the contrast-enhanced MRI imaging. CTV2 encompassed the whole brain. Only the PTV1 dose was escalated (planned dose escalation: 35 Gy, 40 Gy, 45 Gy, 50 Gy) while the PTV2 dose remained the same (30 Gy/3 Gy/fractions). Dose-limiting toxicities (DLTs) were defined as any treatment-related non-hematological adverse effects rated as grade ≥ 3, or any hematological toxicity rated as ≥ 4 by CTCAE scale, v. 4.0. MTD was exceeded if ≥ 2 of 6 patients in a cohort experienced dose-limiting toxicity (DLT).

Results: 27 consecutive patients (pts) were treated (PTV1 dose: 35 Gy, 8 pts; 40 Gy, 6 pts; 45 Gy, 6 pts; 50 Gy, 7 pts). The number of treated brain lesions was: 1 (17 pts), 2 (4 pts), 3 (5 pts) and 4 (1 pt). Three pts experienced a DLT: 1 pt (2nd dose level) developed a grade 3 skin toxicity, 1 pt had a grade 3 neurological toxicity (4th dose level) and 1 pt had a brain hemorrhage (4th dose level). Nineteen pts experienced cutaneous (17 pts) and/or neurological (10 pts) grade 1-2 acute toxicity. The response to treatment was evaluable in 16 pts: 1 pt (6.2%) disease progression, 2 pts (12.5%) stable disease, 10 pts (62.5%) partial response and 3 pts (18.8%) complete response. Median and 1-year overall survival were 13 months and 51.9%, respectively. Late toxicity was not recorded.

Conclusions: This is the first prospective trial demonstrating that a radiation dose of 50 Gy in 10 fractions can be delivered by using a SIB IMRT technique without unacceptable toxicity in patients with ≤ 5 brain metastases. A phase II trial (ISIDE-BM-2) is in progress to evaluate the response and the time to progression.

OC-0059

Validated clinical model for survival prediction after stereotactic radiotherapy for brain metastases

J. Zindler[1], R.J. Beumer[1], E.G.C. Troost[1], A.L. Hoffmann[1], I. Compter[1], J. Jager[1], D. Eekers[1], P. Lambin[1]
[1]MAASTRO Clinic, Radiotherapie, Maastricht, The Netherlands

Purpose/Objective: Stereotactic ablative body radiotherapy (SABR) is the standard treatment modality for a limited number of brain metastases (BM). Several models for survival prediction have been published, such as the commonly used Recursive Partitioning Analysis (RPA), Golden Grading System (GGS), and the Disease Specific Graded Partitioning Analysis (DS-GPA). All published models have limitations for prediction of survival after SABR for BM: e.g. small proportion of patients in the favorable prognostic group, a low sensitivity for the identification of patients with long term survival, and some models are complex to use (e.g. DS-GPA). In this study, a new prognostic model is developed with the aim of overcoming above mentioned limitations.

Materials and Methods: Based on published models and clinical practice a new prognostic model was developed. Its clinical utility was tested for prediction of early death (<3 months) and long term survival (>12 months) in 297 patients with 1 up to 4 newly diagnosed BM treated with Linac-based SABR at our department between July 2004 and July 2014. Prescribed dose at the edge of the PTV was in the range of 15 up to 24Gy in 1 or 3 fractions.

Results: In the published models the two most important prognostic factors were: WHO performance status and presence of extracranial metastases. Poor performance status only was identified as the poor prognostic group according to Dutch guidelines. Remaining patient cohort was divided based on the presence of extracranial metastases. The developed model is a simplified version of the commonly used RPA, and was named Simplified Recursive Partitioning Analysis (SRPA).

- SRPA class I: WHO performance status 0/1 & no extracranial metastases
- SRPA class II: WHO performance status 0/1 & extracranial metastases
- SRPA class III: WHO performance status of 2 or more

Median age was 63 years and the majority of patients had non-small cell lung cancer (64%). The median survival after SABR was 9 months, with 3 months-, 1 year-, and 5 years survival of respectively 81%, 36%, and 9%. The patient distribution was most balanced in the SRPA with 48% of patients in the favorable prognostic class (vs 20%-29% in the other models, Table 1). Sensitivity for prediction of long-term survival was highest using the SRPA (56% vs 16-46% in other classes). The specificity of predicting 3-months death in the poor prognostic class was high in all scores (range 86% up to 98%). The SRPA was valid in an external SABR for 1-3 BM patients data set.

