Personalized chemo-radiation of lung, head and neck cancer
Respiratory epithelial cancers, i.e. lung cancer (LC) and head and neck cancers (HNCs) are leading causes of cancer mortality, in both men and women. Yearly about 9,000 Dutch persons are diagnosed with LC while 8,850 die of the disease. For HNC these numbers are 1,400 and 850. Currently patients with LC and HNC are treated with surgery, radiotherapy and/or chemotherapy. Radiotherapy is often combined with classical chemotherapy such as cisplatin (CDDP) or targeted therapies such as epidermal growth factor receptor (EGFR) inhibitors. While initial response rates can be impressive, survival rates are still disappointingly short, and treatment related morbidity is high.

By linking molecular knowledge of LC and HNCs such as markers of radioresistance with recent advances in molecular imaging and novel techniques for selective irradiation, within the AirForce consortium we aimed for optimally targeted individualized chemo-radiotherapy with improved therapeutic outcome, i.e. survival and quality of life.

AirForce has addressed these unmet clinical needs by developing biomarker tests and imaging approaches to come to (1) better prediction of therapy response, (2) avoidance of ineffective treatment with high morbidity, (3) therapy tailoring: adaptation of treatment when needed, (4) improvement of therapy decision making, and (5) reduction of costs of treatment.

Highlights include the identification of predictive and prognostic candidate biomarkers for chemotherapeutic and/or radiotherapy efficacy and toxicity, such as secreted protein biomarkers, expression markers, methylation markers, markers on tumor stem cells and markers in exhaled breath. Several novel drug targets were identified. A panel of hypoxia tracers was developed and in vivo validated as well as a panel of EGFR, angiogenesis and multi-target tracers derived from monoclonal antibodies and tyrosine kinase inhibitors (TKI). Tracers were clinically evaluated. A large set of PET-CT software tools was developed to allow accurate and reproducible tumor definition and to quantify and characterize tracer uptake. Tools were loaded in a software platform for broad scale data integration called Oncology Research Workstation Imalytics. Mathematical models such as nomograms were developed and validated that predict progression free survival, overall survival and toxicity (dysphagia, dyspnea), and let to the introduction of decision support systems that outperform doctors prediction. Improved strategies for radiation dose boosting were introduced. Some cost effectiveness studies on diagnostic and therapeutic procedures in LC and HNC were performed. Several of these findings have resulted in product development and follow up studies, mostly with private partners, for further clinical implementation.

Prof. dr. Guus van Dongen
Principal Investigator of the AIRFORCE consortium

“In the AIRFORCE consortium academic and industrial partners with unique complementary expertise in the fields of e.g. molecular and cell biology, biotechnology, clinical drug development, informatics, medical technology assessment and electronics will collaborate closely together, aiming the improved treatment of patients with tumors of the upper aero-digestive tract. In this project innovative molecular navigation tools will be developed and exploited for high precision tumor eradication by personalized chemo-radiotherapy. I think working in such a multidisciplinary translational setting is unique for Europe, and the grant we obtained will enable us to make a firm step forwards in a short time period.”
Translational Concept - WP1

BIOMARKERS FOR PERSONALIZED THERAPY

More advanced stage lung- and head-neck cancer are treated by chemoradiation, the combination of systemic cisplatin-containing chemotherapy and concomittant irradiation. Alternative treatments are at hand, but there are no biomarkers available to personalize treatment. Treatment is invasive and cisplatin causes serious toxicities. Development of personalized treatment approaches, improvement of treatment protocols and substitution of cisplatin by targeted radiosensitzers may reduce toxicity and increase treatment efficacy. Toxicity of cisplatin costs 11 M€ per year on hospital stays in head-neck cancer patients only.

CLINICAL NEED

New biomarkers are required to personalize treatment for the specific tumor in the particular patient. Also improved treatment protocols are required with identical or improved efficacy but with less toxicity.

TOOLS

Biomarkers are identified by:

- Genomics, methylomics and proteomics methods.
- In addition, volatile compounds in exhaled breath have been exploited as biomarkers.
- Using genome-wide functional siRNA screens, the relevant genes involved in cisplatin and radiation response are identified, and novel druggable targets are found.
- Finally, prognostic risk models are generated to stratify patients on basis of survival outcome.
PET TRACERS FOR GUIDANCE OF CHEMO-RADIATION

For optimal chemoradiation of lung- and head-neck cancer, accurate delineation of the tumor is a first requirement. However, individual tumors differ in their sensitivity to treatment. It is known that tumor cell metabolism, proliferation and the level of tumor angiogenesis are major contributors to tumor response to radiotherapy. Some drugs directed against targets involved in proliferation and angiogenesis are capable of improving the efficiency of chemoradiation. For high-precision individualized therapy, PET tracers are of value for prediction and monitoring of chemoradiation efficacy.

CLINICAL NEED

New PET tracers are needed to guide the optimal application of chemoradiation: the right treatment, for the right patient, at the right dose, at the right place, at the right time.

TOOLS

A panel of PET tracers for detection/delineation of tumors, and for visualisation and quantification of (1) tumor characteristics related to chemo-radiosensitivity, (2) biodistribution of radiosensitizing targeted drugs, (3) early tumor response.
Development and validation of PET-CT Imaging software tools

Quantification of PET tracer uptake has added value for diagnosis, prognosis, prediction and response assessment. Quantitative PET may therefore play an important role for enhancing individualised medicine. However, quantification of PET radiotracer uptake is limited by several factors, such as patient motion, limited spatial resolution of PET imaging systems, tracer uptake heterogeneity. Moreover, more new radiotracers are needed to allow for a more extensive in vivo assessment of tumor biology and characteristics. This new and more accurate information can then be used to enhance radiotherapy treatment planning, based on either tumor delineation/contouring or on dose painting.

During this projects several tools were developed to address the above mentioned issues. The developed tools will give rise to better diagnosis, reduced inter-observer variation for delineation, and better possibilities for targeting a part of the tumor (dose painting). This work package is primarily aimed towards lung tumors (where motion is an issue), but will be applied in head-neck cancer as well, where PET is used for tumor delineation.

CLINICAL NEED
New image analysis tools are needed to guide the optimal application of chemoradiation: the right treatment, for the right patient, at the right dose, at the right place, at the right time.

