HANARTH FONDS

Complete Research Proposal

Name project:	**Genomics-assisted radiomic machine learning-based models to enable patient outcome prediction for personalized treatment in head and neck squamous cell cancer**
Name applicant:	**Prof. Dr. Michiel W.M. van den Brekel, M.D., PhD. (see supplementary file 1: Change_in_Principal_investigator.pdf)**
Date completed:	**07-06-2021**

PROJECT DETAILS

Name Research Proposal
Genomics-assisted radiomic machine learning-based models to enable patient outcome prediction for personalized treatment in head and neck squamous cell cancer

Have you previously submitted an application with the Hanarth Fonds and if so when and where?
Yes, in 2020, with Martijn Stuiver as principal investigator, on the use of biosensors in head and neck chemoradiation patients. Submittion was rejected

Type of research
Oncoradiogenomics

Is your application also submitted with another institute and if yes, please insert name of institute
No

Please include names of (minimal) 2 external references (both in the area of oncology as Artificial Intelligence, outside your own research institute). Optional: contact details
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Applicant
Name
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Netherlands Cancer Institute (NKI)

Do you have a permanent appointment at this institute?
Yes

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SUMMARY OF THE PROPOSAL

Background

Squamous cell carcinoma of the head and neck (HNSCC) is a heterogeneous group of cancers that accounts for approximately 3% of all cancers in the Netherlands (1,2). Resection by surgery, radiotherapy and cisplatin-based chemo-radiotherapy are the current curative treatment options for this patient population. Advanced stage HNSCC patients have, however, a rather poor prognosis. These patients are often primarily treated by chemo-radiotherapy to allow organ preservation. An average 5-year overall survival (OS) below 50% however underpins the unmet need for more effective and personalized treatment (3). Outcome predictors are particularly important in this context, since half of the patients do benefit from standard treatment while alternative treatments are required for the other half.

The risk for HNSCC is strongly associated with alcohol and/or tobacco abuse which promotes tumorigenesis through carcinogen-induced gene mutations in the exposed mucosal layers of the upper aero-digestive tract. Previous infections with high-risk human papilloma virus (HPV) variants also constitute a strong risk factor for HNSCC, resulting in a subgroup of HPV-positive (HPV**+**) HNSCC. These HPV+ tumors predominantly arise in the oropharyngeal region and are, genetically and molecularly, highly dissimilar from HPV-negative (HPV)(2).

HNSCC is a highly heterogeneous tumor group, complicating the development of accurate outcome predictors. Indeed, there is still a notable lack of strong clinical or radiologic predictors of outcome (2,3). The exceptionally good prognosis associated with HPV-positivity and the distinct biology led to the recognition of HPV**+** HNSCC as a distinct entity in recent years (2). In addition to HPV status, several tumor characteristics, like tumor volume contribute to outcome prediction in HNSCC, including those generated by radiomics-based methods on CT images (4). However, predictive models have not yet led to more personalized treatment protocols.

In contrast, the predictive value of a series of genetic biomarkers that are assessed on pretreatment tumor biopsy material has been repeatedly validated (5). Biological parameters such as hypoxia, EMT and genetic heterogeneity, have been shown to be independent and important factors in outcome prediction in this patient population (4,6). Yet, translation to routine clinical practice is hampered by the invasiveness of the procedure, standardization issues, costs and test result duration. Thus, non-invasive methods that are able to depict such prognostic tumor biology would significantly advance outcome prediction and treatment in these patients.

Recent studies show the potential of radiomic features and models to reliably distinguish HPV**+** from HPV**-** tumors or to determine the extent of hypoxia (7-8), thereby also demonstrating that such biological parameters can influence the appearance of a tumor on radiologic images. With a main focus on Computed Tomography (CT) imaging, the combined analysis of genetic features and quantitative image analysis features, also termed radiogenomics (9), has been increasingly investigated over the last decade. However, to better discern the heterogenous tumoral tissue, MRI is used in routine practice. It is reasonable to assume that MRI would provide more information about the (functional) properties of the tissue that are possibly linked to the genetic, molecular and micro-environmental make-up of the tumor.

Research (preliminary data)

The Head-and-Neck Group at the NKI has a long track record of biomarker research for treatment outcome prediction in HNSCC. In recent years, we conducted multiple biomarker studies to explore the prognostic value of different genetic, radiological and clinical markers and performed DNA/RNA-sequencing on pretreatment tumor specimens in retrospective studies. Given the poor prognosis and lack of reliable prognostic clinical and radiologic factors, studies were focused on advanced HPV-negative HNSCC and revealed the importance of several biological factors in determining outcome in this patient population. Frequently observed in HNSCC, tumor hypoxia strongly affects radiosensitivity, resulting in strong outcome association of multiple hypoxia biomarkers with outcome (Sup-Fig.1)(2,5). Comparing the prognostic value of gene expression signatures for acute and chronic hypoxia, we find a stronger association with poor outcome using the acute hypoxia biomarker for patient classification (5), underlining the need to also incorporate such markers for improved outcome prediction. DNA repair defects and chromosomal instability related features, as determined by DNA repair gene mutations, genomic scar-based methods or by copy number variation signatures, were also consistently associated with poor prognosis (10-11).

Using machine learning techniques and functional endpoints from cellular studies, additional DNA repair defect predicting models were generated that predict outcome in advanced HPV-negative HNSCC patients

after (chemo)radiotherapy treatment (Sup-Fig.1-2)(5,12). Performance of these RNA expression-based models in predicting repair defects was validated in external data sets and its association with poor prognosis in two independent cohorts (5). Machine learning also supported the generation of an HNSCC-specific EMT (endothelial mesenchymal transition) prediction model that robustly predicted poor prognosis for patients with mesenchymal tumors that are also associated with an increased risk for metastasis (Sup-Fig.1 and (6). Together, our studies reveal that hypoxia, DNA repair, stem cell-ness and EMT are important and independent biological factors for outcome prediction (5). Restricting their clinical application, they however rely on limited and invasive tumor material collection.

In contrast, MRI is an integral part in the diagnostic flow of each patient. CT-radiomics-based models have shown limited success in HNSCC outcome prediction (4). MRI might be better suited and has already been established as a feasible option. Further supporting radiogenomic integrated approaches using MRI, our functional imaging studies, conducted under guidance of Prof. Dr. Castelijns, show a role for MRI image analysis in HNSCC outcome prognosis (7). We showed outcome associations with selected MRI features and developed models that identify the HPV-status in HNSCC (Sup-Fig.3)(7). Aiming to classify patients for treatment optimization further, we combined functional imaging techniques of MRI and 18F-FDG-PET, and found several parameters to be predictive of local recurrence–free survival and/or overall survival (Sup-Fig.4)(13).

Since 2010, all HNSCC patients are imaged by MRI at diagnosis or pretreatment supporting the high number of suitable MRI data for this study that amounts to over 200 CRT-treated patients. Our previous research in HPV-negative patients treated with CRT, generated extensive RNA sequencing data for biomarker-based tumor classifications for 50% of these suitable MRI-selected patients, in addition to HPV-positive and surgically treated cases that have also been analyzed.

