ARTFORCE REPORT

Summary

The ARTFORCE project succeeded by introducing very sophisticated imaging and radiotherapy tools into daily clinical practice to improve treatment outcome of patients with advanced Head & Neck and Lung tumours. Within interlinked projects treatment-specific tumour response predictors were developed for selection of the optimal treatment regimen for the combination of drugs and irradiation.

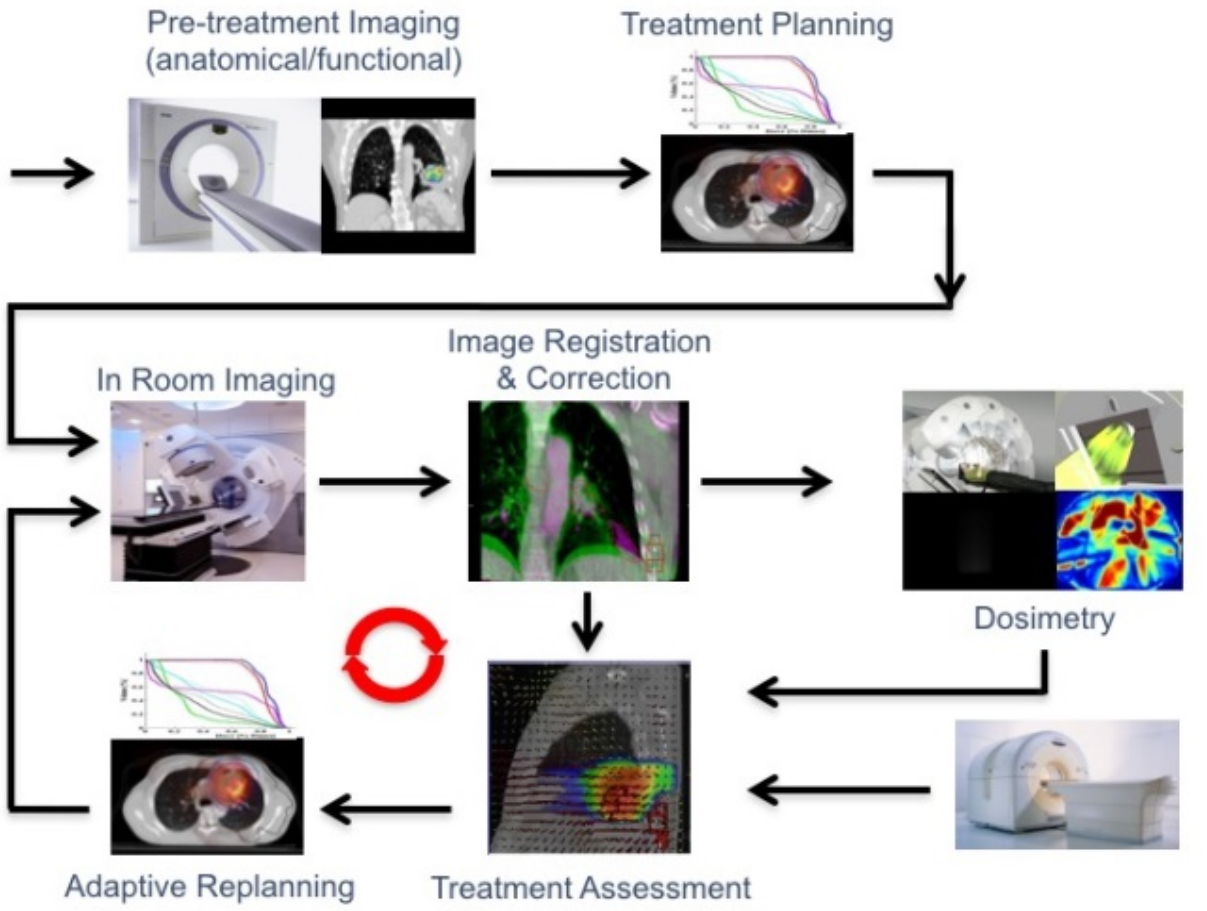

Figure 1:The process of adaptive intensity modulated image guided radiotherapy (IGART).