Table: Clinical utility of prognostic models for prediction of early death or long term survival

	Prediction of early death <3 months in unfavorable classes					Prediction of long term survival (>12 months) in favorable classes					
	N (%)	OS (months)	Sensitivity	Specificity	PPV	NPV	N (%)	OS (months)	Sensitivity	Specificity	PPV	NPV
SRPA	43 (15%)	7	17%	86%	21%	83%	142 (48%)	11	56%	55%	31%	78%
RPA	43 (15%)	7	17%	86%	21%	83%	60 (20%)	11	16%	82%	35%	61%
GGS	8 (3%)	5	6%	98%	38%	83%	86 (29%)	11	21%	74%	34%	60%
DS-GPA	10 (4%)	9	9%	97%	40%	84%	54 (21%)	12	46%	85%	41%	88%

SRPA=simplified recursive partitioning analysis, RPA=recursive partitioning analysis, GGS=Golden Grading Scale, DS-GPA=disease specific Graded Partitioning Analysis, OS=overall survival, PPV=positive predictive value, NPV=negative predictive value

Figure Kaplan Meyer analysis of survival of the SRPA for three prognostic groups
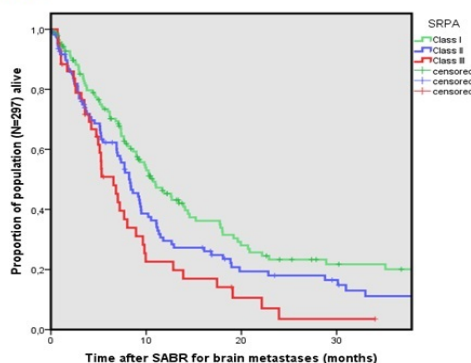
SRPA=simplified recursive partitioning analysis, SABR=stereotactic ablative body radiotherapy

Conclusions: The SRPA had the highest clinical utility for survival prediction after SABR for BM compared to the RPA, DS-GPA, and GGS. The SRPA is very simple in use, assembles to clinical practice, has a balanced patient distribution between the favorable and intermediate group, the highest sensitivity for prediction of long term survival, was specific for prediction of early death, and was validated in an external population. Further research will focus on further validation in other BM populations and exploration of the predictive value of advanced techniques such as radiomics, biomarkers, and statistical modeling.

Joint Symposium: ESTRO-RANZCR: Imaging and tumour biology: Delivery

SP-0060

Image and biological guided adaptive radiotherapy; results from the ARTFORCE project

H. Bartelink[1], X. ARTFORCE Project Partners

[1]Netherlands Cancer Institute Antoni van Leeuwenhoek Hospital, Radiation Oncology, Amsterdam, The Netherlands
On behalf of the Artforce Project Partners : Harry Bartelink

The Artforce (Adaptive and innovative Radiation Treatment FOR improving Cancer treatment outcomE) project is an EU 7th Frame work funded project. The aims of this project are:
1. To deliver higher tumour doses by redistributing the radiation dose towards highly positive in FDG-PET scans areas;
2. Advanced treatment monitoring, in particular daily cone beam CT on the linear accelerator, repetitive FDG-PET imaging and electronic portal dosimetry;
3. To validate specific predictors for tumour response to cisplatin and cetuximab and normal tissue complication;
4. To improve strategies for biological and anatomical adaptive optimisation.
This project includes two on-going randomized clinical trials, aiming at dose redistribution in head and neck and lung cancer.
For these trials the following projects are carried out:
Adaptive radiotherapy: P.I. Jan-Jakob Sonke
All relevant imaging and planning data for improved outcome modelling and data mining were collected to account for anatomical changes. 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 the treatment, the original planning CT is deformed to the average patient model.
Biological adaptive treatment planning P.I. Iuliana Dasu
Assessment of the tumour responsiveness based on two successive FDG-PET scans, one taken at the planning stage, before the start of the treatment, and a second one taken during the second week of treatment, in relation to the delivered dose, was evaluated in 26 NSCLC patients. It showed that it is feasible to determine a threshold value for the effective radiosensitivity of the patients corresponding to good response.
In vivo dosimetry: P.I Wouter van Elmpt
Three dimensional (3-D) in-vivo dosimetry as an integrated quality assurance (QA) procedure to accurately verify dose delivery applicable to all the major teletherapy systems in the EU were developed, validated and implemented.
Biomarkers: P.I. Eric Deutsch and Guido Kroemer
Tumour biopsies are being collected to predict the sensitivity to cisplatin and the radiation response. 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 non-small cell lung carcinoma patients.
Imaging: P.I. Philippe Lambin
Visual analysis of 10 head and neck cancer patients showed heterogeneous uptake of ^{89}Zr-labelled cetuximab within the Gross Tumour Volume (GTV). An analysis in lung cancer patients of the overlap fractions and regions for both FDG- and HX4-PET scans revealed a positive correlation between FDG and HX4 uptake parameters on a GTV level.
Lung cancer trial: P.I. Jose Belderbos and Dirk de Ruysscher
End of 2014, 118 patients were registered and 78 randomized.
The toxicity assessed in November 2014 did not reveal unexpected or serious adverse events.
Head and Neck cancer trial. P.I. Olga Hamming
End of 2014, 32 patients have been randomized. Unfortunately, the supply of cetuximab free of charge was stopped (after May 2014) which necessitated a significant adaptation of the protocol.