TOOLS
Improving tumor tracer uptake quantification and tumor delineation for treatment planning and response assessment by means of development of new methods (1) for tumor delineation, (2) to correct for partial volume effects and (3) patient motion, (4) development of tools to measure changes in tumor tracer uptake and characteristic for treatment response assessment and (5) methods to incorporate motion and biological information into radiotherapy treatment planning system.
Translational Concept – WP4

MOLECULAR DIAGNOSTICS AND TOOLS
Integration and validation of pre-therapeutic molecular diagnostic and molecular imaging information in a user-friendly tool and to use this information in innovative treatment.

- Model prediction outperforms doctors’ prediction for dyspnea, dysphagia and survival
- HX4 uptake represents tumor hypoxia on a macroscopic level
- Uncertainty based planning has the potential to reduce dose to organs at risk

CLINICAL NEED
To improve the accuracy for predicting side effects and survival of lung- and head-neck patients. To gather useful information on the intra-tumor heterogeneity. To deliver specific inhomogeneous radiation doses to the tumor (dose painting).

TOOLS
By using existing validated and published predictive algorithms and improving them with new biomarkers. By comparing new imaging modalities with pathology. By using an innovative treatment planning system and by collecting new “molecular” information about specific tumor cell populations.
ONCOLOGY RESEARCH WORKSTATION (ORW)

The Philips research workstation Imalytics was used as the basis for the ORW. The workstation operates on a local DICOM image database and can be connected to other DICOM network nodes (e.g. PACS systems or imaging equipment). It was extended with a programming interface and that was used to integrate tumor segmentation algorithms, PET motion compensation, advanced image alignment, partial volume correction and remote control for serial analysis.

MULTI-CENTER CLINICAL AND IMAGE DATABASE

WP6 supported the implementation of eCRF for the Umbrella protocol in which treatment information of 1589 lung cancer patients has been collected. To augment this data a possibility has been created to include DICOM scans, dose cubes, etc. from the PACS system for data mining. The eCRF can be exported to standard ODM CDISC format. Of the linked image data, a full anonymized UIDs are included for each event. This means that detailed correspondence between the event and scan is recorded by the submitted hospital avoiding extensive data management at the central site and allowing unattended data analysis (e.g., with Imalytics).

CLINICAL NEED

Easy-to-use integrated software package for optimal and standardized PET-CT imaging for individualized healthcare:

- ORW for lung and head-neck cancer

Better knowledge of treatment parameters and images in clinical trials

TOOLS

- PET/CT analysis
- Workflow & integration
- Data collection through ECRF
- Data mining
Select the optimal treatment regime for individual patients and to find resistant regions within tumors where localized chemo-radiotherapy should be focused.
Organization and Partners

**Advisory board**
ISAC CTMM

**Workpackage leaders**
WP1: Prof. R. Brakenhof (VUMC)
WP2: Prof. G. van Dongen (VUMC)
WP3: Prof. R. Boellaard (VUMC)
WP4: Prof. P. Lambin (MUMC+)
WP5: Prof. H. Groen (UMCG)
WP6: Dr. M. van Herk (NKI)
WP7: Prof. C. Uyl (EUR)

**SteeringCie**
Partner Representatives
CTMM

**Project Team**
PI: Prof. G. van Dongen, (VUMC)
Co-PI: Prof. P. Lambin (MUMC+)
All WP leaders
All industrial partners
Dr. A.C. van Denderen (VUMC)
Dr. E. Caldenhoven (CTMM)

**Partners**
BG Medicine (USA)
Genmab (DK)
MDxHealth (BE)

**CTMM**
Philips
MUCM + Maastricht
Mubio
DSM

**Coordination/Finance/Publications**
NKI
VUmc
Cyclotron
Agenda

**ADVICE**

**DECISIONS**

**OPERATIONS**

**CTMM**
Budget: CTMM manages the flow of funds

Funding:
- 25% Academia
- 25% Industrial
- 50% Government Subsidy

Project costs:
- Personnel
- Materials
- Use of existing equipment
- Investments
- Third parties
- Management (5%)
Facts & Figures

Distribution of the AIRFORCE consortium budgets to perform the R&D activities

**Budget** 16.9 M €  
**Start** 2008  
**End** 2013  
**Partners** 13

**CASH COSTS**

- **Academic cash costs**
- **Industrial cash costs**

**KIND COSTS**

- **Academic in kind costs**
- **Industrial in kind costs**
## Facts & Figures

<table>
<thead>
<tr>
<th>Output</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papers</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>19 papers in submission - mean impact factor all published AIRFORCE papers: 5.6</td>
</tr>
<tr>
<td>Theses</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1 planned for 2016</td>
</tr>
<tr>
<td>Personal Grants</td>
<td>0</td>
</tr>
<tr>
<td>Patent Filings</td>
<td>0</td>
</tr>
<tr>
<td>Spin-off Companies</td>
<td>0</td>
</tr>
<tr>
<td>Raising Capital (&gt; 1 M€)</td>
<td>0</td>
</tr>
<tr>
<td>Awards</td>
<td>0</td>
</tr>
<tr>
<td>Public Media</td>
<td>0</td>
</tr>
</tbody>
</table>