As a first step patient tailored irradiation was introduced with adapted intensity modulated image guided radiotherapy (IGART), based upon CT, MRI and PET imaging before and during treatment. For this precise delivery of the radiation dose novel on line image guided adaptive irradiation techniques were developed, including very advanced quality assurance methods with daily cone beam CT imaging and in vivo dosimetry. This created the possibility of treatment adaption based upon the response of the

tumour. This IGART allowed delivery of higher tumour radiation doses with sparing of the normal tissues. By targeting on the most radioresistant part of the tumour with IGART it aimed at higher tumour control rates, with less side effects and therefore improved quality of life (Figure 1.)
These methods were tested and approved within two major clinical trials carried out in the ARFORCE consortium consisted of 12 university hospitals in 7 European countries:

- A randomised Phase III trial with Cisplatinum or Cetuximab and standard or adaptive high dose radiotherapy for advanced Head & Neck cancer
- Dose-escalation by boosting radiation dose within the primary tumour on the basis of a pre-treatment FDG-PET-CT scan in stage IB, II and III NSCLC: A randomized phase II trial

Withholding ineffective, toxic treatments and to decrease community costs by targeting expensive treatments to those who will benefit was another objective of this project. The combined modality treatment with radiotherapy and Cetuximab for Head & Neck tumours appeared to be less effective than the combination of radiotherapy and Cisplatinum even for patients with patients with known HPV/p16 status. Therefor treatment-specific tumour response predictors were developed for patient selection, i.e. genetic predictors for Cisplatinum and radiation sensitivity as well as functional and anatomical imaging predictors early during the treatment. Further exploration of biomarkers, revealed novel predictors and prognostic biomarkers, including in a multi-centric setting tested innovative imaging modalities with radiomics. Within this project proof of concept was provided that molecular information can be derived from standard medical images with radiomics and it provided prognostic for patients with Head & Neck cancer. The validation of these biomarkers for predicting the Cisplatinum and radiation sensitivity will be performed after closing the ARTFORCE Head & Neck Phase III clinical trial in 2019.
The improvement of the overall level of radiation oncology in Europe by introducing and validating in routine clinical practice the methods for fully-controlled image guided adapted radiotherapy was one of the main objectives. Therefor several by presentations were given at courses and meetings for the European Radiotherapy community: (ESTRO). As a result, the developed methods are now introduced in daily clinical practice in several hospitals. This was accompanied with the publication of newsletters and 222 peer reviewed papers on this ARTFORCE project
The ARTFORCE project officially on 1-10-2017, although a number of activities will continue after closure: i.e. the clinical trials and the final evaluation and validation of the biomarkers.
closed

Summary description of project context and objectives

Background
Surgery, radiotherapy and chemo-radiation, i.e. the combination of radiotherapy with chemotherapeutics such as Cisplatinum or Cetuximab, are treatment options for patients suffering from Head & Neck cancer or Lung cancer. However considerable proportion of patients is diagnosed at a late stage and is treated with a combination of radiotherapy and cisplatin. This combination is effective, although not all patients benefit and less than half of the patients will be cured. By introducing new image guided targeted radiotherapy regimen higher radiation doses to the tumour, while sparing the surrounding normal tissues will lead to higher cures rates without increasing the side effects. To prevent that patients suffer from severe side effects without benefiting from the treatment, specific and sensitive biomarkers are urgently needed to support treatment decision. Withholding ineffective, toxic treatments and while targeting expensive treatments to those who will benefit will lead to improved

quality of life and decreased community costs. To this end, parallel to the novel irradiation and quality assurance programs, treatment-specific tumour response predictors were developed for patient selection, i.e. genetic predictors for Cisplatinum and radiation sensitivity as well as functional and anatomical imaging predictors early during the treatment.

Objectives

The aim of this project was to improve treatment outcome more specifically in advanced Head & Neck and non-small cell lung cancer patients by:

- Redistributing the radiation dose with adaptive image guided and intensity modulated radiotherapy towards the most resistant part of the tumour.
- Introducing novel 3-dimensional (3-D) optimized image guided radiotherapy techniques and quality assurance programs.
- Developing treatment-specific tumour response predictors, biomarkers and radiomics developed for individualizing patient's treatment,
- Disseminate the results to the community by means of exposure through scientific community and development of general applicable software and tools in combination with commercial partners.