The toxicity analysis in March 2014 based upon the first 15 patients demonstrated that all patients could finish their radiation treatment without delay. Acute toxicities are as expected from a curative chemoradiation treatment in the head and neck area.
Participating centres: The Netherlands Cancer Institute, Amsterdam; Karolinska Institutet, Stockholm; Maastro Clinic, Maastricht; Val d'Hebron Hospital, Barcelona; INSERM, Paris; RaySearch, Stockholm; Christie Hospital, Manchester; Institut Gustave Roussy, Villejuif.

SP-0061
Head and neck cancer: FDG imaging and beyond
B.A.W. Hoeben[1], J. Bussink[1], E.G.C. Troost[2], W.J.G. Oyen[3], J.H.A.M. Kaanders[1]
[1]Radboud University Medical Center, Radiation Oncology, Nijmegen, The Netherlands
[2]MAASTRO Clinic, Radiation Oncology, Maastricht, The Netherlands
[3]Radboud University Medical Center, Nuclear Medicine, Nijmegen, The Netherlands

In the age of personalized medicine, information about the tumour characteristics guiding treatment decisions prior to and early during therapy is of crucial importance. While local extension of head and neck squamous cell carcinoma (HNSCC) is mainly assessed by physical examination and anatomical imaging, unfavourable tumour features such as hypoxia, proliferation rate and intrinsic radio-resistance are not reliably depicted. Therefore, the added value of molecular imaging with positron emission tomography (PET) is increasingly explored in head and neck tumours. Integration of PET techniques into therapy selection and adaptation strategies, as well as radiation treatment planning for HNSCC, can serve several purposes. First, pre-treatment assessments can steer decisions about radiotherapy modifications or combinations with other modalities. Second, biology-based objective functions can be introduced to the radiation treatment planning process by co-registration of molecular imaging with planning CT-scans. Thus, customized heterogeneous dose distributions can be generated with escalated doses to tumour subvolumes where radiotherapy resistance mechanisms are most prevalent. Third, monitoring of temporal and spatial variations in these radiotherapy resistance mechanisms early during the course of treatment can discriminate responders from non-responders. With such information available shortly after the start of treatment, modifications can be implemented or the radiation treatment plan can be adapted tailing the biological response pattern. The most commonly applied PET tracer - ^{18}FDG - highlights volumes of increased cellular metabolism, but requires careful interpretation due to uptake in non-malignant tissues or peritumoral inflammation. Several studies have demonstrated a prognostic value of ^{18}FDG PET imaging before and during therapy based on quantification or volumetric characteristics. Ongoing investigations evaluate utilization of ^{18}FDG signal as a basis for radiotherapy dose redistribution. A number of PET tracers associated with tumour cell hypoxia, *e.g.*, ^{18}FMISO and ^{18}FAZA, have shown prognostic value and may guide individualized therapy, *i.e.*, the addition of hypoxia-modulating agents or dose-escalation to radio-resistant tumour subvolumes.
^{18}FLT-PET can be used repetitively to characterize tumour proliferation before and during treatment, facilitating adaptive radiotherapy and other tailored treatment strategies. Antibody-based PET tracers such as ^{89}Zr-labeled cetuximab, specific to the epidermal growth factor receptor (EGFR), can be utilized for assessment of presence,