Plan of Investigation

The ultimate goal is to use non-invasive and rapid MRI-radiomics for outcome prediction models in advanced HNSCC patients. The limited number of HNSCC cases, however, combined with the considerable heterogeneity within HNSCC with respect to (prognostic) clinical and genetic factors, greatly hampers machine learning-based radiomics approaches that train models solely based on outcome association. We therefore propose to increase the performance of such models by linking tumor biology characteristics, as captured by the genomic data, with radiomics. Accordingly, with the help of existing biomarker data, we aim to generate MRI-based radiomic prediction modelsfor outcome-relevant biological parameters first. Using machine learning technologies, these models will be guided by prognostic biomarker-based classifications of these tumors that have been previously established by us. With this we aim to harness their link to outcome. This will be followed by outcome association studies to determine and optimize the performance of these models with respect to patient outcome prediction which can be further developed and validated in patients and databases without biomarker classifications.

Given the relevance, our studies will focus on standard CRT-treated advanced HPV-negative HNSCC. Tumor biology and genetics of HPV-positive is distinct from HPV-negative HNSCC. Our studies also revealed an important disparity in the outcome association of the individual gene-expression-based biomarkers in the HPV-positive, such as for immune markers (in 5) or repair defects (unpublished and 10), further supporting the notion that they are to be handled as a different entity. To reduce the heterogeneousness of the training cohort and because of the largely different prognosis of these HPV-positive HNSCC cases, they will be excluded in this study.

Different strategies will be employed to generate radiomic-based models associated with the prognostic genetic biomarker classifications (Sup-Fig.5 and project description below). For this purpose, we will source our extensive retrospective HNSSC genomics and MRI radiomics databases to amass several distinct cohorts using different predetermined criteria according to the different study objectives (Sup-Fig.6).

MR imaging and processing were as detailed in Sup-Fig.3,7-8 and published in Bos et al (7). Images were acquired in routine pretreatment clinical workup at a 1,5 or 3 tesla MR system and using a standard head and neck coil. Several patients have two pretreatment MRI scans available for diagnostic and CRT-planning purposes. When feasible, both scans will be used. MR imaging parameters and sequences in the resulting MRI-radiomics study patient cohorts are as listed in Sup-Fig.8 and encompass STIR_T2W, SPIR_T2W, T1W, DWI, 3D T1W+C, T1W_TRA+C from diagnostic or radiotherapy planning MRI. Tumor volume delineation on 3DT1W+c will serve for linear image registration and functional DWI will be delineated separately.

In addition, we will conduct a prospective study using surgically resected material from selected patients that aims to strengthen the link of the individual radiomic features or biology prediction models with the biological endpoints. These bioinformatics studies will be conducted in collaboration with Dr. C.Vens and follow previously applied protocols and classifications methods as published (5-6).

Relevance for cancer research

Over the last decade, diagnostic radiology-based outcome prediction by radiomics-based models has increasingly become the focus of recent research that led to promising results, particularly in the head and neck area (4,9,14-15). As the use of these computer-derived quantitative features with any form of artificial intelligence (AI) is becoming more apparent, this will feasibly change the current landscape of clinical radiology to a more AI-integrated field.

Early radiogenomic studies, combining radiomics with genomic components, that used CT or PET data show promise in identifying HNSCC tumor biology (7,16-19. Moving forward however, more accurate outcome prediction models are needed. Superior to CT, MRI however provides more extensive tissue information and is therefore more likely to depict tumor biology such as heterogeneity features that may be linked to genetic instability or features that are linked to hypoxia, EMT or the tumor micro-environmental context (3). Several anatomical scan sequences can be used and MRI is also able to assess tissue microstructures (i.e. cellularity, necrosis, stroma, hemorrhage) using functional imaging techniques like diffusion weighted sequences (DWI).

Linking tumor biology identified by genetic biomarkers to radiology features also enables subsequent studies into the role of the respective biology in HNSCC in general, for treatment response or other treatment options such as immunotherapy. Such radiomic-based models enable the study of different areas within a tumor or, conversely, assisted by the here generated heatmaps, can also determine the volumetric contribution of the individual biological parameters. Presuming high accuracy level, fresh biopsy specimens will not be needed, thereby enabling larger series for other studies into the role of these biologic factors, as also proposed here for validation of this study. Other research areas will profit from such models as the accurate identification and delineation of radioresistant areas (i.e. hypoxic) within a tumor could assist tumor dose intensification strategies or alternative treatment strategies. After adaptation, such models might be usable in other cancer types as well. MRI-based biology prediction models also allow the determination of the spatial distribution of the respective biology and of the changes over time in longitudinal studies during treatment (2). These could further provide mechanistic insights into the role and response behavior of the analyzed genetics and tumor biology.

Use of Artificial Intelligence

For complex cancer types like HNSCC, the integration of multiple data sources for machine learning (ML) generated models (i.e. genomics, MRI and clinical variables) will revolutionize the development of predictors, provide better insights into potential connections and play a key role in optimization methods. As outlined above, this project follows two in parallel conducted strategies to create different outcome prediction models with the help of classifications by genetic biomarkers with a proven outcome association (Sup-Fig.5).

Preceding ML application, the data will be (pre)processed using standard pipelines. Gene expression data analyses and tumor classifications / biomarker scores of the retrospective training cohort have been already conducted in previous research and will be similarly applied in the prospective study (5) MRI data areyet to be processed. After delineating the tumors and preprocessing image data by normalizing signal intensity and standardizing voxel size, radiomic features will be extracted using the open-source package PyRadiomics. This will include first order features, texture, intensity, shape and filter-based features. The stabilityof the different radiomics features will be tested using a one-way Anova model to identify features that are not comparable due to strong intra-observer variability.

Selected features will be used to build a radiomic-based prediction model for tumor biology based on genomic biomarker classifications and to create genomic-based heatmaps. Due to the large number of radiomics features extracted, different methods leading to feature selection will be applied. Methods such as regularization methods (LASSO and Elastic net) as well as non-parametric machine learning approaches (random forest, support vector machines and neural networks) will be prioritized as they showed promise in building predictive models when also using genetic features (10).A nested cross-validation approach will be used to minimize overfitting and to obtain proper hyperparameters. After radiomic feature acquisition and selection, the following two defined ML strategies will be conducted.

Strategy I: Generation of genomics-guided radiomic models. The genetic data will be used to build a classifier in three distinct ways, as there are only a limited number of patients available to test and validate on. The first applies the biomarkers on an individual basis. However, since the combination of the biomarkers renders a more precise predictive value (4), the second incorporates several biomarkers together (Sup-Fig.5). Thirdly, we will make use of all the biomarkers' predictive value combined to an individual prognostic score for each patient.

Strategy II: Genomics-linked radiomic models. The second strategy will make use of multitask learning to integrate selected different prognostic biomarkers and MRI features at the same time and will generate profiles into voxel-wise regional heatmaps. As part of the prospective trial, patients with primary resectable tumors are analysed pre-treatment using the developed heatmap model. This will yield a better understanding of the relationship between the biomarkers and radiomics features. Associations will be tested with the global test allowing for multivariate association testing. Such an approach, unlike univariate testing, has a minimal multiple testing burden, increasing the power of detection of such associations.