| Budget                  | 16.9 M € |
| Start                   | 2008    |
| End                     | 2013    |
| Partners                | 13      |
| Charity                 | 0       |
| Persons                 | 87      |
| FTE                     | 111 (5 years period) |
• Candidate biomarkers identified for cisplatin response prediction with preliminary validation in clinical material.
• Production of the long-lived PET radionuclides zirconium-89 and iodine-124 was established for worldwide distribution.
• BRCA-Fanconi anemia pathway was found as major determinant of cisplatin response in squamous cell carcinomas.
• Over 350 genes sensitize lung cancer cells for radiotherapy.
• Over 300 genes are essential for lung cancer as well as head and neck cancer cells, and form novel druggable gene targets for targeted treatment approaches.
• Novel marker for identification of the cancer stem cells in head and neck cancer was found, and number of stem cells in HPV+ve tumors is associated with outcome.
• HPV-attributable fraction of HPV in oropharyngeal carcinoma was increased from 5% in 1990 till 30% in 2010.
• HPV-based prognostic risk models for oropharyngeal cancer outperform TNM staging.
• P16 immunostaining followed by HPV DNA PCR is a well-validated assay for routine use on archival oropharyngeal cancer specimen and has been introduced in clinical care.
• Models, based on clinical information, have been developed for overall survival, radiation-induced dyspnea and radiation induced dysphagia. www.predictcancer.org. We developed two umbrella protocols one for head and neck cancer one for lung cancer. The lung protocol was published open source.
• Validation of the newly established non-invasive hypoxia PET marker HX4 by comparison with the golden standard immunohistochemical exogenous hypoxia marker pimonidazole showed HX4 uptake does represent tumor hypoxia on a macroscopic level.
• Innovative probabilistic treatment planning system for radiotherapy allowing radiation dose painting: The probabilistic planning and evaluation approaches to head and neck (HNC) and non-small cell lung (NSCLC) cancer patients showed that serious mis-dosage may occur and that this approach is a valid solution for uncertainties management in dose painting by numbers.

Highest Impact Papers – mean 16.0

Mean Impact Factor
International - oncology 4,4
CTMM - oncology 6,8

2 - Mean impact factor based on 200 papers from the CTMM oncology first call projects.
<table>
<thead>
<tr>
<th>Thesis</th>
<th>Partner</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steven Petit</td>
<td>MUMC+</td>
<td>2010</td>
</tr>
<tr>
<td>Maud Starmans</td>
<td>MUMC+</td>
<td>2011</td>
</tr>
<tr>
<td>Cary Oberije</td>
<td>MUMC+</td>
<td>2011</td>
</tr>
<tr>
<td>Patsuree Cheebsumon</td>
<td>VUMC</td>
<td>2012</td>
</tr>
<tr>
<td>Matthijs Kruis</td>
<td>NKI</td>
<td>2014</td>
</tr>
<tr>
<td>Sanne Martens – de Kemp</td>
<td>VUMC</td>
<td>2014</td>
</tr>
<tr>
<td>Eva Schaake</td>
<td>NKI</td>
<td>2014</td>
</tr>
<tr>
<td>Marlies Bongers</td>
<td>VUMC</td>
<td>2015</td>
</tr>
<tr>
<td>Sarah Peeters</td>
<td>MUMC+</td>
<td>2015</td>
</tr>
<tr>
<td>Vikram Rao Bollineni</td>
<td>UMCG</td>
<td>2015</td>
</tr>
<tr>
<td>Gerald Kerner</td>
<td>UMCG</td>
<td>planned</td>
</tr>
</tbody>
</table>
Clinical and Economic Value Creation of AIRFORCE

New ‘products’ for clinical care
**AIRFORCE** aims to develop molecular tools to enable prediction of chemo/radio-therapy response and toxicity in lung- and head and neck cancer patients. Protein-based methods are key for this purpose as proteins (1) are a direct reflection of tumor biology, (2) can be coupled to antibody-based assays, and (3) are compatible with routine clinical pathology practice.

**Discovery and validation of protein markers.**

By using high resolution mass spectrometry-based proteomics, proteins are identified and quantified to yield candidate biomarkers. Promising candidates are selected for immunohistochemical validation in patient tumor tissues. Proteins associated with cisplatin sensitivity and resistance were identified. These proteins are implicated in a wide range of biological processes (DNA repair including members of the BRCA pathway, RNA processing/splicing, membrane/vesicle trafficking among others). Suitable immunohistochemical protocols were developed for 3 candidates of which 2 correlate with survival in a preliminary validation study.

**Leading Company:** MuBio/BGMedicine

**Main results in CTMM:**

- **Protein biomarker identification:** Most chemotherapy regimens in lung- and head and neck cancer include cisplatin. Therefore, we focused on this drug in our discovery study. Candidate predictive protein biomarkers for cisplatin response were identified in a panel of NSCLC cell lines (53 sensitivity and 32 resistance candidates). Based on the level of significant regulation between sensitive and resistant cells and the correlation to the cisplatin IC50 value, the most promising markers were selected for follow-up in NSCLC tumor tissues of patients that received platina-based chemotherapy.

- **Protein biomarker validation:** For 3 candidates suitable immuno-histochemical staining protocols were developed. For 2 proteins, a DNA repair protein and a nuclear methylation protein, a correlation was found with survival in squamous NSCLC carcinoma. A larger sample size is needed to confirm these findings.

**Future outlook:**

Predictive immunohistochemical test for platina-based chemotherapy regimens in lung- and head and neck cancer

**Expected impact of the products**

**Scientific:** The proteomic landscape and cisplatin-related biology uncovered in this project along with promising candidate biomarkers will help to make personalized cancer treatment a reality.

**Societal:** Routine protein-based assays will guide clinicians in a better selection of patients for cancer treatment with burdensome platinum-based therapy.

**Economic:** Tailoring therapy to patients that are likely to respond will ultimately result in improved cost-effectiveness of care.

**Progress obtained in translational pipeline**

**Discovery** Pathways - biomarkers

**Selection** Pathways - biomarkers

**Demonstrator** Development - device

**Clinical** Evaluation - cohorts

**Market access**

**Number of LC and HNC patients per year:** 1.8 and 0.56 million

**Total healthcare cost per year:** US 25-40 billion

**Diagram:**

- **Patient stratification**
- **Early diagnosis**
- **Screening**
- **Treatment & monitoring**

- **Therapy selection**

- **Expected outcome**

- **Progress within CTMM**

- **2008**

- **2013**
A molecular assay was developed and validated which could be used to predict treatment response in (lung-) cancer patients. The molecular assay is based on the chemical analysis of exhaled breath from cancer patients by using thermal desorption coupled to gas chromatography and mass spectrometry (TD-GC-MS). By TD-GC-MS a comprehensive chemical profile of volatile organic compounds (VOCs) in exhaled breath is determined. Cancer treatment and treatment response will cause changes (trends) in the chemical exhaled breath profiles which could be used to predict or personalize the cancer treatment.

The whole assay encloses four main steps:
1) preparation of the TD-tubes and Tedlar bags;
2) Onsite sampling of exhaled breath onto 2 TD-tubes via 2x5 (duplicate) liter Tedlar bags;
3) Analysis of the TD-tubes by TD-GC-MS and
4) Data processing using homemade chemometric tools.

