RESEARCH PROJECTS

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IMAGE AND BIOLOGICAL GUIDED ADAPTIVE RADIOTHERAPY

Results from the ARTFORCE project

HARRY BARTELINK

The ARTFORCE consortium consists of eight European academic hospitals/research institutes, two European small and medium-sized enterprises (SMEs) and ESTRO. This project focuses on two major clinical trials in head and neck cancer and lung cancer. Both clinical trials are integrated with basic, translational and clinical research. The aim of this EU-funded project is to improve treatment outcome for patients with locally advanced head and neck cancer or non-small cell lung cancer (NSCLC) by:

1. Optimising local control by redistribution of the radiation dose, applying heterogeneous dose distribution towards the most active part of the tumour on the PET-CT. The patient's geometry, as well as the delivered dose using image-guided adaptive plan modifications and three dimentsional (3D) *in vivo* dosimetric verification, will be monitored to assure accurate delivery.
2. Maximising the benefit of combined modality treatment by measuring the uptake of cetuximab with ^{89}Zr labelled cetuximab. Radiation and cisplatin-sensitivity will be assessed using biomarkers predicting the response to cisplatin, genetic profiles and human papilloma virus (HPV) status. ▼

Progress made within this ARTFORCE project

Sophisticated novel irradiation techniques for use in clinical practice were developed, including software development for adaptive radiotherapy, 3D *in vivo* dosimetry, identification of biomarkers for treatment response and new imaging methods.

Adaptive radiotherapy

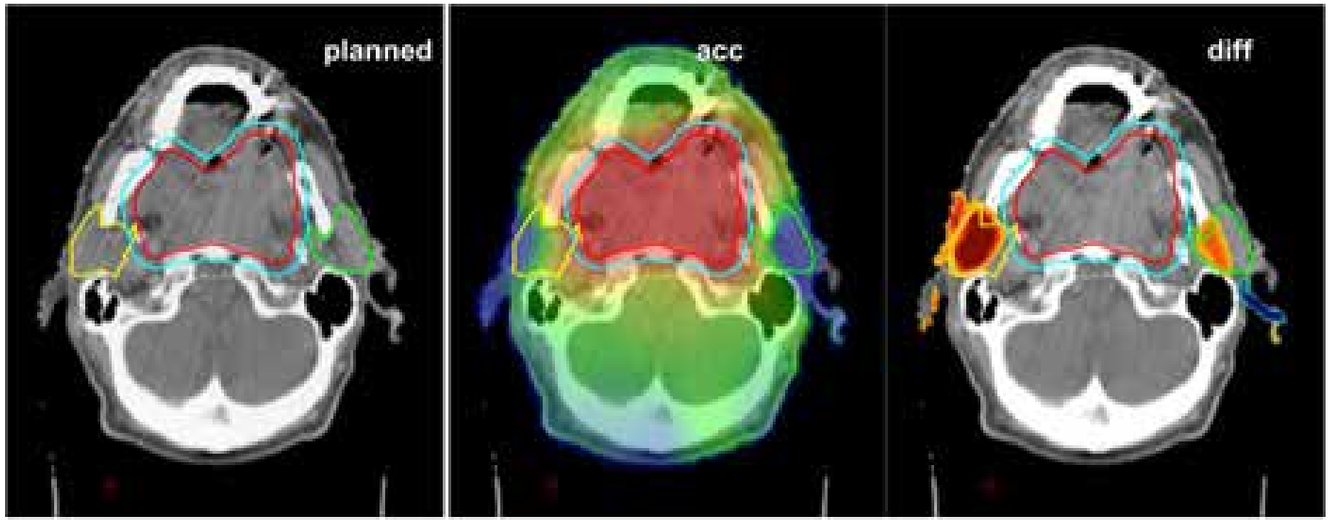
Jan-Jakob Sonke, Netherlands Cancer Institute

In order for adaptive radiotherapy to account for anatomical changes, all relevant imaging and planning data for improved outcome modelling and data mining were collected. A method to update the geometrical patient model was developed and validated. Using deformable image registration of repeat cone beam CT (CBCT) scans acquired during the first part of treatment, the original planning CT is deformed to the average patient model. This method has the potential to obviate the need to acquire extra planning CT scans for adaptive radiotherapy and to improve accuracy beyond the current state of the art.

