from start of study drug administration. Dose escalation decision and recommended dose (RD) were made by an independent safety committee. Blood PK and PD samples were serially drawn along the 3 cycles.

**Results:** Fourteen patients were included in the study. DLTs per dose level (DL) are shown in the table with 3 patients experiencing more than one DLT. The RD of Debio 1143 to be combined with CRT was 200 mg/day (W-MTD). Debio 1143 exposure increased proportionally with dose and did not accumulate over time. Amylase/lipase and ALT/AST increase with higher Debio 1143 exposures. At all dose levels, the PD effect of Debio 1143 was evidenced by the degradation of cIAP1 in PBMCs and a trend in an increase of serum MCP1. 12 patients were evaluable for response by RECIST 10-12 weeks post treatment among which 3 CR, 5 PR and 1 SD.

**Conclusion:** Combination of Debio 1143 with CRT was tolerated, exhibited favourable PK in combination with CRT with significant PD activity. The MTD was found to be 200 mg/day and is now being used in a randomized phase 2 study initiated by GORTEC to evaluate the anti-tumor activity of this combination in LA-SCCHN.

**PV-0519**

The hypoxic radiosensitizer, nimorazole, in RT of HNSCC: pharmacokinetics, toxicity and compliance M.A.H. Metwally, J. Overgaard

Aarhus University Hospital, Department of Experimental Clinical Oncology, Aarhus C, Denmark

**Purpose or Objective:** Study of pharmacokinetics (PK), toxicity, and compliance with nimorazole (NIM) which is currently investigated for its efficacy in three large randomized clinical trials (NIMRAT, EORTC 1219/DAHANCA 29, and DAHANCA 30)

**Material and Methods:** The PK of NIM was studied in 63 patients with HNSCC treated in the DAHANCA-5 trial. While the toxicity and compliance were studied in HNSCC patients treated with NIM, in combination with radiotherapy (RT) or chemoradiotherapy (CRT), in Denmark between 1990 and 2013. Plasma concentration measurements were done using high pressure liquid chromatography following the first day dose; and plasma concentration profiles were subjected to non-compartmental PK analysis using validated PC-based software. The different PK parameters were calculated and correlated with the different patient- and treatment-related variables. Nimorazole was administered as oral tablets in doses of approximately 1.2 g/m² BSA before the first daily radiation treatment. A second dose of 1 g was given before the second RT fraction in the accelerated fractionation regimen (6 fractions/week). The compliance was estimated as the percentage of the initially prescribed dose; and drug-related side effects were reported from the DAHANCA database.

**Results:** A linear relationship between peak plasma concentration and administered dose was detected. The mean peak concentration was 36.8 ± 1.3 µg/ml, and the time of peak concentration ranged between 30 and 180 min (median 60 min). Plasma elimination occurred with a mean half-life of 3.35 ± 0.09 h. There was a statistically significant correlation between area under the concentration-time curve (mean 191 ± 6 µg·h/ml) and administered dose, especially when expressed as g/m². A statistically significant longer elimination half-life in men relative to women (mean difference 0.40 h; 95% confidence interval 0.77-0.03; P 0.03) was detected. A total of 1649 patients were investigated for toxicity and compliance with NIM. The compliance was fair, with both conventional and accelerated RT as well as CRT schedules, with 58% of patients received the full prescribed total dose. Nausea and vomiting were the major complaints representing 87% of the known side effects that caused dose reduction. All side effects ceased when treatment was interrupted, and neither severe nor long lasting side effects were observed. Female patients, and patients received accelerated CRT were significantly less compliant with NIM, and more likely to have nausea and vomiting; while patients who received less than 1100 mg/m² per day were significantly more compliant, and less likely to have nausea and vomiting.

**Conclusion:** The current nimorazole administration practice in clinical trials is acceptable, and the compliance to the drug is fair, either with the conventional or accelerated RT as well as CRT, with tolerable acute, but neither persistent nor late, toxicity.

**Symposium: Dose painting: those pending issues**

**SP-0520**


1De Neve Wilfried, Belgium
2University Hospital Ghent, Radiation-Oncology, Ghent, Belgium
3Ghent University, Radiation-Oncology, Ghent, Belgium
4University Hospital Ghent, Radiology, Ghent, Belgium

**Purpose** To demonstrate that dose painting (DP) is a promising tool to decrease overall treatment time (OTT), to reduce toxicity, to improve palliation or enhance tumor control. The present state of DP will be illustrated through two types of applications. We will also speculate about the potential of DP to integrate with novel systemic treatment approaches.

**Materials and methods**

A. Topographical DP (TDP) in breast irradiation. TDP distributes dose as function of the spatial distribution of subclinical cancer deposits nearby the primary tumor in breast cancer. Patients (n=170) were randomized between prone whole breast irradiation (WBI) followed by a boost (WBI- SeqB: OTT=4 weeks) and WBI with simultaneous integrated boost (SIB) using TDP (WBI-TDP-SIB: OTT=3 weeks). Acute moist desquamation rate was the primary endpoint.

