BiGART 2023

Programme and abstract book

Biology-Guided Adaptive Radiotherapy –
An Acta Oncologica conference

Aarhus, Denmark
June 20-21 2023

WELCOME

Welcome to Aarhus for the 18th edition of the Acta Oncologica conference on Biology-Guided Adaptive Radiotherapy – BiGART 2023.

After the last meeting was organised online, we are happy to finally meet for BiGART again; a conference rich in traditions but with a clear focus on renewal and current developments. This is reflected in the wide-ranging abstracts and programme sessions. Editors Jens Overgaard and Morten Høyer are happy to present an excellent BiGART special issue of Acta Oncologica after the conference.

A new initiative is a virtual-only abstract book. In the next pages, you will find the full programme and abstracts as well as the poster discussion groups and a list of participants.

Programme sessions
Biology-guided and adaptive radiotherapy anno 2023 • Oligo-metastatic disease and reirradiation • Automation and artificial intelligence • Clinical radiotherapy – CNS, head and neck, breast cancer • Proton radiobiology • Clinical radiotherapy – Genito-urinary cancer • Clinical radiotherapy – Gastro-intestinal and lung cancer • Preparing for the future

Invited faculty
Anna Kirby • Armin Lühr • Daniel Zips • Eirik Malinen • Gabriel Adrian • Gerben Borst • Jan Unkelbach • Joseph O. Deasy • Karin Haustermans • Kristoffer Petersson • Marianne Grønlie Guren • Matthias Guckenberger • Nico van den Berg • Remi Nout • Vincenzo Valentini • Yolanda Prezado

Thank you to everyone who contributed to the conference.

Cai Grau, Birgitte Offersen and Jesper Grau Eriksen

BiGART2023 is supported by Acta Oncologica and the Danish Cancer Society

PROGRAMME

Tuesday June 20

08:00: **Registration and breakfast**

08:45: **Welcome**

08:55: **Session 1: Biology-guided and adaptive radiotherapy anno 2023**
Chairs: Karin Haustermans, Jasper Nijkamp

Keynote address
08:55-09:15: Daniel Zips, Charité Mitte, Berlin, Germany
Response-adaptive radiotherapy

Oral presentations

1. **09:15-09:25: Jens Overgaard, Aarhus University Hospital, Denmark**
   Hyperthermia as an adjuvant to radiotherapy of locally advanced breast carcinoma. The ESHO 1-85 multicenter randomized trial by the European Society for Hyperthermic Oncology
2. **09:25-09:35: Azadeh Abravan, The University of Manchester, United Kingdom**
   Value of delta-radiomics features from 18-F FDG-PET in predicting loco-regional failure in head and neck cancer
3. **09:35-09:45: Pieter Populaire, KU Leuven, Belgium**
   Dose to functional lung volume and pulmonary toxicity in esophageal cancer trimodality therapy
4. **09:45-09:55: Simon Nyberg Thomsen, Aarhus University Hospital, Denmark**
   The importance of daily dose calculation for avoiding overdose to OAR in NSCLC patients receiving dose escalation
5. **09:55-10:05: Tord Hompland, Oslo University Hospital, Norway**
   Consumption and Supply based Hypoxia imaging can quantify different hypoxia levels and are strongly related to outcome after prostatectomy

10:05: **Coffee break**

10:35: **Session 2: Oligo-metastatic disease and reirradiation**
Chairs: Azadeh Abravan, Morten Høyer

Keynote address
10:35-10:55: Matthias Guckenberger, University Hospital Zürich, Switzerland
Value of metastases directed radiotherapy: oligometastatic disease and beyond

Oral presentations

6. **10:55-11:05: Anna Mann Nielsen, Copenhagen University Hospital – Herlev and Gentofte, Denmark**
   An interim analysis from a randomized, phase III trial of esophagus sparring radiotherapy for metastatic spinal cord compression

7. **11:05-11:15: Christina Truelsen, Aarhus University Hospital, Denmark**
   Inter-fraction motion robustness in dose-escalated proton re-irradiation for locally recurrent rectal cancer: initial results from the prospective phase II trial, ReRad II
8. **11:15-11:25: Einar Dale, Oslo University Hospital, Norway**
   Re-irradiation with dose painting of head and neck cancer: Clinical outcomes
9. **11:25-11:35: Julie Frikke Depner, Rigshospitalet, Copenhagen, Denmark**
   Treating brain metastases in metastatic breast cancer: Outcomes after stereotactic radiosurgery examined in a retrospective, single-center cohort analysis
10. **11:35-11:45: Julie Kjems, Rigshospitalet, Copenhagen, Denmark**
    The potential for oligometastatic treatment of distant metastatic disease in head and neck squamous cell carcinoma (HNSCC) – a real-world data analysis
11. **11:45-11:55: Mette Felter, Herlev and Gentofte Hospital, Denmark**
    MR-guided stereotactic body radiotherapy in patients with oligometastatic disease in the infra-diaphragmatic region (SOFT): a phase 2, multicenter study
12. **11:55-12:05: Sakina Khan, Aarhus University Hospital, Denmark**
    Remarkable local control and minimal toxicity in small ultra-central lung tumors or solitary lymph nodes after normo-fractionated radiotherapy
13. **12:05-12:15: Yuqing Xiong, University Hospital LMU Munich, Germany**
    Daily plan adaptation in ultra-hypofractionated MRgRT for prostate cancer: comparison of adapted and non-adapted accumulated dose

12:15: **Lunch**

13:15: **Session 3: Automation and artificial intelligence**
Chairs: Stine Sofia Korreman, Anne Holm

Keynote addresses
13:15-13:35: Jan Unkelbach, University Hospital Zürich, Switzerland
Machine learning for supporting clinical target volume definition

13:35-13:55: Nico van den Berg, UMC Utrecht, The Netherlands
AI driven imaging & contouring workflow for MRI guided Radiotherapy

13:55-14:15: Joseph O. Deasy, Memorial Sloan Kettering Cancer Center, New York, USA
AI methods to derive treatment response biomarkers from longitudinal imaging

Oral presentations

14. **14:15-14:25: Bob Smulders, Aarhus University Hospital, Denmark**
    Prediction of dose-sparing by protons assessed by a knowledge-based planning tool in radiotherapy of the brain
15. **14:25-14:35: Camilla Panduro Nielsen, Odense University Hospital, Denmark**
    Consistency in contouring of organs at risk by AI and radiation oncologists in head and neck cancer patients
16. **14:35-14:45: Emma Riis Skarsø, Aarhus University Hospital, Denmark**
    Multi-center auto-segmentation model for internal mammary nodes using clinical data: A DBCG study

17. **14:45-14:55: Maximilian Konrad, Odense University Hospital, Denmark**
    An automatic open-source approach to organs at risk and target structure segmentation for T2 MR-guided brachytherapy of cervical cancer patients using nnU-Net

14:55: **Coffee break**

15:20: **Session 4: Clinical radiotherapy – CNS, head and neck, breast cancer**
Chairs: Birgitte Vrou Offersen, Christian Rønn Hansen

Keynote addresses
15:20-15:40: Anna Kirby, The Royal Marsden, Sutton, United Kingdom
Radiotherapy for Breast Cancer- which outcomes really matter to patients?