Relevance to the patient

Advanced stage HNSCC are treated with platinum-based chemoradiotherapy. In spite of this intensive treatment, some 30%recur locoregionally and distant metastases develop in 20% of the patients. Chemoradiotherapy causes a series of treatment related side effects preventing treatment intensification as cisplatin dose limiting toxicities occur in 50% of the patients (3). This toxicity appears unacceptable but an overall 50% cure rate and organ sparing for improved quality of life outweighs these risks. In the realm of personalized treatment and precision medicine in this patient population, accurate outcome prediction models are therefore badly needed to enable the prediction of these events on an individual basis.

This project is expected to generate i) a strong and robust MRI-based outcome prediction model and ii), in doing so, MRI-radiomics based models predictive for different tumor biology parameters that are relevant to outcome. If successfully established, risk scoring from both, outcome and tumor biology prediction models, would have various benefits for these HNSCC patients. Importantly, an accurate prediction of treatment failures allows deviation from standard treatment. This would minimize side effects from futile treatment attempts with cisplatin and provide opportunities for alternative or experimental treatments. Surgery with or without post-operative (chemo)radiotherapy, the use of different radiosensitizers or neoadjuvant immunotherapy are among the many alternative options available that will ultimately increase the likelihood of treatment success for the individual patient.

In addition, a high recurrence risk, as assessed by such predictive models, may prompt careful treatment follow up and intensified monitoring for early recurrences. Currently, follow-up consists of laryngoscopy and routine MRI/PET-CT, combined with biopsies when needed, to screen for possible tumor recurrence. Ergo, accurate poor prognosis prediction by such models would justify early or frequent imaging or additional invasive procedures for biopsy material collection.

In contrast to methods that require the collection of specimens for outcome prediction, imaging-based predictors minimize invasive procedures that can cause morbidity and complications. Representative biopsy specimens are also not always easy to obtain. A major issue with genomic-based biomarkers is that they are time consuming, expensive and labor-intensive. The implementation into routine clinical diagnostic procedures, of gene expression-based biomarkers in particular, has been also obstructed by difficulties to automate and standardize procedures and to benchmark analysis results for robust model prediction scores and classifications. Non-invasive MRI radiomics based prediction models, in contrast, would make use of routinely applied imaging, thereby limiting costs and the burden on the patient from additional procedures.

Harnessing tumor biology information for selection among different adjuvant or neo-adjuvant drug combination treatment options, subsequent future studies may further evaluate the value of such novel MRI-radiomics-based models for differently treated patients. Finally, the use of such models has also the potential to improve survival in this patient population by revealing targetable biology or tumor vulnerabilities (such as hypoxia and DNA repair defects) for directed treatment. Together, the MRI-based prediction models will, in time, guide monitoring of early recurrences while also aiding in the selection of the most advantageous treatment option for the individual patients.

PROJECT DESCRIPTION

Aim of the study

The primary aim of this project is to generate prognostic MRI-radiomics based prediction models for advanced HNSCC patients. This is to enable personalized treatment for those patients for whom standard treatment is predicted to fail. The comparatively low number of cases, the clinical, pathological and molecular heterogeneity and the heterogeneous treatments hamper the generation of machine learning assisted radiomic features-based outcome prediction models in HNSCC. Here we propose the integration of biomarker data, with proven prognostic value and encompassing HNSCC heterogeneity to a great part, to support model training and improve outcome association for chemo-radiotherapy-treated patients.

A secondary aim is therefore to also establish radiomic profiles linked to relevant tumor biology by association with available prognostic genomics biomarkers. As such they may be prognostic but do also have the potential to greatly advance biology-guided outcome predictions that, to date, are restricted to the availability of suitable biopsy material and expensive molecular assays. Information on spatial distribution of such biology and on changes over time in longitudinal studies are expected to be highly valuable with respect to outcome association and, hence, primary treatment choice.

Part of the diagnostic flow, MRI is more suited than CT for the evaluation of soft tissues and these images are readily available for retrospective studies. Harnessing the improved representation of tissue feature complexity, many projects at the NKI aim to apply AI techniques using MRI imaging, e.g. to accelerate workflows and adapt treatment in MRI-guided treatment systems (20 Importantly, as shown by our recently published preliminary studies, MRI features (ADCGTV, ADCmean, Ktrans, Ve and D*) can be associated with outcome in this patient population (Sup-Fig.4)(13). Individual MRI features have been also successfully associated with gene expression-based biomarkers, such as hypoxia, further supporting MRI-based strategies (8). Genetic heterogeneity markers and stromal contribution are other tumor biology characteristics that are likely to be reflected by particular MRI feature profiles. Our own studies show the success of machine learning assisted models that determine HPV-status on MRI images in HNSCC (Sup-Fig.3)(7). Image pre-processing and feature selection workflows for MRI-based radiomic studies have been established, providing a large in-house database of suitable pretreatment images (n>300)(Sup-Fig.6).

Only few clinical and pathological factors are prognostic in the advanced and chemo-radiotherapy treated HNSCC setting. Negative HPV-status and greater tumor volumes are associated with poor prognosis (2). Low cumulative cisplatin doses do also diminish overall survival; while the impact of tumor site and other factors is comparatively small (5). This further reinforces the need for novel prognostic markers in this setting.

Large MRI-based radio-genomics studies have not been conducted in HNSCC so far. Facilitated by a large biobank from routine collection of tumor biopsy material, extensive genomic data are already available for this patient group at the NKI (n=256). Studies conducted by Dr. Vens and Dr. vd Brekel revealed multiple genetic markers, established and novel, that are significantly associated with outcome in this chemo-radiotherapy treated advanced HNSCC patient population, many after applying machine learning techniques to generate or improve tumor biology association (5,6,10-12). Among the most robust and relevant for patient outcome are markers for hypoxia, mesenchymal properties (EMT), chromosomal instability and DNA repair defects (Sup-Fig.1-2)(5, 10). Overall, gene expression-based biomarkers were superior to those based on gene mutation or copy number variation analysis (5,12). Notably, while patient outcome trained models did not perform well in validation cohorts, the tumor biology-trained did. Here, we aim to follow a similar tactic and take advantage of these biomarker associations with outcome by integrating the most important tumor biology parameters as assessed by the genomic markers for MRI-based prediction model generation. If successful, this would ultimately alleviate the need for biopsies.

The intention is to use the available MRI data with matched biomarker classifications from retrospective studies for model generation (GENRAD cohort). In a prospective study (ExRADGEN) we will collect specimens from resection material that will be matched to MRI profiles to further improve tumor biology linkage. Chemo-radiotherapy (CRT) outcome associations will be tested using retrospective data (CRT-GENRAD) and validated in those devoid of genetic data (NKI-CRT-RAD). Performance of the best MRI-feature based model will be determined using several validation cohorts (Sup-Fig.6) from the Free University Hospital (VU-CRT-RAD) and from publicly available databases (The Cancer Imaging Archive, TCIA).

Plan of Investigation

In contrast to conventional radiogenomic studies in which all genomic and radiomic features are combined, here we use genomic information with a link to tumor biology that proved to be prognostic in the patient population of interest to educate MRI-based radiomics.