Biological adaptive treatment planning

Iuliana Toma-Dasu, Karolinska Institutet

Research infrastructure for the assessment of tumour responsiveness based on two successive FDG PET scans has been developed. The first scan is taken at the planning stage, before the start of treatment, and the second one during ▼



Dose accumulation based upon cone beam CT

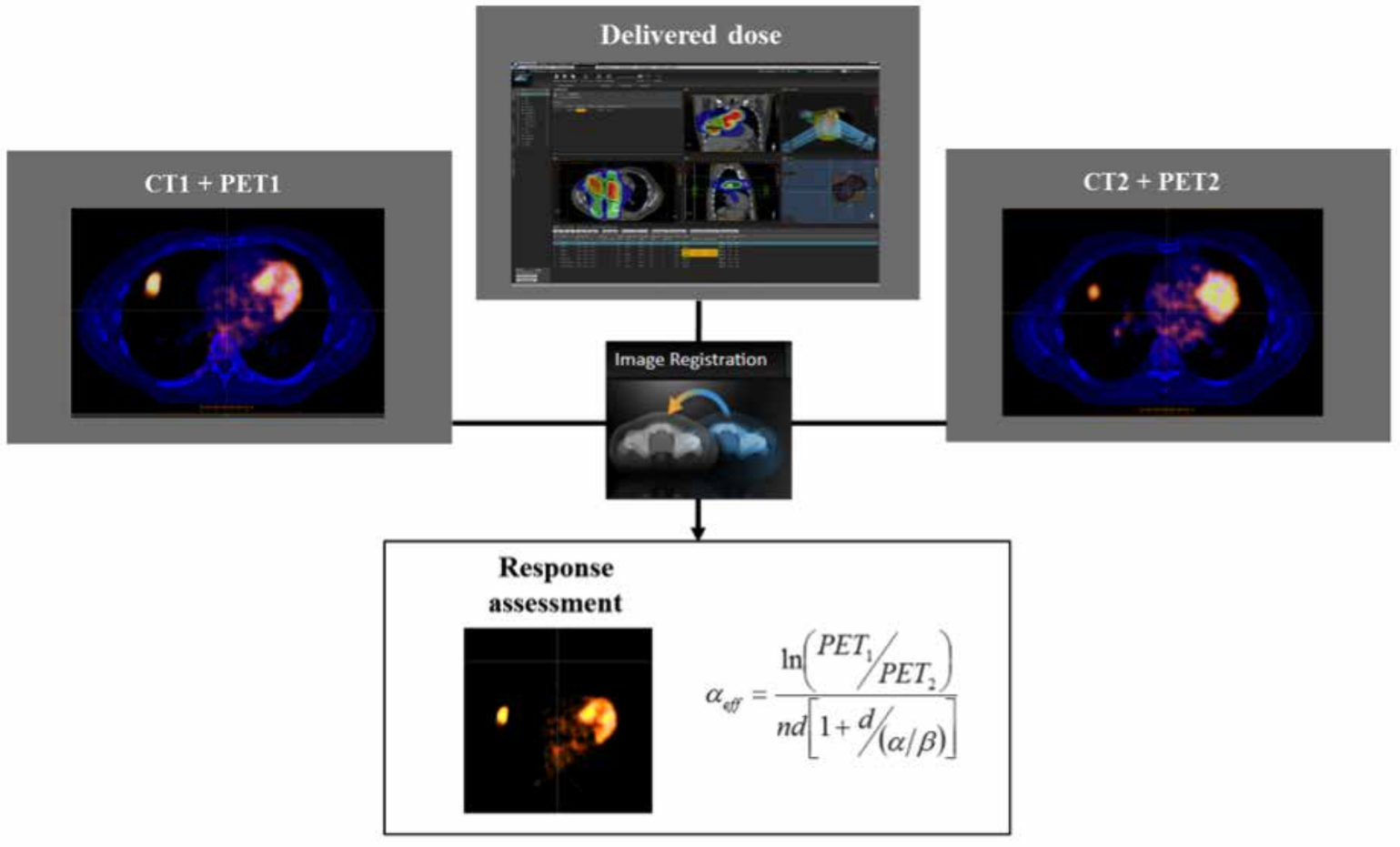
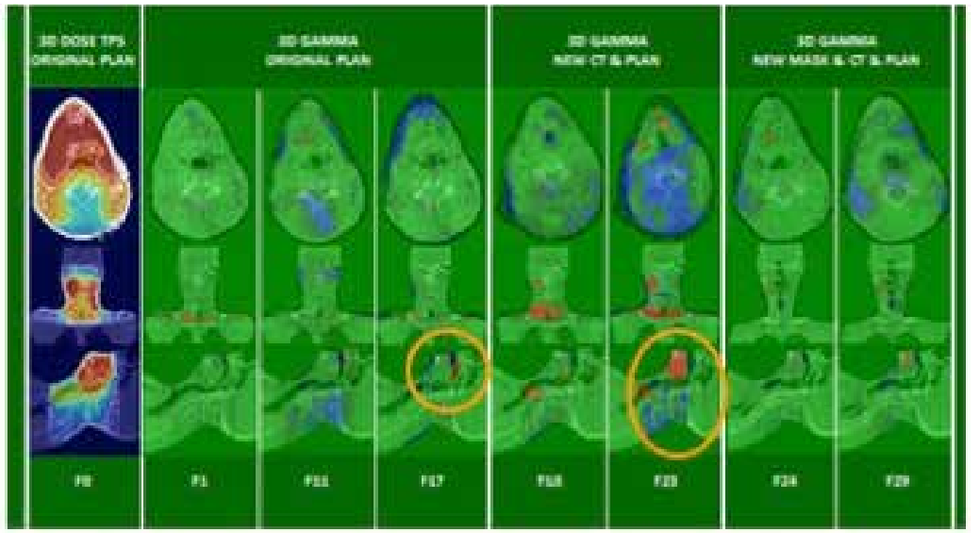
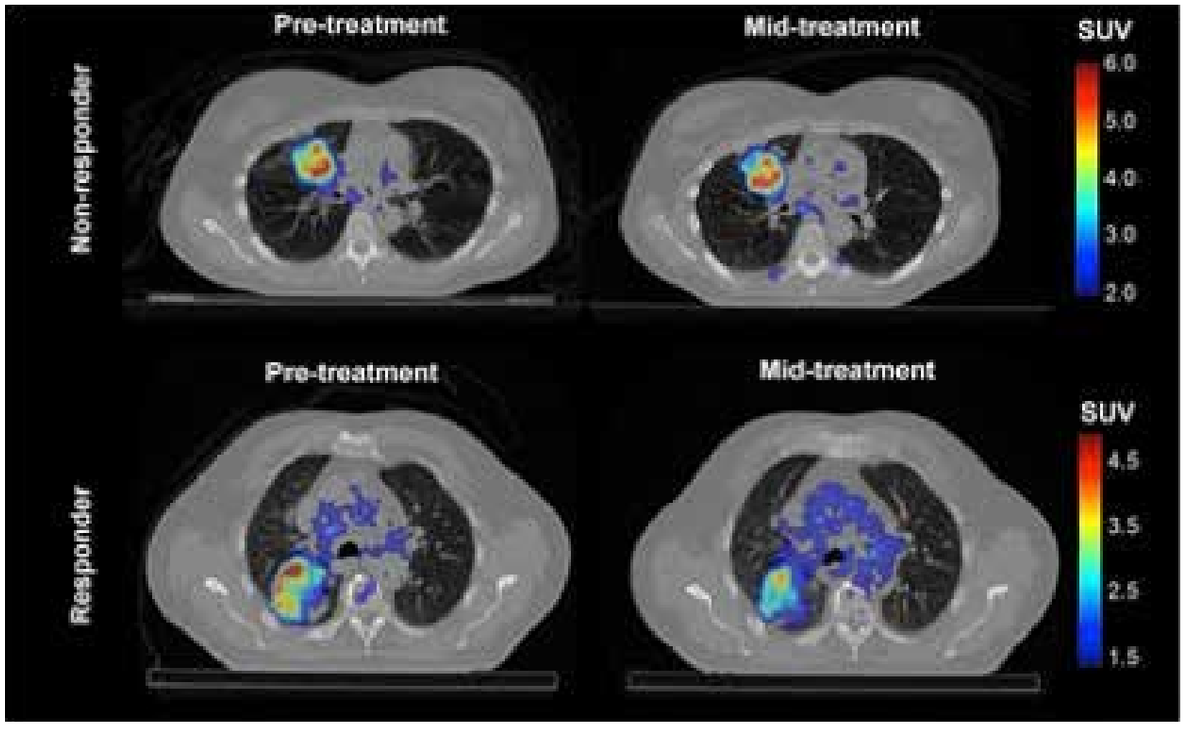