B. DP against bone metastasis pain. There is no dose-response relationship above 8 Gy single dose for the control of pain by uncomplicated bone metastases. This observation triggered the hypothesis that cytokine cascades counteracting palliation are activated by radiation and that their activity is function of the irradiated volume. DP was employed to drastically reduce the irradiated volume. Patients (n=45) were randomly assigned (1:1:1) to receive a single fraction of either 8 Gy with conventional radiotherapy (Conv-8Gy) or 8 Gy with DP (dose range 6-10 Gy) (DP-8Gy) or 16 Gy with DP (dose range 14-18 Gy) (DP-16Gy). The trial was designed for selection of the experimental arm worthwhile of continuing in phase III.

C. DP in loco-regionally advanced head&neck cancer. 18F-FDG-PET-guided DP-treated patients enrolled in 3 dose-escalation studies (n = 72) were matched with standard IMRT-treated patients (n=72) irradiated during the same time period. Median dose in the DP-group was 70.2±8.9 Gy/30-32
fractious against 69.1 Gy/32 fractions in the IMRT group. Endpoints were local control, acute and late toxicity.

Results: A. Interim analysis (n = 150) showed low rates of moist desquamation, mostly located in the inframammary fold (5/75 WBI-SEQ vs 3/75 WBI-TDP-SIB, p = 0.5). Trends in favor of WBI-TDP-SIB were observed for breast edema (p = 0.08) and pruritus (p = 0.1). B. The volume of normal tissue receiving 4 Gy, 6 Gy and 8 Gy was at least 3, 6 and 13 times smaller in the DP-BgY arm compared to Conv-BgY and DP-16Gy (p = 0.05). DP-BgY resulted in a pain response of 80% compared to 53% and 60% for Conv-BgY and DP-16Gy. Quality of life analysis suggests better outcome for patients treated in the DP-BgY arm with the scores ‘painful characteristic’, ‘insomnia’ and ‘appetite loss’ reaching significance (p < 0.05). C. Local control at 5 y was 83.4% and 75.2%. D. The irradiated volume may be a conceptually naive way to use the dose/volume/DLT relationship casts doubt on the safety of WBI-TDP-SIB were observed for breast edema, moist desquamation, mostly located in the inframammary fold (5/75 WBI-SEQ vs 3/75 WBI-TDP-SIB, p = 0.5). Trends in favor of WBI-TDP-SIB were observed for breast edema and pruritus (p = 0.08) and differed according to DP-technique and prescription. Poorly healing mucosal ulcers at the locations of the highest doses were observed in 9 DP- and 3 IMRT-treated patients (p = 0.07) and reflect dose-limiting toxicity (DLT). Analysis of all DP-treated patients showed that DP-planning using a linear relation between 18F-FDG voxel-intensity and dose was associated with high risk of DLT if peak-doses were >84 Gy or the volume receiving >80 Gy was >1.75 cc in 30-fraction schedules (OTT = 6 weeks). Discussion and conclusions The term DP covers a variety of techniques that open a vast spectrum of applications. The use of DTP after breast-conserving surgery allows to integrate boost treatment in WBI without increasing toxicity. In bone metastasis, DP-BgY was selected as a candidate experimental arm to test the hypothesis of improved palliation by reducing the irradiated volume. A confirmatory phase III trial is underway. In locally-regionally advanced head&neck cancer, DP may open a window for improving local control. However, the safety margin for dose-escalation is narrow. Poorly healing mucosal ulcers at the peak-dose regions are DLT of DP. The dose/volume/DLT relationship casts doubt on the safety of linear 18F-FDG voxel-intensity based DP. A phase III trial using non-linear DP is underway. Tumor heterogeneity known for decades supports DP and refutes the use of homogeneous dose distributions. Dose escalation to radiosensitive regions in the tumor or decreasing the irradiated volume may be a conceptually naive way to use DTP. The insight that ionizing radiation can enhance vascular and immune mechanisms of cell death opens a new field for DP characterized by large fraction doses to small sub-volumes of tumor. In these applications, direct cancer cell kill might be subordinate to other goals of DP including amplifying bystander and abscopal effects or breaking immune tolerance. Combination of DP immunomodulating drugs or drugs that target vasculature or immune checkpoints are investigated to validate these concepts.