Retrospective patient data selection: Criteria for inclusion in retrospective studies (NKI-CRT-RAD) are advanced HPV-negative HNSCC, definitive cisplatin-based chemo-radiotherapy treatment and availability of suitable MRI data. Important exclusion criteria are distant metastasis at diagnosis and discontinuation of treatment other than cisplatin. A minimum of 3 years follow-up data will be required for data to establish outcome associations since 90% of progression free survival events will have occurred within that time in HNSCC. Tumor biology linkage studies (i.e. GENRAD, ExRADGEN) require RNA-sequencing data from pretreatment biopsy or resection material with suitable pretreatment MR images (Sup-Fig.5-6).

Data resources and processing:
Biomarker data: As outlined above, previous studies produced genomic and gene expression data for over 190 chemo-radiotherapy treated advanced HPV-negative HNSCC patients. Gene expression-based classifications are available for all these patients (Sup-Fig.1,5) (5) and provide probability scores for the respective tumor biology. Selected biomarkers for initial analyses are: hypoxia (which depicts hypoxic tumors), EMT (which provide an assessment on the epithelial vs mesenchymal scale) and DNA repair/chromosomal instability related (which can drive tumor heterogeneity) (Sup-Fig.1) (5), followed by markers for proliferation and immune cell infiltration.

MRI radiomics data: Radiological data will be processed according to Sup-Fig.3 and 5 and as outlined above. In brief, radiomic features will be extracted using the latest version of PyRadiomic software and wrapper methods will be applied for feature selection through recursive feature elimination. This radiomic workflow work-up has been successfully applied in our studies that provided MRI-based HPV-status prediction models (Sup-Fig.3) (7).

Data analysis strategies:
Two main strategic lines will be followed (Sup-Fig.5). The first (I) will use biomarker-based classifications to train radiomic-based models using supervised learning methods. Model selection for progression into the validation cohorts will be based on outcome prediction performance. Although "biology" of other areas of the tumor may not necessarily match those captured in the biopsy specimens, there is an increased likelihood those to be present in larger areas of the respective tumors, as underpinned by the observed strong outcome associations (19). Recognizing intra-tumor variation and heterogeneity, we will approach this in a two-step process in a second approach (II) that aims to finetune models generated in the GENRAD cohort with samples from a prospective study designed to link radiomics with biological parameters (ExRADGEN).

I. Generation of genomics-guided radiomic models: A first simple strategy aims to train radiomic models using individual biomarker-determined tumor biology classifications (from a set selected based on their prognostic value, Sup-Fig.1). This will be followed by classifications according to combined biomarker scores and according to a total genomic biomarker-based outcome prediction score. The latter approach aims to “amend” the true individual patient outcomes with probabilities as defined by tumor biology for optimized radiomic model training.
II. Genomics-linked radiomic models: Multitask learning will integrate selected different prognostic biomarkers and MRI features to generate voxel wise profiles that can be translated into regional heatmaps and applied to images from resectable HNSCC. Heatmaps assist in the selection of suitable tumors (n>20) for which mapping of specimen from the resected material onto the images is possible (either due to size or closeness to distinctive reference points). Alternatively, if unsuccessful, different ROIs can also be defined by the radiologist. Histology data and RNA sequencing data from multiple intratumor specimens within and outside the ROIs (defined by these heatmaps) will be used for biomarker determination and association with radiomics to test and further optimize the linkage. As in I, comparative outcome association analysis in GENRAD aims to select models for further validation in the different CRT-RAD validation cohorts (Sup-Fig.5-6).

Statistics:
Pairwise tests of superiority, equivalence and non-inferiority will be applied on the models after applying the different prediction models on several independent validation cohorts. Such tests will be used to properly compare the accuracy of the model based on their area under the curve (AUC) as well as sensitivity and specificity. Cox-proportional hazard models for outcome association analyses will include important clinical variables.

Time frame

Our proposed project will encompass all of the possible four years allocated on this grant. The overall schedule is depicted in Sup-table1 and elucidated on in the text below.

Prognostic patient data collection:
As part of the proposed project, about 20 patients will be prospectively included for the improvement of the created models, the ExRADGEN.
Prospective inclusion: Estimated June 2023 – July 2024

All imaging data assessment:
Has already been started for some of the cohorts since 01.07.2020 by a physician researcher of our radiology research department under supervision of a head and neck radiologist with 34 years of experience.

01.07.2020 until November 2022	Finalization of retrospective imaging data assessment
December 2023 until October 2024	Prospective patients (ExRADGEN) imaging data assessment

Extraction and analysis of Radiomic features and development of Machine Learning Computer Models:

May 2023 until December 2023	Development of the models in strategy I on the GENRAD data.
January 2024 until April 2024	Validation on NKI-CRT-RAD and VU-CRT-RAD in strategy I.
December 2022 until May 2023	Development of voxel wise heatmaps in strategy II.
March 2025 until September 2025	Optimisation of the heatmap models on prospective data (ExRADGEN).
October 2025 until November 2025	Validation on NKI-CRT-RAD and VU-CRT-RAD in strategy II

Genetic data collection:
For the proposed prospective study. Model-guided specimens from resected HNSCC will be collected, guided by the researcher and surgeon and frozen by the pathologists in our pathology department. Specimens will be sectioned for DNA/RNA preparation and transferred to our core facility for RNA/DNA sequencing when the collection of specimens for the prospective study has been completed. Sequencing data will subsequently be analyzed by a bio-informatician.
February 2024 – Feburary 2025

Feasibility:

Knowledge, previous research and infrastructure:
This project is well-embedded in existing research lines of the NKI-AvL institute. Within the NKI, the Head and Neck working group, has long lasting research lines in the field of outcome prediction and biomolecular markers. From these insights in the role of DNA repair defect and apoptosis, clinical trials using PARP inhibitors and BCL2 inhibitors have been carried out and new radiosensitizers have recently been developed. Traditionally there have been close collaborations between Michiel van den Brekel (Head and Neck), Adrian Begg and Conchita Vens (Radiobiologists) and Marcel Verheij (Radiotherapy). Several successful research projects have been carried out. In recent years, enabled by KWF (Alpes d'Huzes) research projects together with Ruud Brakenhoff (VUmc), and partly sponsored also by Brunel as well as the Artforce Project (European Grant), about 254 HPV positive and negative patients from the NKI, were genetically profiled using mRNA-sequencing technologies. Consequently, frozen HNSCC specimens have been collected since 2001. Apart from that cohort, also a cohort of about 55 surgically treated patients have been characterized genetically.

Parallel to these genetic studies, some 4years ago, after collaborating in several projects on CT radiomics, our radiology department (chaired by Regina Beets-Tan) together with Michiel van den Brekel, Hugo Aerts and Bas Jasperse started a project on MRI radiomics, which was joined by Jonas Castelijns who has a long-standing interest and extraordinary scientific expertise in MRI of H&N cancer, functional MRI and radiomics/radiogenomics. He published on MRI in H&N cancer as early as 1985. From 1990 on, he explored the value of MRI-parameters for outcome prediction after irradiation treatment. Relevant to this project, this was followed by work on functional MRI and from 2015 he focused his research on radiomics and radiogenomics in H&N cancer. Our PhD student (Paula Bos) will finalizeher PhD thesis by the end of this year. In several publications we have shown that MRI radiomics is feasible using retrospective patients data and found good correlations between MRI radiomic models and locoregional control as well as HPV positivity (7, 13, 15, 20). In this field, moving from CT towards MRI, we were among the first to show the feasibility of MRI radiomics. These findings in fact have shown that MRI radiomic features can be predictive

of the genetic make-up of a tumor, i.c. HPV positivity. In this process we found that tumor delineation is less crucial in predicting HPV status than in general prognostication, pointing to the fact that MRI features based on intratumoral characteristics can depict genetic features. It is therefore likely that other genetic, cellular or tumor biology features, like stemcellness, acute and chronic hypoxia as well as heterogeneity from DNA repair defects or EMT are characterized by specific MRI features.