15:40-16:00: Gerben Borst, The Christie, Manchester, United Kingdom
Individualising treatment strategies for brain tumours

16:00-16:20: Gabriel Adrian, Skåne University Hospital, Lund, Sweden
HNSCC: Why we shouldn't forget about the clonogenic cell (and hopefully increase cure rates)

Oral presentations

18. **16:20-16:30: Alice Clarke, Aarhus University Hospital, Denmark**
    Radiation dose-escalation for Glioblastoma: who may benefit?
19. **16:30-16:40: Jørgen Johansen, Odense University Hospital, Denmark**
    Accelerated Loss of Lean Body Mass in Head and Neck Cancer Patients During Cisplatin-based Chemoradiation
20. **16:40-16:50: Lene Haldbo-Classen, Aarhus University Hospital, Denmark**
    Is radiation dose to sleep-relevant brain structures associated with lower sleep quality in adults with primary non-glioblastoma brain tumours?
21. **16:50-17:00: Maja Olsen, Danish Cancer Society Research Center, Copenhagen, Denmark**
    Socioeconomic differences in the pre-diagnostic interval among patients diagnosed with head and neck squamous cell carcinoma - a nationwide, population-based study from DAHANCA, Denmark, 2008-2019
22. **17:00-17:10: Morten Horsholt Kristensen, Aarhus University Hospital, Denmark**
    Cancer stem cell expression and tumor volume as prognostic markers for radioresistance in HNSCC

17:15: **Poster discussion and refreshments**

19:00: **Conference dinner and networking - Varna Mansion**

Wednesday June 21

08:00: **Session 5: Proton radiobiology**
Chairs: Brita Singers Sørensen, Kathrine Røe Redalen

Keynote addresses
08:00-08:20: Eirik Malinen, Oslo University Hospital, Norway
Proton therapy of head & neck murine models - recent investigations on toxicity and tumor control

08:20-08:40: Armin Lühr, TU Dortmund, Germany
BiG-ART: Biology-Guided Alternatives for proton Radiotherapy Treatment planning

Oral presentations

23. **08:40-08:50: Esther Troost, University Hospital Carl Gustav Carus, Dresden, Germany**
    Multi-parametric MRI for unraveling radiation-induced changes in primary brain tumor patients
24. **08:50-09:00: Fredrik Kalholm, Stockholm University, Sweden**
    Modeling RBE with Qeff significantly improves prediction of cell survival for proton therapy compared to LET
25. **09:00-09:10: Maksym Fritsak, Paul Scherrer Institute, Villigen, Switzerland**
    On the role of treatment uncertainties in the onset of radiation-induced optic neuropathy after proton therapy

09:10: **Session 6: Clinical radiotherapy – Genito-urinary cancer**

Chairs: Remi Nout, Jacob Lindegaard

Keynote address
09:10-09:30: Remi Nout, Erasmus University Medical Center, Rotterdam, The Netherlands

Moving towards risk stratified radiotherapy for locally advanced cervical cancer

Oral presentations

26. **09:30-09:40: Kari Tanderup, Aarhus University Hospital, Denmark**
    Peripheral neuropathy in cervix cancer patients: a trajectory analysis
27. **09:40-09:50: Anne Cobussen, Maastro/Aarhus University Hospital, The Netherlands/Denmark**
    Clinical outcomes using a 3D printed tandem-needle-template and the EMBRACE-II planning aims for image guided adaptive brachytherapy in locally advanced cervical cancer
28. **09:50-10:00: Ingerid Knudtsen, Norwegian University of Science and Technology, Trondheim, Norway** PSMA-PET of prostate cancer patients with biochemical recurrence
29. **10:00-10:10: Marta Pelizzola, Aarhus University Hospital, Denmark**
    Identification of syndromes from temporal evolution of symptoms in cervix cancer patients
30. **10:10-10:20: Simon Buus, Aarhus University Hospital, Denmark**
    Clinical outcome of MRI based high-dose-rate brachytherapy combined with EBRT for prostate cancer
31. **10:20-10:30: Sofia Spampinato, Aarhus University Hospital, Denmark**
    Patient-reported persistent symptoms after radiotherapy and association with quality of life for prostate cancer survivors

32. **10:30-10:40: Trine Tramm, Aarhus University Hospital, Denmark**
    T-lymphocytes and hypoxia predicts survival after brachytherapy in locally advanced cervical cancer

10:40: **Coffee break**

11:10: **Session 7: Clinical radiotherapy – Gastro-intestinal and lung cancer**
Chairs: Esther Troost, Lone Hoffmann

Keynote addresses
11:10-11:30: Karin Haustermans, UZ Leuven, Belgium
Proton therapy in esophageal cancer

11:30-11:50: Vincenzo Valentini, Policlinico Universitario A. Gemelli, Rome, Italy
The logical benefit of mining a large rectal cancer database: thoughts, judgements and imaginations

11:50-12:10: Marianne Guren, Oslo University Hospital, Norway
Improving clinical outcomes after chemoradiotherapy for anal cancer

Oral presentations

33. **12:10-12:20: Karen Wind, Aarhus University Hospital, Denmark**
    Pre-treatment immune-inflammation-related biomarkers and relation to disease-free survival in anal cancer
34. **12:20-12:30: Lise Bech Jellesmark Thorsen, Aarhus University Hospital, Denmark**
    National consensus based automatic delineation of thoracic organs at risk
35. **12:30-12:40: Nina Levin, Norwegian University of Science and Technology, Trondheim, Norway**
    Dose response relationship of acute esophagitis for patients with limited stage small cell lung cancer treated with chemoradiotherapy in a randomized phase II trial

12:40: **Lunch**

13:30: **Session 8: Preparing for the future**
Chairs: Niels Bassler, Kari Tanderup

Keynote addresses
13:30-13:50: Kristoffer Petersson, Oxford University/Lund University, United Kingdom/Sweden
FLASH Radiotherapy

13:50-14:10: Yolanda Prezado, Institut Curie, Paris, France
Divide and conquer: spatial fractionated radiation therapy

Oral presentations

36. **14:10-14:20: Katia Parodi, Ludwig-Maximilians-Universität München (LMU Munich), Germany**
    First in-silico demonstration of a novel platform for small animal image-guided, intensity modulated proton therapy
37. **14:20-14:30: Morten Busk, Aarhus University Hospital, Denmark**
    Development of preclinical orthotopic lung tumor mouse models generated by CRISPR/CAS9 in vivo gene knockout

38. **14:30-14:40: Signe Winther Hasler, Odense University Hospital, Denmark**
    A multicenter study of geometric accuracy of clinical MR sequences used for radiotherapy in Denmark
39. **14:40-14:50: Simon Vindbæk, Aarhus University Hospital, Denmark**
    Motion-induced proton dose change measured by 3D deformable dosimeters in an anthropomorphic phantom

14:50: **Closing session - poster prizes**
Chairs: Ludvig Muren, Jesper Eriksen

15:00: **Farewell**

POSTER DISCUSSION GROUPS

Poster discussion group 1: Preclinical studies

Chairs: Gabriel Adrian, Per Poulsen

40. Anders Tobias Frederiksen, Aarhus University Hospital, Denmark
Evaluating in vitro setup designed for horizontal beamline irradiation at the Danish Centre for Particle Therapy

41. Charlemagne A. Folefac, Aarhus University, Denmark
Targeting Solid Tumors with the combination of Stereotactic Radiation combine with hyperthermia

42. Ingunn Hanson, University of Oslo, Norway
TGF-β3 injections increases severity of radiation induced oral mucositis and salivary gland fibrosis in a mouse model

43. Line Kristensen, Aarhus University Hospital, Denmark
Skin toxicity of FLASH proton radiation within the Spread-out Bragg Peak

44. Olga Zlygosteva, University of Oslo, Norway
Normal tissue response following proton and photon fractionated irradiation of the head and neck in a murine model

45. Toralf Husevåg, University of Oslo, Norway
Predicting saliva production and fibrosis in mice post-irradiation using T2-weighted MRI-based radiomic features

Poster discussion group 2: Biology, biomarkers and adaptation

Chairs: Katia Parodi, Jørgen Johansen

46. Ana Ureba, Stockholm University, Solna, Sweden
Biologically-guided automated treatment planning and evaluation: potential for treatment adaptation in head and neck cancer

47. Demet Özcan, Aarhus University Hospital, Denmark
Exploring the analytical validity of CD20 as a potential biomarker for benefit of post-operative radiotherapy in breast cancer patients