Besides GC-MS also solid phase micro extraction coupled to comprehensive two-dimensional gas chromatography and mass spectrometry (SPME-GCxGC-MS) was investigated. This technique provides a more detailed chemical exhaled breath profile and lower detection limits compared to GC-MS; however sampling with SPME proved to be less practical and less robust than TD.

**Leading Company:** DSM

---

**Main results in CTMM:**
- A molecular assay based on thermal desorption coupled to gas chromatography and mass spectrometry (TD-GC-MS) was successfully developed and validated
  - In collaboration with Mastro Clinic, this assay proved to be a non-invasive and easy sampling for lung cancer patients.
  - Typically between 400 and 600 compounds are detected.
  - Metabolic markers for smoking (e.g. 2,5-dime-furan) are readily detected in smokers breath
  - The assay is robust with respect to sampling and analysis.
  - The limit of detection is at low volume ppt levels.
  - Good reproducibility. Variation (cv%) less than 10%.
- Comprehensive two-dimensional gas chromatography mass spectrometry (GCxGC-MS) proved to be promising with respect to separation power and sensitivity.

**Future outlook:**
- Employing assay to future clinical studies
- Transferring developed TD approach to GCxGC technologies

---

**Expected impact of the products**

**Scientific:**
This assay (full molecular exhaled breath profile) could potentially be used for early diagnosis, prevention, treatment, personalizing treatment and monitoring of lung cancer patients.

**Societal:**
Assay proved to be non-invasive and patient friendly. Assay could assist in early diagnosis and personalizing treatment.

**Economic:**
Assay could lead to early treatment and/or tailoring of therapy thereby increasing efficiency of care.
CD98 based antibody assay for chemoradiation prediction in patients with HPV+ve head and neck cancers

**PRODUCT**

Tumors are organized as normal tissues with cells, also called stem cells, that fuel the tissue and give rise to all cell lineages in the tissue. Mucosal stem cells are assumed to reside in the basal layer. Likewise, cancer stem cells (CSCs) are the fuelling source of the tumor, are generally treatment resistant, assumed to be located in the basal cells of well-differentiated tumors, and the cause of tumor relapses. In order to study the presence and molecular characteristics of (cancer) stem cells, markers are required. CD44 has been suggested as CSC marker, but it is expressed by many cells in the tumor and on the normal mucosa as was also demonstrated in imaging studies within AirForce.

Previously we identified a mouse monoclonal antibody (mAb), specifically staining the basal cells in normal mucosa and well-differentiated tumors. This mAb might be a more suitable tool to enrich and study stem cells in mouse models, and evaluate the relevance of these cells in clinical specimen. Problem is that it can only detect immunoprecipitated antigen.

**PARTNERSHIP**

Progress obtained in translational pipeline

![Diagram of progress within CTMM](image)

**Main results in CTMM:**
- The antigen recognized by mAb K984 is CD98
- CD98high cells are enriched for cancer stem cells
- CD98 immunostaining predicts outcome in patients with HPV+ tumors

**PATIENTS**

**Expected impact of the products**

**Scientific:**
CD98 immunostaining can be implemented for the selection of patients who are candidate for de-escalation therapies.

**Societal:**
Despite a favorable prognosis, patients with HPV-positive head and neck tumors are still treated with high toxicity regimen.

**Economic:**
Reduction of toxicity by de-escalation of therapy will reduce health care costs.

**Leading Company**
Further development by VUmc

**Future outlook:**
Suitable test for selection of patients with HPV-positive tumors in treatment de-escalation trials
Epigenetic predictive biomarkers in lung cancer and head and neck cancer

**RATIONALE**

Epigenetics is the study of changes in gene expression or cellular phenotype, caused by mechanisms other than changes in the underlying DNA sequence, hence the name epigenetics. Most of these changes are heritable. In many diseases, abnormalities in gene expression have been linked to aberrant levels of DNA methylation (epimutations).

MethylCap_Seq is a new high resolution technology to uncover DNA-methylation in a truly genome-wide manner. The approach is based on the identification of DNA CpG methylation by capturing DNA fragments with proteins containing methyl binding domains followed by next-generation nucleotide sequence analysis on the Illumina GA II platform (pair-end tag). Using this approach, we obtained the unique global methylation status of a series of 12 head&neck carcinomas and 6 head&neck cancer cell lines.

The Differential Methylated (DM) markers between N0 and N+ samples as well as between in vitro radiosensitive (RS) and radioresistant (RR) cell lines were ranked by decreasing likelihood of DM. This analysis resulted in a gene list of which some have been associated with cancer development previously (ARHGEF4, TBC1D15, TAL1, WISP1, EMX2, KCNIP1, CNRIP1, SOBP, CCT6A, GPD2, PAX7 and GAS7).

**Leading Company:** MDxHealth

**Main results in CTMM:**

For the technical validation of the MethylCap-Seq approach, we designed and performed MSPs for ARHGEF4, KCNIP1, GPD2, CTPS, TMEM117, SGPL1, NFE2L1, ZDBF2, GAS7 and DLGAP4. MSP analysis of NFE2L1, ZDBF2, GAS7 and DLGAP4 revealed that only methylation of GAS7 showed an association with N-status in a small series of N+ (n=20) and N0 OSCC FFPE tissues (n=20) (p=0.10). GAS7 (for growth arrest-specific protein 7) was previously shown to be epigenetically silenced in cancer. Based on refined filtering we selected 6 additional genes that showed a marked difference in the mean methylation status between the N0 and N+ group for validation by BSP-pyrosequencing and QMSP (NR2E1, GPR135, EDNRB, FAM90A24P, KIF1A and VOPP1).

**Future outlook:**

Test independent cohort to establish clinical utility

**TRANSLATIONAL PIPELINE**

**TOWARDS PATIENTS**

**Scientific:** Biomarkers play a critical role in improving the drug development process as well as in the larger biomedical research enterprise. Understanding the relationship between measurable biological processes and clinical outcomes is vital to expanding our arsenal of treatments for all diseases, and for deepening our understanding of normal, healthy physiology.