Recently, in addition to the existing collaborations and projects using machine learning and bioinformatics, a new division was formed within the NKI that focuses on artificial intelligence to support and initiate research using these techniques. Support from this facility, together with the involvement of Selam Waktola will greatly contribute to the AI aspects and success of this project.

Patients, MRI and Genetic Data:
As many patients are staged using MRI in the NKI, and we tend to make these in the NKI for quality reasons, high quality MRI scans' are available in many patients that have been also characterized genetically. But because MRI protocols changed over time, only MRI scans made after 2008 can be used for this study here. MRI techniques have varied somewhat over the years, but many sequences have been employed routinely. We looked at the MRI quality of the potential cases and found that from the 254 RNA-sequenced patients sufficiently good quality MRI were available in 145 patients , of whom 76 were HPV-negative, CRT treated, and with minimal 3 years follow-up. 24 HPV-negative Neoadjuvant Immunotherapy + Surgery treated patients cases with RNA data can be also used. These 100 patients will be used to build the radiogenomic model on the biomarker-defined categories of their tumors. As the number of events is quite large in the subgroups with poor genetic profiles, the patient characteristics fairly homogeneous (focusing on HPV-positive and by applying three different ways to integrate the genomic/biomarker data, we envisage that good models can be built on this particular cohort, even though limited in numbers of patients.

Based on these MRI radiomic models, heatmaps of these features on MRI will be made for surgically treated patients. This will 1) help us to select suitable tumors for the prospective study to validate the link with the biomarker / predicted biology, 2) minimize the number of samples while optimizing that selected radiomic features/ feature combinations are distinctively present and 3) guide optimal (and multiple) specimen collection from the resected material. Thus, we will take biopsies of these areas, guided by the MRI. We have gained experience in doing so in a recent study on hypoxia HX4-PET-CT scans, in which biopsies of the hypoxic areas were obtained under general anaesthesia. These specimens will then be RNA-sequenced to validate the MRI radiomic signature of that area.

Once the radiomic models for hypoxia, EMT, stemcellness, DNA repair defect and immune cell infiltration are defined, their prognostic significance will first be tested on the test cohort and validated on a much larger MRI database from our institute. If needed, a multicenter validation study might be set up after this research project.

Timeframe;
We envisage that all steps in this project can be carried out within 4 years. The genetic data and tumor categorisation of the 100 patients in the test-cohort are already available, accelerating the process greatly. MRIs are also available and will have to be segmented only in part. Starting at the beginning of 2022, this should be finalised by november 2022. MRI feature extraction and model building can then be completed by december 2023. Development of the voxel-wise heatmaps for specimen collection guidance and protocol approval by the ethical committee will take about 6 months. We anticipate that the prospective data collection and RNA-sequencing/ analysis of the 20 patients will be conducted from july 2024 until 2025 and finalized by december 2025. In parallel, from january 2024 until july 2025, the prognostic validation of the radiomic models will take place on the different patient cohorts.

References

Involved personal in the project are highlighted in bold

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PROJECT EMBEDDING

Already engaged personnel

Prof. dr. Michiel W. van den Brekel (Head & Neck Surgery; NKI; 0,1 FTE in kind / own contribution)
Prof.dr. Jonas A. Castelijns (Radiology; NKI; 0,1 FTE in kind/ own contribution)
Dr. Conchita Vens (Molecular Science; NKI: 0,1 FTE in kind/ own contribution)
Dr. Selam Waktola (Data Science; NKI; 0,1 FTE in in kind / own contribution)
Drs. Renaud Tissier (Statistics; NKI; 0,1 FTE in in kind / own contribution)
Prof.dr. Regina G.H. Beets-Tan (Radiology, NKI; 0,05 FTE in kind / own contribution)
Prof.dr. Lotje C. Zuur (Head & Neck Surgery; NKI; 0,05 FTE in kind / own contribution)
Prof.dr. Jan-Jacob Sonke (Physics; NKI; 0,05 FTE in kind / own contribution)
Dr. Olga Hamming-Vrieze (Radiotherapy; NKI 0,05 FTE in kind / own contribution)

Selection of recent, relevant publications prof.dr. Jonas Castelijns on radiomics and radiogenomics (over 220 peer reviewed publications)

Jansen RW, de Jong MC, Kooi IE, Sirin S, Göricke S, Brisse HJ, Maeder P, Galluzzi P, van der Valk P, Cloos J, Eekhout I, **Castelijns JA,** Moll AC, Dorsman JC, de Graaf P. MR Imaging Features of Retinoblastoma: Association with Gene Expression Profiles. Radiology. 2018 Aug;288(2):506-515.

Jansen RW, van Amstel P, Martens RM, Kooi IE, Wesseling P, de Langen AJ, Menke-Van der Houven van Oordt CW, Jansen BHE, Moll AC, Dorsman JC, **Castelijns JA**, de Graaf P, de Jong MC. Non-invasive tumor genotyping using radiogenomic biomarkers, a systematic review and oncology-wide pathway analysis. Oncotarget. 2018 Apr 13;9(28):20134-20155. Review.

Noij DP, Martens RM, Koopman T, Hoekstra OS, Comans EFI, Zwezerijnen B, de Bree R, de Graaf P, **Castelijns JA**. Use of Diffusion-Weighted Imaging and 18F-Fluorodeoxyglucose Positron Emission Tomography Combined With Computed Tomography in the Response Assessment for (Chemo)radiotherapy in Head and Neck Squamous Cell Carcinoma. Clin Oncol (R Coll Radiol). 2018 Dec;30(12):780-792.

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Bos P, van den Brekel MWM, Gouw ZAR, Al-Mamgani A, Waktola S, Aerts HJWL, Beets-Tan RGH, **Castelijns JA**, Jasperse B. Clinical variables and magnetic resonance imaging-based radiomics predict human papillomavirus status of oropharyngeal cancer.Head Neck. 2021 Feb;43(2):485-495.

Expertise, selection of recent publications of Dr. Conchita Vens on genetics

van der Heijden M, Essers PBM, de Jong MC, de Roest RH, Sanduleanu S, Verhagen CVM, Hamming-Vrieze O, Hoebers F, Lambin P, Bartelink H, Leemans CR, Verheij M, Brakenhoff RH, van den Brekel MWM, **Vens C**. Biological Determinants of Chemo-Radiotherapy Response in HPV-Negative Head and Neck Cancer: A Multicentric External Validation. Front. Oncol., 10 Jan 2020.

https://doi.org/10.3389/fonc.2019.014702020.