Description of work performed and main results

The ARTFORCE project succeeded by introducing very sophisticated imaging and radiotherapy tools into daily clinical practice to improve treatment outcome of patients with advanced Head & Neck and lung tumours. The work carried out in this project aimed at higher tumour control rates with improved quality of life, by using MRI and PET imaging for targeting on the most radioresistant part of the tumour. This was achieved by enabling tailored irradiation to the most active parts of the tumour with the adapted image intensity modulated guided radiotherapy (IGART) based upon CT, MRI and PET imaging before and during treatment.

For precise delivery of the radiation dose novel on line image guided adaptive irradiation techniques were developed and very advanced quality assurance methods with daily CT cone beam imaging and in vivo dosimetry.

This allowed delivery of higher tumour radiation doses with sparing of the normal tissues. These methods were tested and approved within two major clinical trials:

- A randomised Phase III trial with Cisplatinum or Cetuximab and standard or adaptive high dose radiotherapy for advanced Head & Neck cancer
- Dose-escalation by boosting radiation dose within the primary tumour on the basis of a pre-treatment FDG-PET-CT scan in stage IB, II and III NSCLC: A randomized phase II trial

These clinical trials were carried out in the ARFORCE consortium, consisted of 9 university hospitals in 7 European countries: Christie NHS Foundation Trust: Maastro clinics, University Medical Center Utrecht; University Medical Center Groningen; Erasmus Medical Center; Institute Catala de la Salut, Vall d'Hebron; Gustave Roussy Cancer Institute; Karolinska Institute; Netherlands Cancer Institute-Antoni van Leeuwenhoek, and 3 associated university hospitals Academic Medical Center Amsterdam, University hospital Leuven, Rigshospitalet University Hospital Copenhagen

Withholding ineffective, toxic treatments and to decrease community costs by targeting expensive treatments to those who will benefit was another objective of this project. We showed that the combined modality treatment with radiotherapy and Cetuximab for Head & Neck tumours was less effective than the combination of radiotherapy and Cisplatinum even for patients with patients with known HPV/p16 status. Therefor treatment-specific tumour response predictors were developed for

patient selection, i.e. genetic predictors for Cisplatinum and radiation sensitivity as, well as functional and anatomical imaging predictors early during the treatment.

Within the ARTFORCE project there are several interlinked work packages.
Work package 2 (*Adaptive Radiotherapy to account for anatomical changes*) resulted in implementation of adaptive re-planning in all centres participating in the head-and-neck trial. Methods to quantify the accuracy of deformable image registration algorithms were developed. Furthermore, novel methods to adapt treatments together with a decision rule to select patients for adaptive replanning were evaluated.