**Societal:** Better biomarkers will prevent under- and overtreatment.

**Economic:** Predictive biomarkers will be used for more efficient drug development and for tailoring of therapy, ultimately resulting in improved cost-effectiveness of care.
Mitochondrial DNA variation as a marker for stratification of lung cancer patients

AirForce aims to identify and validate prognostic and predictive non-imaging biomarkers. Radiation-induced lung toxicity (RILT) is dose-limiting for radiotherapy of lung cancer and the current prediction parameters in use are only moderately associated with RILT. A contribution of genetic parameters possibly associated with RILT has been postulated. Maastricht Innovations have shown in preliminary results that variants in mitochondrial DNA (mtDNA) are associated with patient related variability in lung toxicity after radiation. In other words mtDNA can be used as predictive biomarkers of lung toxicity.

**Current practice**

All the same low doses: ineffective therapy + more side effects

**Personalised approach**

High doses: more effective

Low doses: fewer side effects

**Leading Company**

Maastricht Innovations / pTheragnostic

**Progress obtained in translational pipeline**

- Discovery Pathways biomarkers
- Selection Pathways biomarkers
- Demonstrator Development device
- Clinical Evaluation cohorts
- Market access

Progress within CTMM:

- 2012
- 2013

**Main results in CTMM:**

Validation of the predictive value of our proprietary mtDNA analysis for radiation induced lung toxicity.

In collaboration with Ghent University Hospital, the proprietary mtDNA analysis was finetuned and validated. Datasets of 321 lung cancer patients treated at Maastro Clinic and 66 lung cancer patients treated at Ghent were available. We considered as an endpoint grade of maximal dyspnea \( \geq 2 \) within 0-6 months after radiotherapy, irrespective of the baseline dyspnea (at the start of radiotherapy). All positions in the mtDNA were analyzed, and the positions with a variant vis-à-vis a reference sequence were noted. Variants were grouped into functional categories which were feeded into the prediction algorithm. The performance of our model was significantly better than the gold standard, mean lung dose.

**Future outlook:**

A collaboration with several international research groups will result in a second external validation cohort for lung toxicity and the testing of the same approach for prostate, breast and head and neck radiotherapy.

**Expected impact of the products**

**Scientific:** Stratifying patients according to their risk level for radiation-induced toxicity and selecting radiation treatment accordingly would provide a promising tool for individualised radiotherapy.

**Societal:** Identifying the patients at low or high toxicity risk will prevent under- and overtreatment.

**Economic:** Treating patients with the optimal dose will result in improved cost-effectiveness of care.
Druggable targets: targeted therapy of HNSCC and NSCLC

The 5-years survival of head and neck cancer patients is 50% and of lung cancer patients a mere 10-20%, despite intensive treatment protocols. These treatments cause toxicity and morbidity, increasing health care costs and suffering. Improved treatment regimens that are preferably less toxic are urgently awaited. We performed genome-wide siRNA screens to identify druggable gene targets to improve treatment of lung and head and neck cancer.

**Main results in CTMM:**
- We found 362 siRNAs that are lethal for both lung and head and neck cancer cells
- Over 80% have been validated in multiple tumor cell lines and not in normal cells
- We found 344 siRNAs that sensitize lung cancer cells for irradiation and 104 siRNAs that sensitize head and neck cancer cell lines to cisplatin
- As proof of principle we tested the drug ispinesib targeting KIF11

**Future outlook:**
There is a wealth of opportunity to improve therapy by targeting the druggable genes that were identified.

**Leading Company**
Further development by VUmc

**Expected impact of the products**

**Scientific:**
Many new drug targets identified for further research.

**Societal:**
Improvement of therapy by targeted agents is urgently awaited to increase the survival rates of these diseases with grim prognosis

**Economic:**
The treatment of cancer is costly and not very effective causing a large burden on health care.
PET tracers to guide high-precision chemoradiation

**Airforce** aims to develop imaging tools for high-precision treatment of lung- and head and neck cancer patients with radiotherapy and/or chemotherapy. Tracers for Positron Emission Tomography (PET) are key for this purpose as they can (1) delineate tumors or resistant tumor areas accurately, (2) guide selective targeting of the disease, and (3) monitor at an early stage whether treatment is effective.

**Imaging makes ‘personalized medicine’ possible**

1. **Airforce**
2. PET radionuclides and tracers
3. **Development PET radionuclides and tracers**

PET radionuclides are produced by cyclotron technology. By using dedicated labeling methods the radionuclides are inertly coupled to diagnostic or therapeutic agents that target tumors selectively to form so-called “PET tracers”. Next to PET radionuclides also fluorescent dyes can be coupled to allow optical imaging. Tracers were developed to image tumor metabolism, proliferation, angiogenesis and hypoxia and to image so-called targeted drugs like monoclonal antibodies and tyrosine kinase inhibitors in the human body.

**Leading Company:** Cyclotron BV

**Partnership**

**Main results in CTMM:**

- **PET radionuclide and tracer production:** Production of the long-lived PET radionuclides zirconium-89 and iodine-124 was established for worldwide distribution. Among others, a series of hypoxia tracers was developed. Reagents and standard protocols were made worldwide available for Good Manufacturing Practice-compliant labeling of antibodies (immuno-PET, photoimmuno-detection) and TKIs (TKI-PET).
- **Tracer validation:** in collaboration with many large international pharma companies the value of aforementioned PET tracers was assessed. Imaging tools as developed within AirForce were implemented in two new initiatives aiming for more efficient drug development and application: The Dutch Imaging Hub and the European Infrastructure for Translational Medicine (EATRIS).

**Future outlook:**

(wide-range) distribution of PET radionuclides and tracers of value for drug, development and image-guided therapy.

**Expected impact of the products**

**Scientific:** PET studies with new tracers will allow more precise detection and biological characterisation of tumors, better understanding of drugs, more precise targeting of therapy, and earlier assessment whether therapy is effective.

**Societal:** High precision quantitative PET imaging will prevent under- and overtreatment.

**Economic:** Tracers will be used for more efficient drug development and for tailoring of therapy, ultimately resulting in improved cost-effectiveness of care.