48. Eleni Kanouta, Aarhus University Hospital, Denmark
Scintillation imaging for in vivo monitoring of pre-clinical mouse treatments with conventional and FLASH proton pencil beam scanning

49. Guillermo Garrido Hernandez, Norwegian University of Science and Technology, Trondheim, Norway
FDG-PET-based mid-treatment dose escalation of proton therapy in head and neck cancer

50. Jacob Lilja-Fischer, Aarhus University Hospital, Denmark
HPV subtype not prognostic in p16+ oropharyngeal squamous cell carcinoma

51. Marie Tvilum, Aarhus University Hospital, Denmark
Using image biomarkers to predict pattern of failure for patients with locally advanced NSCLC

52. Sara Linde, Aarhus University Hospital, Denmark
Early radiologic and metabolic response to chemotherapy in patients with limited disease small cell lung cancer

53. Tiril Hillestad, Oslo University Hospital, Norway
Early microenvironmental changes to radiation therapy in cervical cancer patients

Poster discussion group 3: Clinical studies A

Chairs: Slavka Lukacova, Mette Felter

54. Daniella Østergaard, Rigshospitalet, Copenhagen, Denmark
Dose-accumulation analysis of target and organs at risk with clinical outcome after re-irradiation of diffuse midline glioma

55. Hendrik Hansen, Maastricht University Medical Center, GROW School for Oncology and Reproduction Maastricht, the Netherlands
Automated plan quality monitoring for patient cohorts using dashboards: demonstration for a 'RapidPlan introduction' use case

56. Hjørdis Hjalting Schmidt, Aarhus University Hospital, Denmark
Do changes in treatment over time affect survival and pattern of failure in 177 consecutive patients treated with chemoradiotherapy for limited disease small-cell lung cancer (LD-SCLC)?

57. Ida M. H. Borgen, Oslo University Hospital, Norway
Assessing cognitive functioning in patients with diffuse glioma grade 2 and 3 in the PRO-GLIO trial –advantages and disadvantages of a cognitive screening battery versus a full neuropsychological assessment

58. Liv Cathrine Heggebø, Radiumhospitalet, Oslo University Hospital, Norway
Quality of life, perception of treatment, and life perspectives in diffuse low-grade glioma patients – initial presentation of a qualitative sub-study in the PRO-GLIO trial

59. Michael Ruben Teindl Laursen, Copenhagen University Hospital – Herlev and Gentofte, Denmark
Protocol: OLIGO-DK - Local ablative therapy of oligometastatic disease

60. Sandy Mohamed, Aarhus University Hospital, Denmark
The value of MRI in response evaluation after primary (chemo-) radiotherapy for head and neck squamous cell carcinoma

61. Slavka Lukacova, Aarhus University Hospital, Denmark
Examining clinical patterns in the referral of brain tumor patients to proton therapy: A single center retrospective study

Poster discussion group 4: Clinical studies B

Chairs: Camilla Kronborg, Einar Dale

62. Anders W. Mølby Nielsen, Aarhus University Hospital, Denmark
Difference between planned and delivered dose to the internal mammary nodes in high-risk breast cancer patients

63. Anne Lindegaard, Copenhagen University Hospital – Rigshospitalet, Denmark
A systematic review on clinical adaptive radiotherapy for head and neck cancer

64. Camilla Kronborg, Aarhus University Hospital, Denmark
Organ specific secondary cancer risk after radiotherapy for seminoma. Comparison of robust intensity modulated proton therapy (IMPT) vs IMRT and VMAT photon plans

65. Camilla Skinnerup Byskov, Aarhus University Hospital, Denmark
Facility questionnaires from the European multicentre PROTECT phase III trial randomising proton vs. photon beam therapy in oesophageal cancer

66. Maja Bruvo Lazovic, University College Absalon, Næstved, Denmark
Potential early predictors of permanent xerostomia following head and neck radiotherapy

67. Johannes Tjelta, Haukeland University Hospital, Bergen, Norway
Radiation exposure to parent-in-treatment-room during pencil beam scanning pediatric proton therapy

68. Tine Bisballe Nyeng, Aarhus University Hospital, Denmark
Risk of large intra-fractional target shift during stereotactic treatment of peripheral lung lesions.

69. Veera Ahtiainen, Helsinki University Hospital, Comprehensive Cancer Center, Finland
Concept of individual dosing of Lu-177-PSMA radionuclide treatments based on prediction of tumor control and kidney tolerance

Poster discussion group 5: Imaging

Chairs: Anne Vestergaard, Mikko Tenhunen

70. Anne Bisgaard, Odense University Hospital, Denmark
Longitudinal DWI for response assessment in patients with rectal cancer treated on MRI-linac

71. Anne Vestergaard, Aarhus University Hospital, Denmark
Image changes after proton therapy of low and high grade gliomas

72. Jesper Folsted Kallehauge, Aarhus University Hospital, Denmark
National Quality Assurance of Quantitative Diffusion Tensor MR Imaging in Patients with Glioblastoma Multiforme

73. Laura Toussaint, Aarhus University Hospital, Denmark
A framework for quantifying longitudinal MRI changes after pediatric brain irradiation

74. Marte Kåstad Høiskar, Norwegian University of Science and Technology, Trondheim, Norway Quantitative dynamic contrast-enhanced MRI in head and neck cancer: a systematic comparison of different modelling approaches

75. Minea Jokivuolle, Odense University Hospital, Denmark
Mapping tumor microstructure with time dependent diffusion MRI on a clinical 1.5 T MRI system

76. Moritz Rabe, University Hospital, LMU Munich, Germany
Accuracy and reproducibility of brain diffusion-weighted imaging at a 0.35 T MR-linac in volunteers

77. Nadine Vatterodt, Aarhus University Hospital, Denmark
Cross-platform assessment of CBCT-based dose evaluations for head and neck cancer proton therapy

Poster discussion group 6: Proton therapy A

Chairs: Armin Lühr, Michael Horsman

78. Amit Ben Antony Bennan, German Cancer Research Center (DKFZ), Heidelberg, Germany
Impact of variable RBE models on jointly optimized (JO) photon – proton combined treatment plans

79. Evangelia Choulilitsa, Paul Scherrer Institut, Villigen, Switzerland
Dosimetric benefit of Online Daily Adaptive Proton therapy for Head and Neck cancer patients

80. Fardous Reaz, Aarhus University, Denmark
Design and commissioning of a proton minibeam collimator at the Danish Center for Proton Therapy for experimental studies on Spatially Fractionated Radiotherapy - current status and need for standardized reporting

81. Jacob Johansen, Aarhus University Hospital, Denmark
Assessing the Effectiveness and Toxicity of Boron in Proton Therapy: Monte Carlo Simulations and In Vitro Clonogenic Assay

82. Michael Horsman, Aarhus University Hospital, Denmark
Using immunotherapy to enhance the response of a C3H mammary carcinoma to proton radiation

83. Niels Bassler, Aarhus University Hospital, Denmark
Variable Relative Biological Effectiveness in proton therapy is better described with experimentally obtained Qeff than LET

84. Peter Lægdsmand, Aarhus University Hospital, Denmark
Relative Biological Effectiveness in Pencil Beam Scanning Proton Therapy of Pediatric Brain Tumors Near Brainstem

85. Villads Jacobsen, Aarhus University Hospital, Denmark
Investigating Neutron Dose to Pregnant Patients Undergoing Proton Therapy: Validation of a MC Framework with H*(10) Measurements

Poster discussion group 7: Proton therapy B

Chairs: Esben Worm, Eirik Malinen

86. Andreas Havsgård Handeland, Haukeland University Hospital, Bergen, Norway
Robustness evaluation of linear energy transfer in proton therapy of paediatric posterior fossa tumours

87. Anne Holm, Aarhus University Hospital, Denmark
Does proton radiotherapy have an advantage in ipsilateral radiotherapy (RT) for neck metastases from unknown primary squamous cell carcinoma (CUP) in the primary and recurrent setting?