Drug Sensitivity Prediction Models Reveal a Link between DNA Repair Defects and Poor Prognosis in HNSCC. Essers PBM, van der Heijden M, Verhagen CVM, Ploeg EM, de Roest RH, Leemans CR, Brakenhoff RH, van den Brekel MWM, Bartelink H, Verheij M, **Vens C**. Cancer Res. 2019 Nov 1;79(21):5597-5611.

Epithelial-to-mesenchymal transition is a prognostic marker for patient outcome in advanced stage HNSCC patients treated with chemoradiotherapy. van der Heijden M, Essers PBM, Verhagen CVM, Willems SM, Sanders J, de Roest RH, Vossen DM, Leemans CR, Verheij M, Brakenhoff RH, van den Brekel MWM, **Vens C.** Radiother Oncol. 2020 Jun;147:186-194.

Genetic Factors Associated with a Poor Outcome in Head and Neck Cancer Patients Receiving Definitive Chemoradiotherapy. Vossen DM, Verhagen CVM, van der Heijden M, Essers PBM, Bartelink H, Verheij M, Wessels LFA, van den Brekel MWM, **Vens C**. Cancers (Basel). 2019 Mar 29;11(4):445.

Ovarian cancer-derived copy number alterations signatures are prognostic in chemoradiotherapy-treated head and neck squamous cell carcinoma. Essers PBM, van der Heijden M, Vossen D, de Roest RH, Leemans CR, Brakenhoff RH, van den Brekel MWM, Bartelink H, Verheij M, **Vens C**. Int J Cancer. 2020 Sep 15;147(6):1732-1739.

Acute Hypoxia Profile is a Stronger Prognostic Factor than Chronic Hypoxia in Advanced Stage Head and Neck Cancer Patients. van der Heijden M, de Jong MC, Verhagen CVM, de Roest RH, Sanduleanu S, Hoebers F, Leemans CR, Brakenhoff RH, **Vens C**, Verheij M, van den Brekel MWM. Cancers (Basel).

Comparative genomic analysis of oral versus laryngeal and pharyngeal cancer. Vossen DM, Verhagen CVM, Verheij M, Wessels LFA, **Vens C**, van den Brekel MWM. Oral Oncol. 2018 Jun;81:35-44.

DNA Repair Molecular Beacon assay: a platform for real-time functional analysis of cellular DNA repair capacity. Li J, Svilar D, McClellan S, Kim JH, Ahn EE, **Vens C**, Wilson DM 3rd, Sobol RW. Oncotarget. 2018 Aug 3;9(60):31719-31743.

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Verhagen CVM, Vossen DM, Borgmann K, Hageman F, Grénman R, Verwijs-Janssen M, Mout L, Kluin RJC, Nieuwland M, Severson TM, Velds A, Kerkhoven R, O'Connor MJ, van der Heijden M, van Velthuysen ML, Verheij M, Wreesmann VB, Wessels LFA, van den Brekel MWM, **Vens C**. Oncotarget. 2018 Apr 6;9(26):18198-18213.

Expertise and selected publications of Dr. Selam Waktola on artificial intelligence and machine learning

Waktola S, Babout L, Grudzien K. ‘3D segmentation of funnel flow boundary during silo emptying’ Image Processing & Communication; 2014: vol. 19, no. 2-3, pp.141–150.

Waktola S, Grudzien K, Babout L. ‘3D reconstruction of funnel flow boundary using automatic point set extraction.’ Image Processing & Communication; 2015:, vol. 20, no. 3, pp. 35–43.

Waktola S, Bieberle A, Barthel F, Bieberle M, Hampel, M., Grudzie?, K, Babout, L. ‘Study of flow behavior of granular material inside cylindrical silo using ultrafast X-ray imaging technique’ , Image Processing & Communications, 2017; vol. 22, no. 2, pp.49–56 .

Waktola S, Bieberle A, Barthel F, Bieberle M, Hampel M, Grudzie? K, Babout L. ‘A new data processing approach to study particle motion using ultrafast X-ray tomography scanner: case study of gravitational mass Flow’, Experiments in Fluids,2018; 59(4), p. 69.

Haak, H.E., Gao, X., Maas, M., Beets-Tan, R.G.H., Beets, G.L., Leerdam, M. van., **Waktola, S**. ,and Melenhorst, J. The use of deep learning on endoscopic images to assess the response of rectal cancer after chemoradiation. 2020; Surgical Endoscopy. (Submitted)

Waktola , S. , van der Velden, D., F. Castagnoli, R. Beets-Tan. ‘ Interpretable machine learning for predicting stereotactic body radiation therapy early response in liver colorectal cancer metastasis’, 2021; ESGR 2021 Virtual Congress. (Accepted)

Personal Honors and Awards of prof.dr. Jonas Castelijns

Award “Cum Laude” for academic thesis, entitled “MRI of laryngeal cancer”,
Amsterdam 11th December 1987
Gold-Medal Life-time achievement Award by the European Society of Head and Neck Radiology.
Lisbon, 29th September 2017.
Ridder in de Orde van de Nederlandse Leeuw (= “Order of Knighthood Dutch Lion”)
Amsterdam, 21th June 2019.

Relevant accepted grants of prof.dr.Jonas Castelijns

Assessment of lymph node metastases in the neck: a radiological study. Snow, Castelijns. Granted by: Koningin Wilhelmina Fonds (year 1988):

Improved tumour cell detection by molecular genetic markers in ultrasound guided fine needle aspirates from sentinel cervical lymph nodes of head and neck cancer patients. Snow, Castelijns.Granted by Koningin Wilhelmina Fonds (VU 99-1967):

Predictieve waarde van MRI parameter in 2 gebieden van Hoofd Hals Oncologie.
Granted by: VAZ-doelmatigheid (VAZ-2003-01244). De Bree, Castelijns **€ 61.373**

High resolution ocular MR Imaging: towards improved detection of retinoblastoma tumor extent. 2006
Granted by ODAS, Stichting Oogfonds, LSBS, Blindenhulp (2006). Castelijns, Moll **€ 107.264**

Clinical and experimental high resolution ocular MR Imaging: towards improved detection of retinoblastoma tumor extent.
Granted: by ODAS, LSBS (2007) Castelijns,Moll **€ 80.857**

Networking between European Expertise Centres for Retinoblastoma”.
Granted by ODAS 2008 **€ 133.729**

Multicenter implementation of MRI studies in children with retinoblastoma for assessment of response to chemotherapy and early detection of pineoblastoma and cranial-facial second primary malignancies.
Granted by ODAS 2012 Castelijns, Moll **€ 302.026**

Philips-exhibit “Comprehensive assessment of Head&Neck cancer using PET-MRI.
Granted by Philips, 2013. Lammertsma, Castelijns **€ 92.000**

Multimodality and multi-parametric PET/MRI analysis for enhancing diagnosis, prognosis and response prediction in advanced stage head and neck cancer. Granted by ZON-MW,IMDI.
(10-10400-98-14002/104003002) 2015 Boellaard, Castelijns
€ 1.002.105