Illustration of the method used for the assessment of the tumour response based on two successive FDG-PET images in relation to the dose delivered by the time of the second FDG-PET acquisition [1]



Fraction 17: Adaptation necessary due to different placement of tongue separator compared to planning PET/CT scan
Fraction 23: Adaption performed because fixation (mask) did not fit patient anatomy anymore, new mask and new treatment plan created.

Example of a dose verification procedure for a patient in the head and neck ARTFORCE trial



Example of a repeated PET/CT in NSCLC (week 2 of radiotherapy after ± 20 Gy) [2]

the second week of treatment, in relation to the delivered dose. A method for the evaluation of the early response and the calculation of an operational parameter called effective sensitivity to treatment was developed and applied to 26 NSCLC patients. We showed that it is possible to determine a threshold value for the effective radiosensitivity of patients presenting a good response. The method based on the evaluation of the effective radiosensitivity is able to identify patients presenting poor response to treatment with 75% sensitivity and 100% specificity. The validation of the method for head and neck cancer patients is ongoing.

In vivo dosimetry

Wouter van Elmpt, MAASTRO

A 3D *in vivo* dosimetry was developed and implemented as an integrated quality assurance (QA) procedure to accurately verify dose delivery. This is applicable to all the major teletherapy systems in the EU. We have designed a method for the calibration of the on-board CBCT imager currently installed on linear accelerators. This step is necessary for accurate dose verification measurements. This verification can be performed using the software developed in this work package, but users/clinics may also use the CBCT calibration procedure for a quick recalculation of the dose distribution within the new anatomy derived from the CBCT in their own treatment planning system.

Biomarkers

Eric Deutsch/Lorenzo Galluzzi, Institut Gustave Roussy

During the first period of the project, we identified pyridoxal kinase (PDXK), the enzyme generating bioactive vitamin B6, as a prognostic marker in three independent cohorts of NSCLC patients. We have demonstrated that the metabolism of vitamin B6 is implicated in the response to cisplatin of head and neck carcinoma cells *in vitro*. However, we failed so far to identify a correlation between PDXK expression levels in head and neck carcinomas and disease outcome in clinical settings. We are actively investigating the reasons underlying this. In addition, we identified single nucleotide polymorphisms (SNPs) in Toll-like receptor 4 (TLR4) and ▼

autophagy related 16-like 1 (ATG16L1) that influenced evolution-free survival (but not overall survival) in 189 head and neck cancer patients. We are considering validating these findings in an independent patient cohort.