88. Andreas Havsgård Handeland, Haukeland University Hospital, Bergen, Norway
First application of an LET-inclusive NTCP model for brainstem necrosis following paediatric proton therapy in an independent cohort

89. Esben Worm, Aarhus University Hospital, Denmark
Motion variability and setup accuracy in CBCT-guided exhale-gated spot scanning proton therapy of hepatocellular carcinoma

90. Ivanka Sojat Tarp, Aarhus University Hospital, Denmark
Clinical benefit of range uncertainty reduction in robust optimization for proton therapy

91. Simon Heebøll Vindbæk, Aarhus University Hospital, Denmark
Investigating the dose degradation around gold markers in spot-scanning proton therapy using 3D dosimeters

92. Nina Ubbesen, Aarhus University Hospital, Denmark
Dose to heart substructures between photon and proton therapy for esophageal cancer patients

93. Sarah Eckholdt, Aarhus University Hospital, Denmark
Patient-Specific Quality Assurance Using Monte Carlo Dose Calculations in Patients with Early Breast Cancer Treated with Proton Therapy

Poster discussion group 8: Treatment planning, automation, artificial intelligence A

Chairs: Joseph Deasy, Ditte Sloth Møller

94. Anne Andresen, Aarhus University Hospital, Denmark
Auto delineation of organ at risk in brain cancer patients using deep learning

95. Helena Vivancos Bargalló, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain
Laterality and lumpectomy/mastectomy classification for AI contouring of breast targets

96. Jintao Ren, Aarhus University Hospital, Denmark
Highly uncertain regions reveal potential errors: uncertainty analysis for improving deep learning segmentation of head and neck cancer tumor

97. Kristoffer Moos, Department of Clinical Medicine, Aarhus University Hospital, Denmark
Deep learning-based segmentation of organ-at-risk in the thorax region using a high-quality curated dataset

98. Armin Lühr, TU Dortmund University, Germany
CT or stopping power ratio prediction by deep learning for MR-only proton dose calculation?

99. Rasmus Klitgaard, Aarhus University Hospital, Denmark
The impact of range and treatment uncertainties on normal tissue complication probability models based on the rectum volume vs. wall during proton therapy of high-risk prostate cancer

100. Sofie Tilbæk, Aarhus University Hospital, Denmark
Evaluation of plan robustness in proton therapy for high-risk prostate cancer patients included in a national clinical trial

Poster discussion group 9: Treatment planning, automation, artificial intelligence B

Chairs: Thomas Ravkilde, Ebbe Lorenzen

101. Karolina Klucznik, Aarhus University Hospital, Denmark

Accuracy of motion-including prostate dose reconstruction based on pre- and post-treatment cone-beam CT scans

102. Katrin Håkansson, Copenhagen University Hospital – Rigshospitalet, Denmark

Online adaptive radiotherapy for head and neck cancer – first experience analysis of plan difference and synthetic CT uncertainty

103. Laura Kaplan, Zealand University Hospital Næstved, Denmark

An automated planning method to spare the rectal wall in treatment of prostate cancer

104. Lars Hjorth Praestegaard, Aarhus University Hospital, Denmark

Comprehensive automated structure QA in radiotherapy

105. Line Ring, Aarhus University Hospital, Denmark

Evaluation of manual and DirectOrgans algorithm for the delineation of organ at risk in thorax and pelvic radiation therapy

106. Morten Nielsen, Odense University Hospital, Denmark

A systematic approach to estimation of residual tolerances of organs being re-irradiated

107. Saber Nankali, Aarhus University, Denmark

Spot scanning proton therapy of hepatocellular carcinoma: Intrafraction tumor motion monitoring and dose reconstruction

108. Thomas Ravkilde, Aarhus University Hospital, Denmark

An easily extendible framework for advanced automated plan checks

ABSTRACTS

Tuesday June 20

Session 1: Biology-guided and adaptive radiotherapy anno 2023

1. 09:15-09:25: Jens Overgaard, Aarhus, Denmark

Hyperthermia as an adjuvant to radiotherapy of locally advanced breast carcinoma. The ESHO 1-85 multicenter randomized trial by the European Society for Hyperthermic Oncology

J Overgaard1, MCCM Hulshof2, O Dahl3, G Arcangeli4, on behalf of the ESHO clinical committee.

1Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark 2Amsterdam University Medical Centers, Department of Radiotherapy, University of Amsterdam, The Netherlands. 3Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway 4 Regina Elena National Cancer Institute, Rome, Italy

Introduction
ESHO 1-85 is a multicenter randomized trial investigating the value of hyperthermia (HT) as an adjuvant to radiotherapy (RT) in treatment of locally advanced breast carcinoma. The trial is one of the largest studies of HT and RT but has not been previously published.

Patients and methods: In the period 1987 to 1993, 155 tumors in 151 patients were included (4 pts had bilat. tumors). Tumors were stratified according to institution and size (T2-3/T4) and randomly assigned to receive RT alone (2 Gy/fx, 5 fx/wk) to a total dose of 65-70 Gy, incl. boost, or the same RT followed once weekly by HT (aimed for 43 °C for 60 min). Primary endpoint was local control in the treated area. A total of 147 tumors were evaluable, with a median obs time of 21 months. Seventy tumors were randomized to RT alone and 77 to RT+HT. Size was T4 in 92, and T2-3 in 55 tumors.

Results
Compliance to RT was good, with all but 12 pts fulfilling the planned RT treatment. HT was fair but associated with moderate to severe pain and discomfort in 15% of the treatments. In 83% of the heated pts a least one heat treatment achieved the target temperature.
Addition of HT did not increase the acute nor late radiation reactions.
Overall, the 5-year local failure rate was 57%. Univariate analysis showed a significant influence of HT (RT alone 66% vs RT+HT 48%, p = 0.011), and of tumor size (T4 72% vs T 2-3 35%, p = 0.003). A Cox multivariate analysis found the same factors to be the only significant prognostic parameters: HT (HR: 0.58 [0.36-0.94] and tumor size (HR: 0.49 [0.29-0.83]). More pts given RT+HT (38%) survived free of disease, than after RT alone (20%), p = 0.019).

Conclusion
A randomized multicenter study showed that adding weekly HT to RT of locally advanced breast cancer significantly enhanced tumor control and yielded more patients surviving free from cancer. The results substantiate the potential clinical benefit of hyperthermic oncology.

2. 09:25-09:35: Azadeh Abravan, Manchester, United Kingdom

Value of delta-radiomics features from 18-F FDG-PET in predicting loco-regional failure in head and neck cancer

Abravan, A.1,2, O'Leary, P.1, Tomos, C.1, van Herk, M.1,2, Price, J.1,2, McPartlin, A.3, Vasquez Osorio, E.1,2

1 Division of Cancer Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom 2 Department of Radiotherapy Related Research, The Christie National Health Service (NHS) Foundation Trust, Manchester, United Kingdom 3 Princess Margaret Cancer Centre, Toronto, Canada

Purpose
Majority of radiomics risk models developed to predict clinical outcome, are based on pre-treatment scans. However, follow-up scans may improve the predictive performance of such models. Here, we compared the performance of radiomics risk models of loco-regional failure (LRF) based on 1) pre-treatment features and 2) Δfeatures (pre-post features) from FDG-PET/CT scans of head and neck cancer.

Materials and methods
Pre- and post-PET/CT (taken 3 months after radiotherapy completion) of 50 patients treated with radical radiotherapy at a single institution were collected. The pre- and post-treatment PET/CT scans were registered to the planning CT following 3 steps: initial alignment, rigid registration, and non-rigid registration. Clinical target volume (CTV) was then propagated from the planning CT to the pre- and post-treatment scans. First order features and features from the texture matrices were extracted for pre- and post- PET scans (n=93, Pyradiomics v2.2.0). Unsupervised feature selection was utilized (interclass correlation coefficient >0.8 and Spearman rank correlation <50%). All features were standardized to mean zero and unit variance. Cox analysis was used to test the ability of features in predicting LRF in addition to known clinical factors.