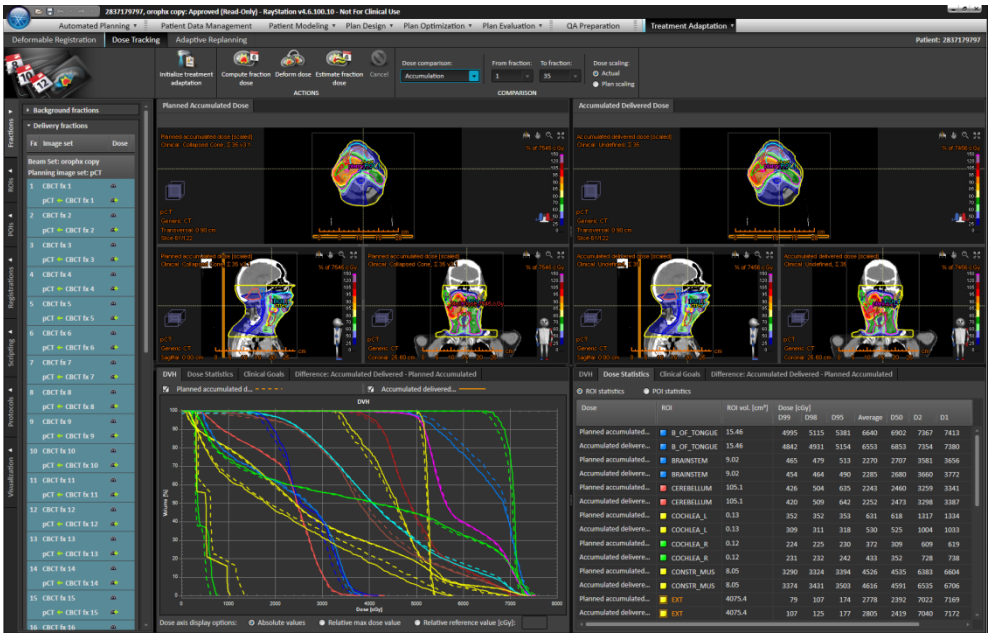

Figure 2: Screenshot of the dose accumulation graphical user interface comparing the planned and accumulated dose distribution

In work package 3 (*Biological adaptive treatment planning in the presence of advanced techniques*) algorithms were developed for biologically optimized treatment planning aimed at eradication of the tumour with minimal normal tissue morbidity based upon interim PET scans and recurrence pattern in the clinical trials. Also, implementation was achieved of the algorithm as an add-on module into a treatment planning system intended to estimate accumulated dose and patient specific treatment response making it possible to replan and eventually biologically adapt the treatment based on this additional information.

Work package 4 (Three dimensional in-vivo dosimetry) implemented and validated three dimensional in-vivo to allow early on-line detection of errors in treatment delivery of sophisticated radiotherapy in each participating centre. It a calibrated on-board flat panel electronic portal imaging device to act as a two dimensional dosimeter to capture the actual radiation delivered during the treatment. Additionally it uses the on-board cone-beam CT scanner to capture the anatomy at the time of treatment. These were combined into a QA platform to make a comprehensive verification platform that works for all major linear accelerator vendors.

Work package 5 (Biological *markers to predict the response of Head & Neck tumours to Cetuximab or Cisplatinum + Radiotherapy*) provided important prognostic and predictive information. A meta-analysis revealed prognostic impact of the immune infiltrate: novel organ-specific features of the immune infiltrate in distinct cancer types, as well as a strategy for defining new prognostic biomarkers.

The calreticulin expression constitutes a new powerful prognostic biomarker that reflects enhanced local antitumour immune responses in the lung. While the importance of formyl peptide receptor 1 mutation (FPR1) was highlighted in chemotherapy-induced anticancer immune responses. It was shown that overexpression and hyperactivation of poly(ADP-ribose) polymerase 1 (PARP1) and the downregulation of pyridoxal kinase (PDXK), correlated with elevated apoptosis resistance. Further exploration showed that PAR and PDXK were predictive biomarkers in non-small cell lung cancer:
For Head & Neck cancer radiomics features provided an added value to HPV status as prognostic and predictive biomarker treated with the combined modality radiotherapy with Cisplatinum or Cetuximab (Figure 3).