SP-0521 The biological rationale of dose painting: is it realistic? M. Alber1

1Aarhus University Hospital, Department of Clinical Medicine - Department of Oncology, Aarhus, Denmark

Any additional dose that can be applied without harm will lift tumour control in a patient population. Dose painting (DP) claims to make better use of dose than an indiscriminate or random escalation: by virtue of functional imaging, it should be more effective, more selective and more patient-specific. Still, on a pragmatic level, DP can often be summarized by “we boost because we can”. What does it take to go more biological? Obstacles lie in quantitative functional image acquisition, image interpretation, dose prescription and collection of evidence. Unfortunately, quantitative functional imaging is notoriously capricious. The problem tends to grow specific in terms of tumour biology and imaging modality is - which is one of the reasons for the popularity of FDG-PET, being arguably one of the least specific modalities. A specific modality may be more intriguing scientifically, but obviously shows only a narrow aspect of tumour biology, which may create a need for a combination of multiple modalities. Imaging modalities usually operate at length scales far greater than the phenomena to which they are sensitive. This can make the interpretation of images challenging, especially when tracer kinetics need to be considered. Imaging sophistication alone reveals little of the import of some physiological or biological trait for treatment outcome. Only clinical data can fill this gap in biological understanding with some confidence. Further, a single image is just a snapshot of a dynamically evolving tumour, and if taken pre-treatment, says little about the tumour’s response to therapy. Therefore, without any highly suggestive clinical evidence, the prospects for naïve (i.e. model-based) DP are bleak. Accordingly, in the domain of DP trials to date are pragmatic in their choice of imaging modality and -protocol, and dose prescription. In addition to being practical, especially in a multi-centric setting, this also ensures that a proof of benefit (of both boosting and imaging) can eventually be made. The essential advantage of “we boost because we can” over sophisticated “dose painting by numbers” is, that it generates the data needed to reach said sophistication. From this pragmatic standpoint, neither today’s imaging capabilities nor the understanding of their relevance to tumour treatment are sufficient to speak of an established biological rationale for DP. Some clinical evidence exists in few instances that links certain functional imaging to lack of tumour control or even location of recurrence. Given this, workable DP concepts today are rather shaped by considerations about image sensitivity and specificity and organ mobility, than biology.

SP-0522 Dose prescription and treatment delivery at the voxel scale: a fantasy? J. Lee1, D. Di Perri2, S. Differding1, X. Geets2, V. Grégoire3

1Université Catholique de Louvain, Box B1-54.07, Brussels, Belgium
2Université Catholique de Louvain, Molecular Imaging-Radiotherapy- Oncology, Brussels, Belgium

Purpose/Objectives: This work aims at formally identifying the methodological issues that hinder the implementation and adoption of dose painting (DP) in radiotherapy. DP entails the use of functional imaging to set up a non-uniform dose escalation, either with sub-contours or voxel-to-voxel variations. Although theoretically appealing, DP has not headed to other modalities in the clinical arena. Several technical challenges exist that prevent widespread use. Dose prescription and treatment delivery at the voxel scale are demanding tasks for modern radiotherapy treatment planning systems. A single image is just a snapshot of a dynamically evolving tumour, and if taken pre-treatment, says little about the tumour’s response to therapy. Therefore, without any highly suggestive clinical evidence, the prospects for naïve (i.e. model-based) DP are bleak. Accordingly, in the domain of DP trials to date are pragmatic in their choice of imaging modality and -protocol, and dose prescription. In addition to being practical, especially in a multi-centric setting, this also ensures that a proof of benefit (of both boosting and imaging) can eventually be made. The essential advantage of “we boost because we can” over sophisticated “dose painting by numbers” is, that it generates the data needed to reach said sophistication. From this pragmatic standpoint, neither today’s imaging capabilities nor the understanding of their relevance to tumour treatment are sufficient to speak of an established biological rationale for DP. Some clinical evidence exists in few instances that links certain functional imaging to lack of tumour control or even location of recurrence. Given this, workable DP concepts today are rather shaped by considerations about image sensitivity and specificity and organ mobility, than biology.

Method: The following steps occur in PET-based DP: acquisition of PET images (before and/or during treatment, with one or several tracers), conversion of the uptake(s) into a dose increment, treatment plan optimization, fractionated treatment delivery, accumulation and assessment of the delivered dose, and optional treatment adaptation. Every step or piece of data in this path can be modeled to investigate its shortcomings. All PET tracers are characterized with their specificity and sensitivity as a surrogate of some biological variable of interest in given conditions (e.g., before or during radiotherapy). PET images are described by their resolution and signal-to-noise ratio. Treatment plan quality is assessed by a quality-volume histogram (QVH), namely, a DP-specific dose-volume histogram that considers the ratio planned dose over prescribed dose. Random and systematic patient setup errors are quantified with their respective standard deviation. Non-rigid registration of pre- and per-treatment images is used to approximate the cumulated dose, taking into account patient movement (tumor regression, possible weight loss).

Results: Our main result is the formal proof that PET-based DP cannot lead to delivered dose that is strongly correlated with the tracer uptake at the microscopic level. This weak correlation is caused by: i) The limited information conveyed by heterogeneities observed in PET images. Current PET systems have a low resolution and a low signal-to-noise ratio,