**Number of LC and HNC patients per year:** 1.8 and 0.56 million

**Total healthcare cost per year:** $US 25-40 billion
PET-CT software tools for high precision chemoradiation: Motion compensation

Motion and deformation of the target during imaging is a limiting factor for quantification of PET data. Therefore, methods are required for motion correction of PET images using information about motion (deformation) within the patient during PET scanning.

We have developed a motion compensation method for 4D PET/CT data. It constructs a motion model from the 4D CT data, which is used to deform the 4D PET data, after which the frames of the 4D PET are summed together.

The motion compensation tool has been integrated into the Imalytics, Philips’ research workstation (see below).

Figure 1. Screenshot of the motion compensation tool within the Imalytics framework.

**Progress obtained in translational pipeline**

Discovery Pathways biomarkers
Selection Pathways biomarkers
Demonstrator Development device
Clinical Evaluation cohorts

Progress within CTMM

Main results in CTMM:

We have tested the product on phantom data, and investigated the effects of motion compensation in terms of detected tumour volume and local uptake concentrations for lung and liver data. Furthermore we have investigated how the use of 4D PET/CT improves attenuation correction, in comparison to 3D data.

For both lung and liver tumours, motion compensation led to an increase in tracer concentration (up to 25%) and a decrease in tumour volume (extremes up to 50%). Furthermore we found that ungated attenuation correction can introduce tracer uptake errors of up to 25%.

**Figure 2. Phantom respiration effects for different sphere sizes.** Static, moving (2cm amplitude) and motion compensated PET data are shown.

Future outlook:
Investigation of effects of motion compensation on radiotherapy plans

**Expected impact of the products**

**Scientific:**
Motion compensation will make PET imaging more quantitative, which improves reproducibility of results in scientific studies.

**Societal:**
Motion compensation will lead to better visibility of tumours, and thereby improves the diagnostic value of the modality. Target volumes for radiotherapy will be smaller and need smaller margins.

**Economic:**
The product will improve image quality without increasing tracer dose or scan duration.
PET-CT software tools for high precision chemoradiation: Pharmacokinetic modeling and data analysis

**Pharmacokinetic modeling** is a technique to describe the absorption, distribution, metabolism and excretion of a drug based on dynamic medical imaging data.

In order to obtain quantitative parameters from those images, we have used **Voxulus**, the Pharmacokinetic modeling tool of **Imalytics**, Philips research workstation.

Voxulus performs an efficient voxel-wise estimation, while allowing complete control over the model parameters as well as a flexible combination of models for the input and target functions.

**Leading Company:** Philips Research

---

**Main results in CTMM:**

Pharmacokinetic modeling tools implemented and adapted for tracers developed within the Airforce project.

Assessment of optimal data analysis strategies, i.e., quantitative measures and kinetic analysis methods for tracers developed within the AirForce project.

Implementation and optimization of PET based tumor delineation methods for deriving quantitative tracer uptake measures from PET/CT studies.

**Future outlook:**

Use of voxulus toolbox for PET pharmacokinetic analysis and quantification of (new) tracers *in vivo*.

---

**Expected impact of the products**

**Scientific:**
Advanced pharmacokinetic modeling implemented in a worldwide available research software platform.

**Societal:**
Patients profit from more precise diagnostic, treatment and monitoring procedures based on advanced pharmacokinetic modeling.

**Economic:**
Knowing and understanding the exact distribution and retention of the agent inside the body helps for personalized usage of drugs.
PET-CT software tools for high precision chemoradiation: Partial volume correction

Due to the limited resolution of a given imaging system, the apparent activity in small objects or regions (partial volume) can be underestimated. Therefore, in order to compensate this effect, it is necessary to apply the so called Partial Volume Correction, a series of techniques that modifies the volume-of-interest statistics to ensure a proper quantification, which takes into consideration spill-overs and spill-ins between regions.

In this project we worked with Imalytics, Philips’ research workstation, which offers four different algorithms for the correction of the Partial Volume Effect:
- Recovery-Coefficients-Method
- Geometric-Transfer-Matrix-Method
- Lucy-Richardson-Deconvolution
- Blind-Deconvolution

Leading Company: Philips Research

Main results in CTMM:
Within Airforce the performance of several commonly used and new PET based tumor delineation and PVC methods were developed, implemented and evaluated. Delineation methods included were absolute and relative (%) isocontour based on SUVmax or SUVpeak both with and without local contrast corrections. Moreover, iterative and gradient based methods were evaluated as well. Evaluations were based on mathematical phantoms and clinical data and a comparison was made with pathology derived tumor sizes.

This research has shown that an automated PET delineation method based on 50% isocontour of SUVpeak corrected for local contrast showed best test-retest performance and correlated well with pathology derived tumor sizes. Moreover, use of PVC results in more accurate quantification of radiotracer uptake.

Future outlook:
Metrics to characterize and quantify tracer uptake distributions and heterogeneity have become available and will be further explored and more metrics will be implemented

Expected impact of the products
Scientific:
Achieved results on correction for partial volume effect allow careful selection of the correction methods for different applications
Societal:
Images corrected for partial volume effect and analysed using optimal tumor delineation methods can provide higher diagnostic value because of enhanced (more accurate and more precise) image quantification
Economic:
Implementation of PVC may allow to increase diagnostic quality and therefore be more cost effective
Radiomic analysis as tool for treatment planning of both lung and head and neck cancer

AIRFORCE aims to develop image analysis tools to identify and validate prognostic and predictive imaging biomarkers. Human oncologic tissues exhibit strong phenotypic differences, such as intratumour heterogeneity or an irregular shape (figure 1).

Advances in both acquisition and analysis methods of medical imaging technologies, allow for the extraction of reliable and informative image features to quantify these differences. This is an emerging field and many of these phenotypic characteristics are not routinely quantified or yet used in clinical decision-making. Radiomics addresses this issue by converting medical images into minable data with the high-throughput application of data-characterization algorithms (figure 2).

Leading Company
ptTheragnostic / Maastro Innovations

Progress obtained in translational pipeline

Main results in CTMM:
A radiomic signature for NSCLC and HNSCC: A total of 440 radiomic features, quantifying phenotypic differences based on tumor image intensity, shape and texture, were extracted from computed-tomography (CT) images of 1019 patients with lung or head and neck cancer and analyzed for their association with overall survival. A large number of radiomic-features were found to have strong prognostic power.