Imaging

Philippe Lambin, MAASTRO

Assessment of innovative imaging modalities is being carried out in a multi centre setting, allowing better prediction of outcomes and the individualisation of treatment. Visual analysis of head and neck cancer patients showed heterogeneous uptake of ^{89}Zr-cetuximab within the gross tumour volume (GTV). We concluded that the uptake of ^{89}Zr-cetuximab is visually heterogeneous and that uptake differs in patients with head and neck squamous cell carcinoma. Quantification shows higher tumour-to-background uptake levels of tracer and drug distribution for scans acquired on day 7 post-injection than on day 4. On the scans of day 7, eight out of ten patients had significant tumour uptake (defined as tumour blood ratio > 1.4).

An analysis in lung cancer patients (including those of the PET-BOOST lung trial) has been performed on the overlap fractions and regions for both FDG and HX4 PET scans. We concluded that there is a positive correlation between FDG and HX4 uptake parameters on a GTV level. Hypoxic volume was larger for lesions with high FDG-uptake values and larger GTV volumes. Comparison of the heterogeneous uptake patterns shows a large diversity. In general, a reasonable voxel-wise correlation is observed for the two PET tracers, although there are exceptions. The added value of HX4 in dose boosting strategies will be to define more accurately the therapy resistant voxels and to limit the boost volume.

Lung cancer trial

Jose Belderbos, Netherlands Cancer Institute
Dirk de Ruysscher, University Hospital, Leuven

The randomised phase II PET-boost trial investigated dose-escalated radiotherapy to the primary tumour as a whole or redistributed to FDG-active regions within the tumour using an integrated boost (24 fractions/5 weeks). The principal of isotoxic radiotherapy is applied during treatment planning. From April 2010 to March 2014, of 107 patients registered 63 were randomised. Thirty-two patients were randomised to arm A and 31 patients to arm B. Forty-eight patients received concurrent chemo-radiotherapy. Median follow-up was 25.5 months. Mean prescribed fraction dose to the planning target volume of the primary tumour was 3.3 Gy (range 3.0-4.0 Gy) in arm A and 3.9 Gy (range 3.2-5.4 Gy) in arm B. Grade ≥3 dysphagia and dyspnoea during treatment occurred in seven and two patients (11% and 3%) respectively. Grade ≥3 oesophagitis and pneumonitis after treatment was seen in 11 and six patients (17.5% and 9.5%) respectively. Haematological toxicity grade ≥3 was observed in 5% of patients. Four out of 63 patients (6.3%) died due to pulmonary haemorrhage. This interim toxicity analysis of the randomised phase II PET-boost trial showed that dose-escalation is feasible. No excessive or unexpected toxicity was observed during and after treatment.

Head and neck cancer trial

Olga Hamming, Netherlands Cancer Institute

To increase the therapeutic ratio for head and neck cancers by pre-treatment selection and dose redistribution, a head and neck cancer trial was designed. In the initial phase, 24 patients were randomised and treated according to this protocol in three centres. The first toxicity analysis was carried out in March 2014. All 15 patients who had finished treatment for more than three months were included in this analysis. Median follow up was 5.4 months. The worst grade acute toxicity was scored, during treatment and up to three months after treatment. All patients finished their radiation treatment without delay. These acute toxicities were as expected from a curative chemoradiation treatment in the head and neck area. Overall, 20% of patients (3/15) were able to maintain oral feeding during treatment and 12 of 15 patients received tube feeding. Of these patients, two started tube feeding before treatment and the remainder on average in week 4 of treatment. Since all patients received at least one dose of cetuximab, dry skin and rash were common. One patient had a grade 3 rash, from which he fully recovered. We conclude that based upon the first toxicity analysis, this study protocol is feasible, given that all patients finished the radiation treatment as planned with toxicity as expected.

Further follow up is needed to evaluate long term results.

Unfortunately, the free-of-charge delivery of cetuximab was halted (after May 2014) which necessitated a significant adaptation of the protocol. The major modification is no pre-treatment imaging with ^{89}Zr-labelled cetuximab. The standard arm has been changed to standard treatment of radiotherapy (35 fractions in seven weeks) and cisplatin 100 mg/m^2 every three weeks in the participating hospitals, making the trial easier to explain to patients.

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