Result
During follow-up, 18% of the patients had LRF. Baseline clinical model of LRF included CTV, smoking status, and pre-SUMmax. Selected features were first order (minimum), GLCM (correlation and inverse variance), GLDM (dependence entropy and variance). Model performance (C-Index) of risk models in predicting LRF was improved from 0.83 for clinical model only to 0.86 for clinical model+pre-radiomics and to 0.93 for clinical model+Δfeatures.

Conclusion
Following validation, integration of pre- and follow-up PET scans in radiomics risk models may be a promising way to improve clinical treatment adaption such as selecting patients that may benefit from treatment modification or adjuvant approaches in head and neck cancer.

3. 09:35-09:45: Pieter Populaire, Leuven, Belgium

Dose to functional lung volume and pulmonary toxicity in esophageal cancer trimodality therapy

P. Populaire(1,2), G. Defraene(2), Ph. Nafteux(3,4), L. Depypere(3,4), K. Haustermans(1,2)

(1)UZ Leuven, Department of Radiotherapy, Leuven, Belgium; (2)KU Leuven, department of Oncology, Laboratory of Experimental Radiotherapy, Leuven, Belgium; (3)UZ Leuven, Department of Thoracic Surgery, Leuven, Belgium; (4)KU Leuven, department of chronic diseases and metabolism (CHROMETA), laboratory for respiratory diseases and thoracic surgery (BREATHE), Leuven, Belgium

Objective
Postoperative pulmonary complications (PPC) are side effects in trimodality therapy of esophageal cancer (EC). Dose to the anatomical lung volume (ALV) can be used to predict PPC. Meanwhile, dose to 4D-CT derived functional lung volumes (FLV) has shown promising results in predicting toxicity in lung cancer. Clinical routine however, uses pulmonary function tests (PFT) to assess operability at baseline (BL) and after neo-adjuvant chemoradiotherapy (anCRT).
This exploratory analysis examines if FLV-dose influences toxicity in terms of (1) PCC risk and (2) changes(Δ) in PFTs.

Materials and Methods
All EC-patients undergoing trimodality therapy at our center between 01-2018 and 06-2022, using 4D CT-simulation were included. FLVs were defined using the methodology described by Nyeng et al. (Acta Oncol. 2021). Dose and volume parameters (DVP) of ALV and FLV (V40Gy, V30Gy, V20Gy, V10Gy, V5Gy, MLD) were extracted. PFT (FEV1 and DLCO) at BL vs anCRT were compared using paired t-test. DVPs and PFTs were compared between patients with/without PCC using unpaired t-test. Correlation between ΔPFTs and dose to ALV or FLV was tested using Pearson's r.

Results
Of 51 patients, 12 developed PPC. ALV was smaller while FLV10Gy and FLV20Gy were bigger in the PPC-group (respectively 3141±858mL vs 3601±635mL, p=0.025; 360±216mL vs 264±139mL, p=0.038; 166±106mL vs 118±63mL, p=0.030). No difference in ALV-dose was detected. BL FEV1 was significantly lower in the PPC-group (102±20%pred vs 90±17%pred, p=0.033) while no other PFT was significantly different between both groups. DLCO was the only PFT that decreased significantly between BL and anCRT (85±17%pred vs 68±15%pred, p<0.001). ΔDLCO was not indicative of PPC nor correlated to dose to ALV or FLV.

Conclusion
Small size ALV and large FLVs exposed to intermediate-high dose increase the risk of PPC though probably not by mechanism of ΔPFTs. These findings contribute to toxicity risk prediction and reduction strategies.

4. 09:45-09:55: Simon Nyberg Thomsen, Aarhus, Denmark

The importance of daily dose calculation for avoiding overdose to OAR in NSCLC patients receiving dose escalation

Thomsen SN (1,2), Møller DS (1,2), Knap MM (1), Khalil AA (1,2), Nyeng TB (1), Hoffmann L (1,2).

(1) Dept. of Oncology, Aarhus University Hospital, Aarhus, Denmark. (2) Dept. of Clinical Medicine, Faculty of Health Sciences, Aarhus University, Aarhus, Denmark

Introduction
Large anatomical changes may occur during radiotherapy (RT) of lung cancer, potentially leading to over-dosage of organs at risk (OAR) or tumor under-dosage. The daily delivered dose can be calculated based on CBCT scans used for patient positioning. We report on actual delivered dose in lung cancer patients included in the NARLAL2 dose-escalation trial.

Materials and methods
We investigated heterogeneous dose escalated plans created for the experimental arm of the NARLAL2 trial for 11 patients (pts). The dose escalation was driven by the GTV part with the highest FDG-PET uptake but limited in favor of OAR constraints. Pts were set up according to the GTV-T position on the daily CBCTs. If deviations above tolerance were seen in 3 consecutive fractions, the pts were referred for a rescan. Contours delineated on planning CT (pCT) were deformably propagated to each CBCT using the online registration (MIM Software). The dose was calculated for the CBCTs based on stoichiometric calibration curves yielding mean deviations for the mean dose of 0.2%±0.7%. Dose to 99% of CTV-T and CTV-N and D1cc to OAR were analyzed.

Results
The pts had 0-4 plan adaptations. In all patients, full coverage of CTV-T was maintained, whereas under-dosage was seen for CTV-N in four patients. In one patient adaption of the RT plan could have been avoided. In two pts overdosage was seen for esophagus, bronchi, and heart, with median [range] doses of 73Gy [71, 75], 78Gy [75, 80], and 83Gy [75, 93] respectively. No overdosage was seen for trachea or spinal cord. Overdosage of the esophagus and bronchi was originating from tumor shrinkage.

Conclusion
Heterogeneous dose escalation in lung cancer patients may lead to overdosage to OAR due to anatomical changes during the seven weeks of RT. Daily dose calculation based on CBCT used for setup, can be a tool for improved assessment of when to adapt a treatment plan, leading to less overdosage of OAR and fewer unnecessary plan adaptions.

5. 09:55-10:05: Tord Hompland, Oslo, Norway

Consumption and Supply based Hypoxia imaging can quantify different hypoxia levels and are strongly related to outcome after prostatectomy

Hompland T, Hole KH, Seierstad T, Lyng H

Oslo University Hospital

Introduction
Tumor hypoxia limits the effect of radiation therapy (RT) and is associated with poor outcome after RT in prostate cancer (PC) patients. However, a lack of feasible methods for its assessment limits biological studies and makes an introduction of tumor hypoxia in treatment planning unattainable. We have biologically validated a MR imaging tool for visualizing hypoxia in PC patients, termed CSH imaging. Recently we showed that CSH can provide information on different hypoxia levels (severe to mild) in cervical cancer patients and here we aim to confirm this result in PC and study the biology associated with different hypoxia levels.

Methods
104 patients received pimonidazole and multi b-value diffusion weighted MR prior to prostatectomy. From the DW images CSH hypoxia signal was estimated. From the surgical specimens, pathological parameters like, Gleason score, T stage, lymph node metastasis and lymphovascular invasion was determined. Furthermore, the presence of aggressive growth patterns like intraductal carcinoma (IDC), cribriform and comedo necrosis was examined. Outcome to prostatectomy was defined by PSA relapse.

Results
Comedo necrosis can be regarded as a morphological end stage of hypoxia, and its presence was used as a biological estimate of severe hypoxia. In line with our hypothesis, the lower signal intensities of CSH imaging were strongly associated with the presence of comedo necrosis ($p<0.0001$). We have previously demonstrated that CSH imaging can measure moderate hypoxia, showing that different levels of hypoxia can be measured in PC patients. Severe hypoxia were more strongly associated with aggressive growth patterns, lymphovascular invasion and lymph node metastasis, and PSA relapse than moderate hypoxia.