A radiomic-signature capturing intra-tumor heterogeneity, was strongly prognostic in independent validation datasets of lung and head and neck cancer patients, and associated with underlying gene-expression patterns. These results suggest that radiomic-features decode a prognostic phenotype existing in both lung and head and neck cancer, which may generalize to other tumors.

Future outlook:
the results should stimulate further research of image-based quantitative features and be applied to other image modalities (e.g. PET, MR).

Expected impact of the products
Scientific: Imaging is routinely used in clinical practice, worldwide, in all stages of diagnoses and treatment, Radiomics will allow for more precise tumor characterization and better early assessment of treatment effect.

Societal: Radiomics may aid to prevent under- and overtreatment

Economic: Radiomics provides an unprecedented opportunity to improve medical decision-support, which may in turn result in an overall improved cost-effectiveness of care.
www.predictcancer.org: A prediction tool for treatment planning of both lung and head and neck cancer

Although many clinical prediction models have been developed, validated and published, they are seldom used in daily clinical practice. To stimulate this, models should be easy to understand and to use. Moreover, clinicians should have easy access to the models.

Therefore, the aim of this (sub)project was to develop a website on which the prognostic and predictive models are published, results of AirForce can be disseminated, and the use of the models can be stimulated (See Figure).

**Progress obtained in translational pipeline**

**Main results in CTMM:**

The website (www.predictcancer.org) was launched in May 2010 and contains models for outcome prediction for NSCLC patients (dyspnea, dysphagia and survival), and Head and Neck cancer (overall survival, local recurrence and cost effectiveness of proton versus photon treatment). For each model extensive information is given as well as an interpretation of the model output.

**Future outlook:**

Models will be updated and improved with new predictive and prognostic variables. Models for other outcomes and other cancers will be added.

**Expected impact**

**Scientific:**

The website facilitates dissemination of the results of our project. It stimulates use and implementation of the models in daily clinical practice.

**Societal:**

Clinicians and patients are provided with additional prognostic information. This also facilitates the shared decision making process.

**Economic:**

The use of the models will result in less over- and undertreatment and thus decrease health care costs.
Optimized uncertainty based planning system for radiotherapy

Radiotherapy treatments need accurate patient position uncertainties management. Standard approaches as margin expansion are not always effective. Prescribing non uniform dose distributions based on functional or molecular imaging is becoming increasingly more common. When this approach is followed, and dose prescription is voxel-based, uncertainties management can become impossible with standard tools as margin expansion requires volume-based prescription.

**FIG. 1:** A head and neck cancer patient planned with standard technique (left) or probabilistic planning (right).

Probabilistic planning and evaluation provides a tool to incorporate uncertainties into the treatment workflow even when margin expansion is not feasible. Using monte carlo sampling of errors, potentially allows the most personalized treatment strategies.

**Leading Company:** Philips Research

Main results in CTMM:
Our studies showed that uncertainty based planning has potential to reduce dose to organs at risk, minimizing the overlap area between the irradiated volume and the surrounding structures. This way also treatment toxicity can be reduced. We also proved that when uncertainties are not properly taken into account in voxel-based prescriptions major discrepancies can occur between the calculated and the delivered dose distributions, resulting in serious target underdosage.

In particular, we realized that voxel-based dose painting approaches, without accommodations for geometric uncertainties, suffer from an intrinsic difficulty in controlling the high peak areas.

**Future outlook:**
This work is being implemented in the Pinnacle treatment planning system and hopefully will become a standard planning tool.

**Progress obtained in translational pipeline**

<table>
<thead>
<tr>
<th>Year</th>
<th>Discovery</th>
<th>Selection</th>
<th>Demonstrator Development device</th>
<th>Clinical Evaluation cohorts</th>
<th>Market access</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2013</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Expected impact of the products**

**Scientific:** increased awareness of the risks of underestimating uncertainties when planning with the advanced strategies described.

**Societal:** Dose painting strategies allow for more aggressive therapies on the target, e.g. allowing dose escalation strategies. This increases treatment efficacy and therefore patients survival rates.

**Economic:** The work performed was implemented in a plugin for a treatment planning system (Philips Pinnacle) increasing its clinical value and making it a more interesting tool for hospitals willing to approach new advanced planning strategies.

**Number of LC and HNC patients per year:** 1.8 and 0.56 million
**Total healthcare cost per year:** $US 25-40 billion
Oncology Research Workstation (ORW) for lung and head and neck cancer

The Philips research workstation Imalytics was used as the basis for the Oncology Research Workstation (ORW). The workstation operates on a local DICOM image database and can be connected to other DICOM network nodes (e.g. PACS systems or imaging equipment). During the course of the project the ORW was extended to include:

- A programming interface for external algorithms
- DICOM-RT support
- Advanced PET segmentation algorithms from the VU
- Motion compensation from NKI
- Image alignment for response monitoring from UMCG
- Partial volume correction
- Serial image analysis

Leading Company: Philips Research

Progress obtained in translational pipeline

Main results in CTMM:
The integration of partner’s algorithms provided an independent test of these algorithms and allowed all Airforce partners to use them for their research projects.

Example: image analysis workflow for response monitoring used at UMCG

Future outlook:
The method of integration of research algorithms in a commercial image analysis system should be adopted by other products.

Expected impact of the products
Scientific: Enables PET tracer studies where advanced image processing, registration and segmentation algorithms provide a higher accuracy of the response measurement, allowing earlier adaptation of non-optimal chemo- or radiotherapy.

Societal: A timely adaptation of cancer treatment to replace, e.g., non-effective drugs will lead to better patient outcome in terms of quality of life, response and complications

Economic: Selected tools will become part of Philip’s novel imaging products
Release of ECRF PACS connection as open source software

Many clinical trials use Electronic Case Report Forms (ECRF), e.g., from OpenClinica. Trial data is augmented if DICOM scans, dose cubes, etc. from the Picture Archiving and Communication System (PACS) are included for data mining. Unfortunately, there is as yet no structured way to collect DICOM objects in trial databases. In this paper, we obtain a tight integration of ECRF and PACS using open source software. Methods: DICOM identifiers for selected images/series/studies are stored in associated ECRF events (e.g., baseline). Our ECRF centric approach supports automatic data mining by iterating over the cases in the ECRF database, providing the identifiers to load images and the clinical data to correlate with image analysis results.