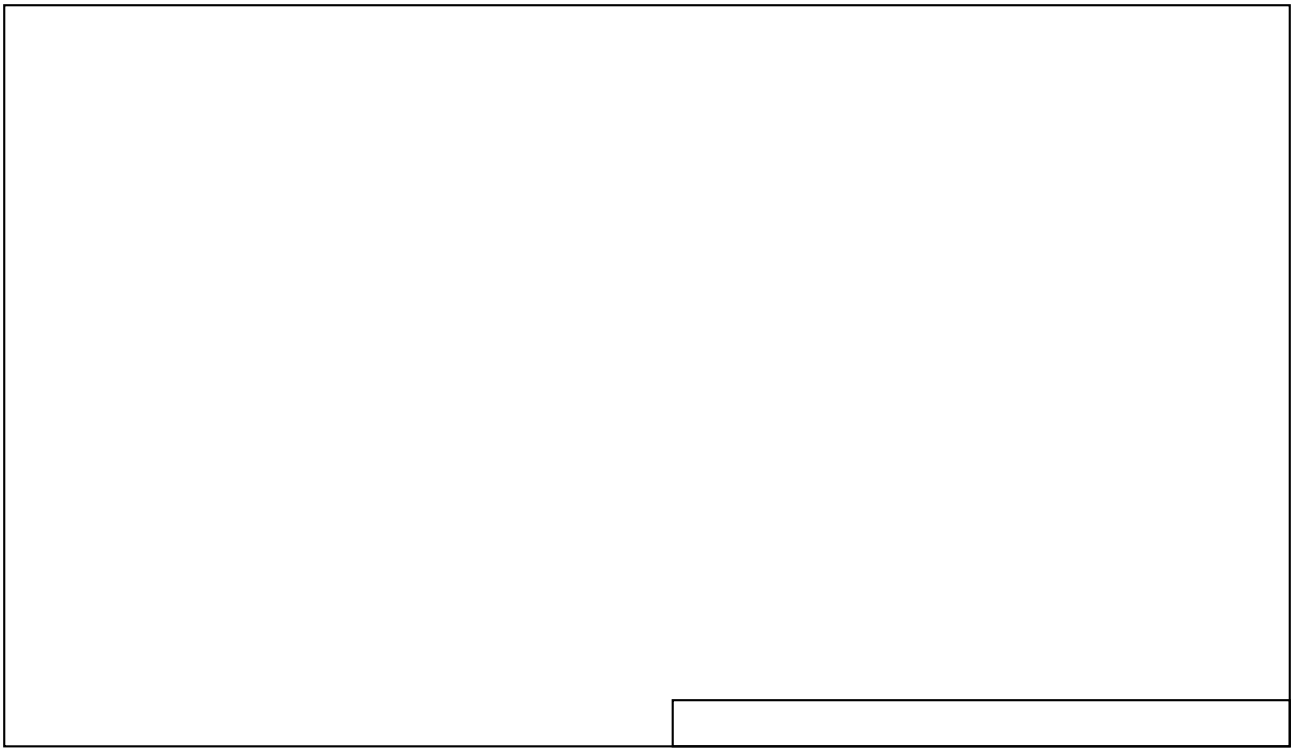
Requested personnel

A PhD-student is needed for the duration of 4 years (1.0 FTE).

A post-doc computer scientist (0.1 FTE/4yrs).
A bio-informatician (HBO-level) is needed for the duration of 1 year (0.5 FTE).
Scientific statistical support (0.1 FTE/2yrs).

Motivate requested personnel

One full time position will be assigned to a medical professional (MD) that coordinates the study and will, in line with their own research ambitions, produce, process and analyze the combined data. Part of the requested personnel budget will therefore be used for a full time position in the context of a PhD thesis (MD-PhD-student) for the total duration of the project (4 years). This person will hands on, conduct large part of the proposed analyses in the project by performing the delineations under guidance of an experienced radiologist, running the radiomic pipeline and working closely together with the computer scientists and geneticists.
A post-doc computer scientist is requested, to aid in the extraction automatic segmentation and machine learning model development and validation. In addition, a bio-informatician is needed for the duration of 1 year (0.5 FTE) to carry out the DNA/RNA sequencing analyses to support the prospective study (ExRADGEN) . While classification have been already done for the retrospective study, a statistician can assist in the computation of a prognostic-score classifier based on the outcome association of each biomarker. This bioinformatician and statistician position could be shared with another department or these activities could be covered by institute services or outsourced to outside collaboration partners.



FTE: 0

BIOSKETCH OF INVESTIGATOR

Applicant

Title(s) / Name

Prof. Dr. Michiel W.M. van den Brekel M.D., PhD. (see supplementary file 1: Change_in_Principal_investigator.pdf)

Year of PhD (if applicable), Supervisors / promotor, Title of dissertation

Date: 24-4-1992
Supervisors: Prof. Dr. Jonas A. Castelijns, Prof.Dr.G.B.Snow, Prof.Dr.C.J.L.M.Meijer, Prof.Dr.J.Valk
Title: Assessment of lymph node metastases in the neck: A radiological and histopathological study
Award: Cum Laude

Current position

1. Professor at the University of Amsterdam, ACLC – Faculty of Humanities
2. Chairman Dept of Head and Neck Oncology and Surgery, Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX, Amsterdam
3. Staff at Department of Oral – Maxillofacial Surgery, Amsterdam UMC

Professional experience

Relevant education and training

• Medicine at the Catholic University in Leuven 1980-1987
• Doctoral, cum laude
• Medical Degree, cum laude
• ECFMG degree (American Medical Degree) 1987
• Researcher for the Dutch Cancer Society in the Free University Hospital in Amsterdam (project: IKA 88-19: detection of lymph node metastases in the neck)
1988-1990:
• Resident in training for otolaryngology at the Free University Hospital in Amsterdam, the Netherlands (Chairman: Prof.Dr.G.B.Snow) 1990-1994
• Clinical-research fellow of the Dutch Cancer Society 1995-1996
  o NKI-AVL, Amsterdam, the Netherlands
  o University of Toronto, Canada
• BROK certificate valid until 2025
• Basiskwalificatie Onderwijs (BKO), UvA 2016

Relevant professional experience

• Assistant professor in Otolaryngology-Head and Neck Surgery of the Academic Hospital Free University, Amsterdam (Prof.G.B.Snow). 1997-2000
• Teacher Head and Neck Surgery at BIGRA, Hogeschool Holland, Diemen 1999-2007
• Staff Otorhinolaryngology/Head and Neck Surgery at the NKI-AVL, Amsterdam Since 2000
• Staff Otorhinolaryngology Academic Medical Center, University of Amsterdam, Amsterdam 2002-2013
• 2nd trainer (waarnemend opleider) of Residents Otolaryngology of the University of Amsterdam Since 2006
• Chairman of the department of Head and neck Surgery, NKI-AVL Since Aug 2009
• Part time professor at the Faculty of Humanities, University of Amsterdam (ACLC) Since Nov 2011
• Staff Maxillofacial Surgery Academic Medical Center, University of Amsterdam, Amsterdam Since 2013
• Leader and first applicant of many research projects in the field of rehabilitation, biomarkers, translational medicine and imaging.