Conclusions
CSH imaging can quantify both moderate and severe hypoxia. Severe hypoxia is most strongly associated with an aggressive PC disease. CSH imaging may be useful for selecting patients in need of lymph node irradiation.

Session 2: Oligo-metastatic disease and reirradiation

6. 10:55-11:05: Anna Mann Nielsen Copenhagen, Denmark

An interim analysis from a randomized, phase III trial of esophagus sparring radiotherapy for metastatic spinal cord compression

Nielsen AM (1), Storm KS (1), Laursen MRT (1), Sibolt P(1), Suppli MH (2), Behrens C (1,3), Vogelius IR(2,4), Persson GF(1,4)

(1) Dept. of Oncology, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark (2) Dept. Of Oncology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark (3) Danish Technical University, Lyngby, Denmark (4) Dept. of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Background
The phase III ESO-SPARE trial investigates the effect of esophagus sparring VMAT with any fractionation in patients with metastatic spinal cord compression (MSCC) in the cervical/thoracic spine. Dose to the esophagus is spared by compromising dose to the anterior spine. Co-primary endpoints are peak patient reported dysphagia (PRO-CTC-AE) within 5 weeks and ability to walk (EQ-5D) at 9 weeks after treatment start. Due to the fragile patient population, we anticipated low compliance. According to power calculations 124 of 200 planned patients had to complete 9 weeks follow-up. We performed a planned interim analysis of dosimetry, compliance, re-irradiation within 90 days, and mortality after inclusion of 100 patients.

Methods
In the experimental arm, sparring of the esophagus was achieved by prioritizing strict esophageal constraints (Dmax=8 Gy in EQD2) over PTV and CTV coverage. Only dose plans from the initial 34 patients were evaluated. Patients reported dysphagia daily for 5 weeks and compliance required ≥ 4 completed reports per week. EQ-5D and EORTC-QLQ-C30 were reported weekly for 9 weeks.

Results
Half the dose plans were esophagus sparing. Esophagus constraints were respected in all 17 plans and only three patients had PTV V90% < 90%. Median esophagus dose was 10 Gy (range, 5-14 Gy) in the experimental arm and 26 Gy (8-31 Gy) in the standard arm. From May21 – Nov22, 100 patients were included from 2 centers. Compliance was 51% and 40% at 5 and 9 weeks. One in five patients had died before completing 9 weeks follow-up. No patients needed re-irradiation.

Conclusion
Sparring of the esophagus while maintaining reasonable CTV and PTV coverage was possible. Compliance was lower than anticipated and an expansion of the study cohort is needed to ensure the required number of evaluable patients.

7. 11:05-11:15: Christina Truelsen, Aarhus, Denmark

Inter-fraction motion robustness in dose-escalated proton re-irradiation for locally recurrent rectal cancer: initial results from the prospective phase II trial, ReRad II

Truelsen C.G (1,2), Rønde H.S (2), Kallehauge J.F (2), Poulsen L.Ø (3), Havelund B.M (4), Pedersen B.G (5), Iversen L.H (6), Spindler K.G (1,7), Kronborg C.S (2)

1.Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark 2.Danish Centre for Particle Therapy, Aarhus University Hospital, Denmark 3.Department of Oncology, Aalborg University Hospital, Denmark 4.Department of Oncology, University of Southern Denmark, Lillebaelt Hopital, Vejle, Denmark 5.Department of Radiology, Aarhus University Hospital, Denmark 6.Department of Surgery, Aarhus University Hospital, Denmark 7.Department of Oncology, Aarhus University Hospital, Denmark

Introduction
Pelvic re-irradiation is challenged by the robustness of delivered dose due to inter-fraction motion caused by constant anatomical variations ascribed to target movement, bowel- and bladder filling. To ensure treatment robustness in the prospective phase II study, ReRad-II; the aim was to quantify the dosimetric impact of inter-fraction motion in dose-escalated proton re-irradiation for locally recurrent rectal cancer (LRRC).

Material and methods
The initial 12 patients included in the Re-Rad II trial were evaluated. Re-irradiation was delivered as robustly optimized (14 scenarios), hyperfractionated Intensity Modulated Proton Therapy (IMPT), 55-65 Gy (RBE) (Eclipse, Varian Medical Systems). IMPT plans consisted primarily of 3 posterior fields. Organs at risk (OAR) were delineated according to RTOG guidelines on planning CT scans (pCT, n=12) and on weekly repeat CT scans (rCT, n=47). Target coverage and dose to OARs were recalculated on each CT. Dose was evaluated by comparing ratios between pCT and rCT (p/r-ratio), planned OAR mean doses below 0.5 Gy were omitted due to clinical insignificance.

Results
The median CTV target volume was 139.5 cm3 (range: 20.3-587.3). IMPT provided excellent target coverage to all recurrences (including two T-site recurrences), with a mean p/r-ratio of 1.000 (range:0.998-1.008). The median pCT (Dmean) bladder dose was 8.1 GyRBE (IQR: 3.1-14.1). In comparison, the median rCT Dmean bladder dose was 6.0 GyRBE (range: 0.5-10.1), resulting in a mean p/r-ratio of 1.3 (range:0.5-4.7). For bowel bag and bowel loops the median pCT Dmean were 1.5 GyRBE (IQR:0.2-2.4) and 3.8 GyRBE (IQR:2.9-6.1) with p/r-ratios of 0.9 (range:0.0-1.9) and 1.0 (range:0.1-2.2), respectively.

Conclusion
Robustly optimised IMPT for re-irradiation of LRRC shows excellent target coverage, which is robust against inter-fraction anatomical variation. As expected, greater variability was seen for OARs, of which the bladder had the largest variance.

8. 11:15-11:25: Einar Dale, Oslo, Norway

Re-irradiation with dose painting of head and neck cancer: Clinical outcomes

Dale E (1), Evensen ME (2), Amdal CD (1), Furre T (3), Moan JM (1), Løndalen AM (4), Heggebø LC (1), Malinen E (3,5)

(1) Department of Oncology, Oslo University Hospital, Oslo, Norway. (2) Section of Oncology, Drammen Hospital, Vestre Viken Hospital Trust, Drammen, Norway (3) Department of Medical Physics, Oslo University Hospital, Oslo, Norway. (4) Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway. (5) Department of Physics, University of Oslo, Oslo, Norway.

Introduction
Dose painting (DP) may increase loco-regional control (LRC) in head and neck cancer (HNC) without added morbidity. Recurrent or second primary disease is a clinical problem due to the limited tolerance of the irradiated tissues. These patients could benefit from DP, as the focus is on delivering maximal dose to areas of high tumor burden while not exceeding dose constraints to organs at risk. In this study, we compare the clinical outcome of one group receiving our standard re-irradiation regimen with a group receiving FDG-PET/CT guided DP by contours (DPBC).

Materials and methods
Our conventional re-irradiation regimen is hyperfractionated radiotherapy (RT) 1.5 Gy twice daily over four weeks, giving a total dose of 60 Gy. For DPBC, we defined two FDG-based prescription volumes receiving at least 65 Gy and 70 Gy. Thirteen patients who followed our conventional re-irradiation protocol were compared with 10 patients who received DP. Toxicity (CTCAE v3.0) was scored for 13 parameters at baseline, 3, 6 and 12 months after baseline. Furthermore, a composite score; the mean value of all 13 parameters was calculated. Disease-related endpoints were LRC, disease-free survival (DFS) and overall survival.

Results
The mean toxicity score was maximal three months after RT, with some variation between specific toxicities. Comparing each time point, no significant difference in toxicity was found except for dysphagia at 12 months where the standard group had worse dysphagia scores ($p=0.01$). One-year DFS was 50% and 15% for DP and conventional RT, respectively, although log-rank tests for the various disease endpoints did not reveal any significant differences.