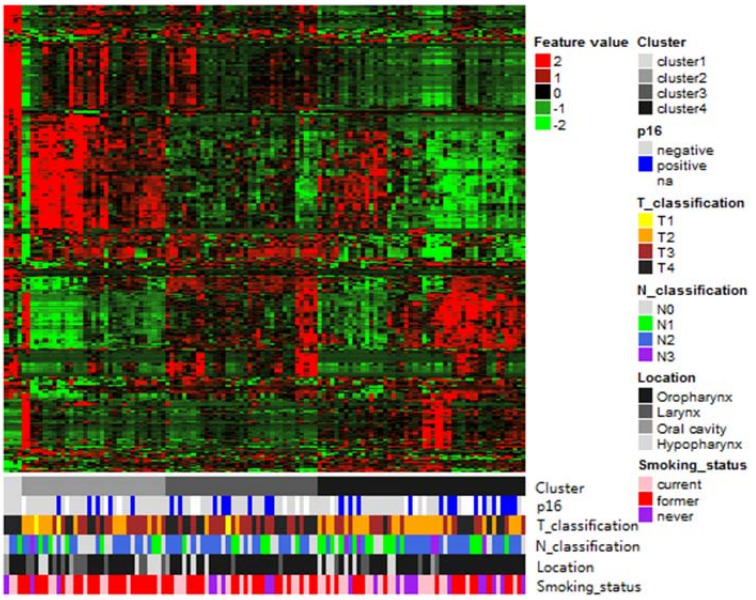

Figure 3. Heatmap displaying Z-scores of the feature values for the 544 radiomics features for the whole cohort (N = 120). Unsupervised clustering revealed 4 clusters of patients with similar radiomics expression patterns. We compared the 4 clusters of patients with clinical parameters, and found significant correlation with T classification (P = 3.3 * 10-5), primary tumour location (P = 0.01) and a nonsignificant correlation with smoking status (P = 0.09), whereas no correlation was observed with p16 status (P = 0.19) and N classification (P = 0.22).

The combination of microvascular density and CA-IX expression might give additional prognostic information in these patients with known HPV status. High CD8+ TIL level was an independent prognostic factor independent of HPV/p16status. CD8+ TILs and PD-L1 expression could provide complementary information to HPV status in selecting subpopulation for treatment de-intensification. Intraepithelial macrophage expression may play different roles in patients with p16+ vs. p16- disease. CD163+ cells density in stroma may provide information for selecting suitable patients for concurrent Cetuximab or Cisplatinum with radiotherapy. Established molecular signatures were assessed for their response prediction value in HNSCC patients treated with Cisplatinum and radiotherapy. Drug response and DNA repair defect linked expression markers were therefore developed and further improve the detection of poor prognosis patients. The validation of these biomarkers for predicting the Cisplatinum and radiation sensitivity will be performed after closing the ARTFORCE Head & Neck Phase III clinical trial in 2019.

Work package 6 (*Standardisation and innovative molecular imaging for prediction and decision making*), The main objective of the work package was to asses, in a multi-centric setting, innovative imaging modalities allowing better predicting outcome and individualizing. We investigated the possibilities of imaging of hypoxia and the presence of EGFR in patients with PET and DCE-CT. Predictive value of HX4 PET and DCE-CT imaging (Figure 4). A combined analysis of the patients in

the PET-boost trial and another trial in non-small cell lung cancer with the same pre-treatment imaging protocol (NCT01210378), showed that HX4 PET is a prognostic marker for overall survival.

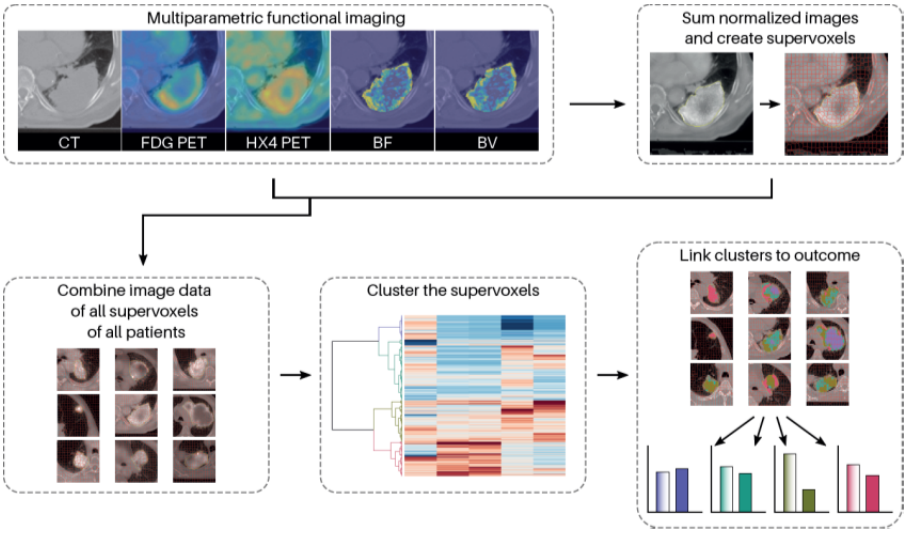

Figure 4. The workflow of the data analysis:

Also, radiomics was explored as a high-throughput mining of quantitative image features from standard-of‑care medical imaging that enables data to be extracted and applied within clinical-decision support systems to improve diagnostic, prognostic, and predictive accuracy. Our study provides proof of concept that molecular information can be derived from standard medical images and shows potential for radiomics as imaging biomarker of HPV status. The interchangeability was investigated of planning CT and conebeam CT (CBCT) extracted radiomic features. Furthermore, a previously described CT based prognostic radiomic signature for non-small cell lung cancer (NSCLC) patients using CBCT based features was validated. The previously developed radiomics signature has prognostic value for overall survival in three CBCT cohorts, showing the potential of CBCT radiomics to be used as prognostic imaging biomarker.

In work package 7 (*Dose-escalation by boosting radiation within primary tumour based on a pre-treatment FDG-PET-scan*): a randomized phase II clinical trial in locally advanced NSCLC: was carried out. Three extra centres have contributed patients to this trial, without formerly entering the consortium. An interim analysis on toxicity showed toxicity profiles in line with iso-toxic dose escalation. All patients received a follow-up FDG PET-CT scan, 3 months post treatment. These scans reveal increased CT densities and PET-uptake in irradiated normal lung tissue compared to scans acquired prior to treatment. Subsequently, a dose effect relationship for density changes and PET uptake was investigated. Both imaging modalities demonstrate a linear dose effect relation between 15Gy and 60 Gy although the slope differed substantially between patients. Above 70 Gy the relationship plateaus indicating a saturation of the dose-effect relationship. Moreover, severe damage was rare peripherally in the lung. These relationships could be exploited in plan optimization. The first toxicity results of the PET-boost trial showed that individualized dose-escalation up to normal tissue constraints was feasible and not related with unexpected acute or late toxicity. Therefore, it was concluded that dose-escalated radiotherapy to the primary tumour or regions with high FDG-uptake within the primary tumour did not reveal an unexpected or excess of acute and late toxicity. The trial is now closed with 107 randomized and 150 registered patients. The final analysis for the end results will be performed in 2018, when all patients have at least one year follow up.

In work package 8: (*Increasing the therapeutic ratio for Head & Neck cancers by pre-treatment selection and dose redistribution*) the phase III ARTFORCE clinical trial: A randomised study with Cisplatinum or Cetuximab and standard or adaptive high dose radiotherapy for advanced Head & Neck cancer after initial delays is well underway it accrued already 181 patients and will finish in the beginning of 2019. In the first approved version of the protocol, the trial consisted of a 2x2 design with four treatment arms, comparing 1. Cisplatinum versus Cetuximab and 2. Standard radiation dose to a dose-redistribution based on the FDG-PET activity. Furthermore, a pre-treatment Zirconium Cetuximab scan was done to improve future patient selection and an additional PET scan in de second week of treatment to facilitate development of biological adaptive radiotherapy in WP3. Patients with locally advanced (at least T3-T4) tumours of the oropharynx, hypopharynx or oral cavity who are fit for treatment with concurrent chemotherapy can be included. In 2014, after inclusion of 17 patients, the treatment schedule was amended because the pharmaceutical company stopped the free provision of Cetuximab. Therefor the trial was changed to a two-arm study comparing standard radiotherapy to dose-redistributed radiotherapy, with in both arms a conventional fractionated radiotherapy scheme with 3-weekly cisplatin. The Zirconium scan was replaced by a radiomics task, as well as an optional hypoxia imaging task with HX4 PET scans. The Head & Neck trial will be finalized in the beginning of 2019. At that time we will start with analysing the data from the patients in the clinical trial and work package 5 with validation of the predictive assays.

WP 9 (*Distribution of knowledge and expertise*) took care of the dissemination of the results aiming at improvement of the overall level of radiation oncology in Europe. This was achieved by introducing and validating in routine clinical practice the methods for fully-controlled image guided adapted radiotherapy Therefor several by presentations were given at courses and meetings for the European Radiotherapy community (ESTRO). This was accompanied with the publication of newsletters and 222 peer reviewed papers on this ARTFORCE project