Please include any earlier grants at other institutes

Detection of Minimal Residual disease in resection Margins. KWF Grant 1997-2001, VUmc (VU97-1524) (van den Brekel, Brakenhoff, Snow). PhD V van Houten (**± Fl.500.000)**

Sentinel node and molecular techniques to detect occult lymph node Metastases in the Neck. KWF grant 1999-2003, VUmc (VU99-1967_ (vd Brekel, Castelijns, Brakenhoff). PhD E Nieuwenhuis (**± Fl.500.000)**

Development of a transgenic Mouse model for Oral Cancer. NKI Grant 2001-2006 (van den Brekel, A.Berns) **(± 350.000 Euro)**

Clinical and molecular factors predicting outcome. NKI Grant 2004-2008 (Balm, van den Brekel). PhD G van den Broek.

Expression Profiling to predict outcome after Chemoradiation. KWF grant 2005-2009 (NKI 2005-3420) (van den Brekel, Begg). PhD J Pramana **(± 200.000 Euro)**

Expression Profiling in small laryngeal cancer to predict outcome after radiotherapy. KWF grant 2007-2010 (NKI 2007-3941) (van den Brekel, Hoebers, Begg). PhD MC de Jong **(± 250.000 Euro)**

Grant Verwelius Foundation to support Head and Neck Research (van den Brekel): Annual 75.000 Euro 2010-2021 **(825.000 euro)**
- Patient doctor communication (PhD M van der Laaken)
- Biomarker: DNA repair and Fanconi (PhD C Verhagen)
- Virtual Therapy and patient counseling (PhD K Kappert, M. van Alphen)
- 3D techniques in reconstruction and anaplastology (PhD S Brouwers de Koning, T Bannink)

Laryngectomy and Chemoradiation Rehabilitation Research and Medical device development. ATOS Medical grant 2014-2021 (van den Brekel, Hilgers). PhD: JK Zuur, R Scheenstra, C van den Boer, J Timmermans, L Lansaat, S Kraaijenga, R Clapham, M Petersen, K van Sluis , AJ Beck, R Karsten, M Leemans. (**3.958.312 Euro).**

3D Technologies in anaplastology and 3D reconstruction (Balm, van den Brekel). De Graaf grant 2015-2021
(225.000).

Biomarker Development and bioinformatics. Brunel Grant (van den Brekel, Vens) 2014-2020. PhD D Vossen **(290.000 Euro)**

Immunotherapy and translational Medicine; Development of a radiosensitizer .Riki Stichting (2015 - 2021)(Zuur, van den Brekel, Neefjes): PhD: J Elbers, A Dohmen, J Vo **(810.000 Euro)**

Speech Rehabilitation and Machine learning in pathological speech recognition. European Grant (van Son, van den Brekel) EEG-CEC / EU TAPAS grant 766287 2017-2021. PhD B Halpern (**238.174 euro)**

Decision aid development. St.Michel Keijzerfonds, 2018-2019 (Smeele, van den Brekel). Phd R Karsten **(27.260 Euro)**

DESIGN (Biomarker research) KWF Design-A6C7072 (with VUmc) 2016-2021 (Vens, van den Brekel). PhD M van der Heijden **(400.000 Euro)**

Rehabilitation of Swallowing. W.M. de Hoopstichting 2018 (van den Brekel). PhD R Karsten **(34.700 euro)**

Immunology biomarker research (Zuur, van den Brekel). W.M. de Hoop Stichting 2014
(73.700 Euro)

International activities

• Lecturer at more than 150 international conferences
• Regular Reviewer of more than 15 international journals, and several international Funding Agencies
• Editorial board member of journals: Cancers, Oral Oncology, International Archives of Otolaryngology
• Program Chair of the IAOO international congress in Rome 2019
• Member of the Program Committee of IFHNOS and AHNS congresses
• Initiator and PI of several multicenter international studies
• Organizer of 12 international Conferences on head and Neck Cancer Treatment in Amsterdam
• Organizer of the IFHNOS world tour in Amsterdam in 2012
• Board member of the IAOO: International Academy of Oral Oncology (2019-)
• Chairman of the Global Postlaryngectomy Rehabilitation Academy (2016-)

Honors and awards

• European Federation of Otorhinolaryngological Societies Scientific award 1992
• PhD cum Laude 1992
• Dutch ENT-Duphar year award for the best thesis "Assessment of lymph node metastases in the neck, A radiological and histopathological study" 1993
• Poster prize Dutch Society of ORL and Cervicofacial Surgery: Assessment of tumor invasion of the mandible; a comparison of different imaging techniques 1996
• Visiting Professor at the University of Toronto 17 and 18 November 2004
• Lifetime Honorary Member of the Indian Foundation for head and Neck Oncology October 2007
• Visiting professor at Memorial Sloan Kettering Cancer Center 19-21 December 2007
• Honorary Member of the Israeli Society of Head and Neck Surgery and Oncology 2010
• Member of prestigious CORLAS: Collegium Otorhinolaryngologicum Amicitia Sacrum 2011

• Honorary Member of South African Society of Otorhinolaryngology Head and Neck Surgery 2013
• Guest of honor ISHNOS, 29-31 October, 2015, Hagoshrim, Israel 2015
• Honorary member of the German ENT society 2018

Selected publications

Selection of publications of prof.dr M. van der Brekel -- (over 270 peer reviewed publications)

Bos P, **van den Brekel MWM**, Gouw ZAR, Al-Mamgani A, Taghavi M, Waktola S, Aerts HJWL, Castelijns JA, Beets-Tan RGH, Jasperse B. Improved outcome prediction of oropharyngeal cancer by combining clinical and MRI features in machine learning models. Eur J Radiol. 2021 Jun;139:109701.

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Brakenhoff RH, **van den Brekel MWM**, Bartelink H, Verheij M, Vens C. Cancer Res. 2019 Nov 1;79(21):5597-5611.

Keek S, Sanduleanu S, Wesseling F, de Roest R, **van den Brekel M**, van der Heijden M, Vens C, Giuseppina C, Licitra L, Scheckenbach K, Vergeer M, Leemans CR, Brakenhoff RH, Nauta I, Cavalieri S, Woodruff HC, Poli T, Leijenaar R, Hoebers F, Lambin P. Computed tomography-derived radiomic signature of head and neck squamous cell carcinoma (peri)tumoral tissue for the prediction of locoregional recurrence and distant metastasis after concurrent chemo-radiotherapy. PLoS One. 2020 May 22;15(5):e0232639.

Epithelial-to-mesenchymal transition is a prognostic marker for patient outcome in advanced stage HNSCC patients treated with chemoradiotherapy. van der Heijden M, Essers PBM, Verhagen CVM, Willems SM, Sanders J, de Roest RH, Vossen DM, Leemans CR, Verheij M, Brakenhoff RH, **van den Brekel MWM**, Vens C. Radiother Oncol. 2020 Jun;147:186-194.

Genetic Factors Associated with a Poor Outcome in Head and Neck Cancer Patients Receiving Definitive Chemoradiotherapy. Vossen DM, Verhagen CVM, van der Heijden M, Essers PBM, Bartelink H, Verheij M, Wessels LFA, **van den Brekel MWM**, Vens C. Cancers (Basel). 2019 Mar 29;11(4):445.

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DOCUMENTS

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