Locoregional Recurrence and/or Nodal metastasis.

From the microarray data, 60 genes were chosen for further analysis, of which 20 were associated with Overall Survival, 20 with Locoregional Recurrence and 20 with the presence of Nodal metastasis.
## Gene selection

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| Reserve list |                        |          |                              |
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| 6            | A_24_P281913 MLL         | 6        | SEC11L1 A_23_P380917         |
| 7            | A_23_P26511 GDPD3        | 7        | LARP6 A_23_P117782           |
Gene selection

- These genes were transferred to an RT-qPCR platform that is more stable, user-friendly and widely applied, which will favour clinical implementation.

- For further gene selection on this platform, the genes were tested on 20 cases for which the DNA Microarray data were available and 20 independent cases.

- In total 54 genes showed promising results, and 6 genes had to be substituted (total 60 genes).
The OraMod prognostic signature of 60 genes selected from DNA Microarray analysis, transferred to an RT-qPCR platform, improved by *ad interim* analysis, was validated on 125 independent oral cancers to improve N-staging and outcome prediction.

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