Conclusions
DP of recurrent or second primary HNC did not increase toxicity compared with conventional re-irradiation. We did not find any evidence of improved disease control with DP. Still, DP is expected to give a benefit in selected patients, and a challenge in future studies is to identify these patients.

9. 11:25-11:35: Julie Frikke Depner, Copenhagen, Denmark

Treating brain metastases in metastatic breast cancer: Outcomes after stereotactic radiosurgery examined in a retrospective, single-center cohort analysis

Depner JF (a), Berg T (ab), Ejlertsen B (abc), Andreasen LW (b), Møller S(b), Maraldo MV (b)

a: Danish Breast Cancer Cooperative Group, Rigshospitalet, Copennhagen University Hospital, Copenhagen, Denmark, b: Department of Clinical Oncology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, c: Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Introduction
We examined the role of receptor profiles and other prognostic factors in survival outcomes after stereotactic radiosurgery (SRS) for brain metastases in breast cancer patients.

Materials/method
We included 149 patients who received SRS between 2012-2019 at University Hospital of Copenhagen, Rigshospitalet, Denmark. Overall survival (OS) was determined through the Kaplan-Meier method while CNS progression free survival (CNS-PFS) was determined through competing risk analysis. Prognostic factors for both OS and CNS-PFS were evaluted through uni- and multivariate Cox regression and Fine-Gray models, respectively. The proportional hazards assumptions were tested through Schoenfeld residuals and non-proportionality was accounted for by the inclusion of time-dependent variables.
Results: Median OS for the entire cohort was 14.8 months and was as follows for the four receptor profiles: 33.3 months for ER+/HER2+ (ER: estrogen receptor, HER2: human epidermal growth factor receptor 2), 11.0 months for ER+/HER2-, 17.7 months for ER-/HER2+ and 5.3 months for ER-/HER2-. In the multivariate model, the ER-/HER2- receptor profile (hazard ratio (HR): 2.00, 95% confidence interval (CI): 1.09-3.67) and the presence of extracranial, visceral metastases (HR: 2.90, 95% CI: 1.53-5.50) were associated with worse OS. The ER+/HER2+ receptor profile (HR: 0.43, 95% CI: 0.19-0.96) and 5+ lines of treatment (HR: 0.40, 95% CI: 0.20-0.82) were both associated with improved OS. For CNS-PFS, 5+ lines of treatment (sub-distributional hazard ratio (SHR): 2.88, 95% CI: 1.06-7.81) was associated with worse CNS-PFS, while extracranial, visceral metastases (SHR: 0.54, 95% CI: 0.30-0.97) was associated with reduced risk of CNS progression – which is primarily due to patients with extracranial metastases dying before developing new CNS progression.

Conclusion
Extracranial disease and the ER-/HER2- receptor profile were associated with poor survival outcomes following SRS.

10. 11:35-11:45: Julie Kjems, Copenhagen, Denmark

The potential for oligometastatic treatment of distant metastatic disease in head and neck squamous cell carcinoma (HNSCC) – a real-world data analysis

Kjems, J. (1), Kristensen, C.A. (1), Gothelf, A. (1), Bernsdorf, M. (1), Specht, L. (1), Berthelsen, A.K, Vogelius, I.R. (1), Friborg, J. (1)

1: Department of Oncology, Rigshospitalet, Copenhagen, Denmark

Introduction
Limited real-world data exists on the treatment of patients with distant metastases (DM) in head and neck cancer. We aim to describe the DM treatment in a complete cohort and address the oligometastatic potential for future protocols.

Materials and Methods
In the time period 2008-2017, 1703 patients with HNSCC of the larynx or pharynx were diagnosed at Rigshospitalet, Copenhagen. The patients were identified in the Danish Head and Neck cancer database (DAHANCA) and patient files were manually reviewed in case of a DM recurrence. The extent of DM, the therapeutic intent (radical/palliative) and type of treatment (surgery, radiotherapy (RT) and chemo(immuno-)therapy) were recorded. Survival is reported as the time between date of DM treatment and date of death or end of follow-up (Dec 1st, 2022). Oligometastatic disease (metachronous) was defined as 1-5 DMs identified on the recurrence scans.

Results
A total of 124 patients (7 %) developed DM. Among these, 44 (35 %) received no therapy, either due to comorbidity, physician's decision or personal choice. RT was given to 51 patients (41 %) and 43 (35 %) had chemotherapy at some point in their treatment. After radiological review, 66 (53 %) patients had polymetastatic and 58 (47 %) oligometastatic disease. Of the oligometastatic patients, 23 were not candidates to radical intended therapy due to inoperable locoregional recurrence, poor performance status or treatment refusal. Fifteen of the remaining patients were already treated with radical intent for their DM (all with surgery, one patient surgery + RT) and the median overall survival in this group was 37 months. Twenty patients were potentially treatable, yielding 35/124 (28 %) as potential candidates for oligometastatic protocols.

Conclusions
Approximately 7 % of HNSCC patients develop DM and 47 % of these were found to have oligometastatic disease. Half of these appeared to be potential candidates for oligometastatic protocols.

11. 11:45-11:55: Mette Felter, Herlev, Denmark

MR-guided stereotactic body radiotherapy in patients with oligometastatic disease in the infra-diaphragmatic region (SOFT): a phase 2, multicenter study

Felter Ma, Møller PKb, Josipovic Mc+g, Bekke SNa, Bernchou Ub+f, Serup-Hansen Ea, Parikh Pd, Kim Jd, Geertsen Pa, Behrens CPa+e, Madsen Ka, Vogelius IRc+g, Fink Topsøe Ja, Berthelsen AKc, P›hl Mc, Schytte Tb+f, Persson GFa+g

a Department of Oncology, Herlev and Gentofte Hospital, Herlev, DK; b Department of Oncology, Odense University Hospital, Odense , DK; c Department of Oncology, Copenhagen University Hospital - Rigshospitalet, Copenhagen, DK; d Department of Oncology, Henry Ford Hospital, Michigan, US; e Department of Health Technology, Technical University of Denmark, Roskilde, DK; f Department of Clinical Research, University of Southern Denmark, Odense , DK; g Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, DK.

Introduction
Stereotactic body radiotherapy (SBRT) has proven safe and effective in patients with oligometastatic disease (OMD). However, concerns of severe toxicity have been raised when employing SBRT in the infra-diaphragmatic region close to radiosensitive organs at risk. The SOFT study was designed to test the feasibility and safety of an OMD strategy in infra-diaphragmatic soft tissue metastasis treated on an MR-linac (clinicaltrials.gov ID NCT04407897).

Methods and Materials
This phase II, single-arm, multicenter study was conducted at four hospitals in Denmark and US. Patients with OMD (≤ 5 metastases in max. 3 organs) and patients with oligo-progressive disease (OPD) (≤ 3 metastases) were eligible. A risk-adapted strategy was applied with three fractionation schemes available (45 Gy/3 fractions (f), 50 Gy/5 f, and 60 Gy/8 f). The primary endpoint was cumulative grade ≥ 4 SBRT-related toxicity (TRAE).

Results
The study closed in February 2022 after including 121 patients with a variety of primary tumors. A total of 147 metastatic lesions were treated mainly in the liver (41%), lymph nodes (35%), or adrenal glands (14%). Many of the treated lesions had an unfavorable location, with 48% of the lesions within 10 mm from a radiosensitive OAR. The median follow-up time was 12.3 months (95% CI 10.6-11.7). No Grade 4 or higher TRAEs were registered. The cumulative incidence of grade 2 and 3 TRAE was 41.0% (95%CI, 32.4%-50.6%) and 4.1% (95%CI, 1.4%-9.4%), respectively. We saw 19 (13%) local failures in 17 (13%) patients within the first year of FU. The median PFS was 7.1 months (95% CI 6.0- 9.4). Twenty-two patients (18%) died within the follow-up period.