A small button allows linking anonymized PACS data with case reports for clinical trials – a technique not available in any trial database system up to now.

Leading Company:
Further development by NKI/AvL

Main results in CTMM: The connection of an ECRF and a PACS allows safe, simple and unambiguous collection of any DICOM data that is associated with clinical trial patients. This provides researchers working with clinical trial data with much more information about individual treatments, allowing better analysis and discovery of novel imaging biomarkers.

Expected impact of the products
Scientific: Rather than collecting image and dose metrics as variables in a clinical trials, the system allows collection of the full image data. The collected data will allow discovery of novel imaging biomarkers.
Societal: The increased power of clinical trial data analysis, will allow faster hypothesis generation to define new trials. As a result, novel improved treatments will be introduced faster.
Economic: The system is open-source and is used in open-source OpenClinica and closed-source FormsVision.
Early HTA: Key Elements and Findings

Elements of early HTA

Health economic modeling
Cost-effectiveness studies in cancer care are often health-economic evaluations alongside clinical trials or relatively simple health-economic models in which a homogeneous cohort of patients is simulated. These models are easy to understand for decision makers, transparent and relatively easy to build. However, as decision making in health care is becoming increasingly complex, disease models need to include more detail. With the shift towards individualized therapy, treatments are increasingly tailored to the specific characteristics of a patient and a tumour. To obtain clinical predictions that accurately estimate patient outcomes, integration of the clinical, molecular and imaging information on patient and tumours in is needed. This means that for a proper evaluation of long-term costs and effects of individualized strategies, cost-effectiveness models need to incorporate patient and tumour features that may affect treatment decisions, disease progression, survival, adverse events and quality of life.

Cost-effectiveness analysis
Cost-effectiveness analysis (CEA) involves a comparative analysis of the health and cost consequences of alternative courses of action. To support decision making, there is an urgent need for economic evaluations in the area of radiotherapy, comparing new technologies with each other and with conventional schemes.

Key findings AIRFORCE

There is a dearth of cost-effectiveness evaluations of radiotherapy treatment in non-small cell lung cancer (NSCLC).

On the basis of a model-based cost-effectiveness evaluation, we conclude that positron emission tomography (PET)-based isotoxic accelerated radiation therapy treatment (PET-ART) is likely to be cost-effective compared to conventional fixed-dose CT-based radiation therapy treatment in NSCLC. We found a 36% probability that PET-ART improves health outcomes at reduced costs and a 64% probability that PET-ART is more effective at slightly higher costs.

Model-based assessment of optimized sequential and concurrent chemo-radiation strategies revealed that these more effective and cost-effective than the current conventional sequential and concurrent strategies in NSCLC. Concurrent chemo-radiation with a daily low dose cisplatin regimen is the most cost-effective treatment option for locally advanced inoperable NSCLC patients.
Early HTA: Potential Impact of New Technologies

Health economic model

We developed a micro-simulation model for cost-effectiveness analysis of individualized radiotherapy in lung cancer. Four clinical states were included in the model: ‘Alive without progression’, ‘Local Recurrence’, ‘Metastasis’, and ‘Death’. Individual patients are simulated by repeatedly sampling a patient profile, consisting of patient and tumour characteristics. The model tracks clinical events over time and takes patient and tumour features into account. The transitioning of patients between the health states is governed by personalized time dependent hazard rates, which were obtained by multi-state statistical modelling.

Model outcomes are life years, QALYs, and costs. The time horizon is life time. A hospital perspective was taken. Two types cost-effectiveness evaluations were carried out using the model.

Cost-effectiveness analysis of positron emission tomography (PET)-based isotoxic accelerated radiation therapy treatment (PET-ART)

The average incremental costs per patient of PET-ART were €569 for 0.42 incremental Qys and 0.33 QALYs gained. The base-case scenario resulted in an ICER of €1360/LY gained and an ICUR of €1744/QALY gained. The probabilistic sensitivity analysis gave a 36% probability that PET-ART improves health outcomes at reduced costs and a 64% probability that PET-ART is more effective at slightly higher costs. On the basis of the available data, individualized PET-ART for NSCLC seems to be cost-effective compared with conventional fixed-dose CT-based radiation therapy.

Cost-effectiveness analysis of optimized sequential and concurrent chemo-radiation strategies

Four strategies were evaluated: PET-CT based isotoxic accelerated sequential chemoradiation (SRT2) and concurrent chemo-radiation with daily low-dose cisplatin (CRT2) to standard sequential (SRT1) and concurrent chemo-radiation (CRT1). Compared to the reference strategy (SRT1), the ICER was €38024/QALY for CRT1, €6249/QALY for SRT2, and €346/QALY for CRT2. CRT2 was highly cost-effective compared to SRT1. Moreover, CRT2 was more effective and less costly than CRT1 and SRT2. Based on our model, optimized sequential and concurrent chemo-radiation strategies are more effective and cost-effective than the current conventional sequential and concurrent strategies.

Model structure

[Diagram of health states and transitions with hazard rates indicated]
List of Publications


List of Publications


37. van Velden FH, Boellaard R. Reply to: Area under the cumulative SUV-volume histogram is not a viable metric of intratumoral metabolic heterogeneity. Eur J Nucl Med Mol Imaging. 2013 Sep;40(9):1469-70
List of Publications


List of Publications


Co funded by

Netherlands Enterprise Agency

International Scientific Advisory Committee

Prof. R.S. Reneman, Ph.D. (Chair)
Prof. J.A. Andersson, M.D., Ph.D.
J.P. Armand, M.D., MSc.
R.S.B. Balaban, Ph.D.
J.B. Bassingthwaighte, Ph.D.
R.G. Blasberg, M.D.
Prof. L. Degos
H. Hermjakob, Ph.D.
W.J. Jagust, Ph.D.
Prof. D.J. Kerr
Prof. U.D.A. Landegren, M.D., Ph.D.
R.I. Pettigrew, M.D., PhD.
A. Tedgui, Ph.D.
Prof. T.P. Young