Conclusion
SBRT to soft tissue metastases in the infra-diaphragmatic region treated on an MR-linac was found safe with no grade 4-5 CTCAE toxicity and a low rate of grade 3 TRAE at 4%, even though a large proportion of the lesions were unfavorably located close to radiosensitive organs.

12. 11:55-12:05: Sakina Khan, Aarhus, Denmark

Remarkable local control and minimal toxicity in small ultra-central lung tumors or solitary lymph nodes after normo-fractionated radiotherapy

S.K. Khan a, L. Hoffmann a b, D.S. Møller b, A.A. Khalil a, M.M. Knap a

a Department of Oncology, Aarhus University Hospital, Aarhus N, Denmark; b Department of Clinical Medicine, Aarhus University, Aarhus N, Denmark

Introduction
In peripheral lung tumors, stereotactic body radiotherapy (SBRT) is superior to normo-fractionated (nf) RT. SBRT has also shown high local control (LC) in centrally located tumors, but there is a high risk of severe toxicity. Data on the effect of RT to central (C) lung tumors are limited and no standard exists. An ongoing Danish trial examines if risk-adapted SBRT for ultra-central (UC) tumors (STARLung NCT05354596) is feasible. In this study, we examined overall survival (OS), LC, and toxicity in patients with UC tumors that could have been candidates for SBRT but received nf-RT.

Materials and methods
Retrospectively, we evaluated 50 lung cancer patients (pts) that between 2007-2021 received RT (50-70Gy in 2Gy fractions) for a solitary tumor or lymph node with diameter <5cm located <2cm from the bronchial tree, esophagus or heart. All tumors were pathologically verified; 31 were primary lung tumors (T1b-T4) and 19 were solitary lymph nodes (T0N1-N2). Chemotherapy was administered as concomitant (29) or sequential (5). OS and LC were analyzed using Kaplan Meier. Cox proportional hazards model for OS was performed including tumor volume, histology, sex, T- vs N-site and chemotherapy. Toxicity was scored.

Results
In 42 patients, the tumor was located <1 cm to mediastinum. Median follow-up time was 43 months (range:7-123). The median OS was 51 months (CI:14-88). OS at 1-, 3- and 5-year was 88% (SE:5), 58% (SE:7) and 49% (SE:7). Local recurrences occurred in 16 pts resulting in 1-, and 3-year LC rates of 78% (SE: 6) and 64% (SE: 8). The majority occurred within 3 years after RT. In multivariate analyses there was no independent factor for OS. No pts experienced grade 4-5 toxicity. Seven patients developed grade 3 toxicity (5 esophageal stenosis, 2 pneumonitis).

Conclusion
Normo-fractionated RT for pts with small UC lung tumors or solitary lymph nodes is feasible. Median OS was 51 months, and toxicity was low with no grade 4-5 events.

13. 12:05-12:15: Yuqing Xiong, Munich, Germany

Daily plan adaptation in ultra-hypofractionated MRgRT for prostate cancer: comparison of adapted and non-adapted accumulated dose

Xiong Y, Rabe M, Kawula M, Nierer L, Klüter S, Hörner-Rieber J, Belka C, Niyazi M, Corradini S, Landry G, Kurz C

Dept. of Radiation Oncology, University Hospital LMU, Munich, Germany; German Cancer Consortium, Munich, Germany; Dept. of Radiation Oncology, Heidelberg University Hospital, Germany; Heidelberg Institute of Radiation Oncology, National Center for Radiation Oncology, Heidelberg, Germany; Clinical Cooperation Unit Radiation Oncology, German Cancer Research Center, Heidelberg, Germany; National Center for Tumor Diseases, Heidelberg, Germany; German Cancer Consortium, Heidelberg, Germany

Introduction
Ultra-hypofractionated online adaptive magnetic resonance-guided radiotherapy (MRgRT) is a promising treatment for prostate cancer. Online adaptation allows tailoring a baseline plan to the daily patient anatomy. The true impact of MRgRT on target coverage and organ-at-risk (OAR) sparing at the level of accumulated dose has not yet been reported. Using deformable image registration (DIR)-based dose accumulation, we compared the delivered adapted dose with simulated non-adapted dose.

Materials and methods
13 prostate cancer patients treated at a 0.35 T MR-linac following the SMILE study protocol (5×7.5 Gy) were included in this study. The fraction MR images were deformably registered to the planning MR image. Subsequently, both non-adapted and adapted fraction doses were warped with the corresponding vector fields and accumulated using a research version of the RayStation treatment planning system (Version 10B-R). Two DIR approaches were implemented. For the comparison, PTV* (PTV minus a 2 mm expansion of the urethra) D95%, CTV* (CTV minus urethra) D98%, and OARs (urethra, bladder, and rectum) D0.2cc were evaluated.

Results
On average (± 1σ), normalized to the baseline plan, the PTV* D95% improved by 4.5% ± 1.4% through the adaptation compared to no adaptation, and the CTV* D98% by 2.4% ± 1.5%. For the OARs and the adapted plans, the bladder D0.2cc decreased by 0.5% ± 0.7%, the urethra D0.2cc by 1.0% ± 0.3%, while the rectum D0.2cc increased by 5.4% ± 1.7%. For all patients, rectum D0.2cc was still below the clinical constraint after adaptation. Both DIR approaches led to results differing on average by 0.1%.

Conclusions
The average improvement from adaptation in ultra-hypofractionated MRgRT for prostate cancer is limited for the CTV and OARs. However, for individual patients with strong anatomical variations, adaptation played a crucial role. Analysis of additional patient cases from a second institution will be presented at the conference.

Session 3: Automation and artificial intelligence

14. 14:15-14:25: Bob Smulders, Aarhus, Denmark

Prediction of dose-sparing by protons assessed by a knowledge-based planning tool in radiotherapy of the brain

Smulders B.2,1, Stolarczyk L.1, Seiersen K.1, Nørrevang O.1, Sommer Kristensen B.2, Schut D.2, Thomsen K.2, Lassen-Ramshad Y.1, Høyer M.1, Muhic A.2,1, Vestergaard A.1

1 Danish Centre for Particle Therapy (DCPT), Aarhus University Hospital, Aarhus, Denmark 2 Department of Oncology, University Hospital of Copenhagen, Rigshospitalet, Copenhagen, Denmark

Introduction
Proton radiation therapy has become increasingly the treatment of choice for brain tumours, due to the decreased integral dose to the brain and sparing of organs at risk. The Danish Neuro-Oncology Group (DNOG) has set the following criteria for sparing of OAR for potential proton treatment: ΔDmean and ΔV30Gy Brain-CTV > 20%, ΔD40% Hippocampii > 20%, ΔDmean Pituitary > 20%, ΔDmean contralateral Cochlea > 10%. To ease and speed up the referring process in Denmark, the prediction of RapidPlanTM (EclipseTM, Varian Medical Systems) was analyzed. This study compares retrospectively the proton dose to the specific OARs generated by RapidPlanTM with the original created treatment plans.

Materials/Methods
The RapidPlanTM brain model is trained on 90 brain tumour patients treated at the DCPT with prescribed doses of 50.4, 54, or 59.4 GyRBE. 30 independently planned patients were used in the test of the RapidPlanTM model. The regression correlation (R) between predicted and optimized/calculated dose to the OARs (as indicated from the selection process) was analysed and the standard deviation (σ) of the differences in dose to the OARs was calculated.

Results
The plans produced by the model were comparable to the clinical plans considering target coverage, robustness and maximum doses to the OAR. There was a good agreement between the predicted and final dose in terms of the mean dose and V30GyRBE for brain-CTV with R = 0.99 for both objectives and σ = 0.7 GyRBE and σ=1.3 cm3, respectively. A plausible agreement for the D40% of Hippocampii is seen with R = 0.97 and σ= 4.7GyRBE, but more data is needed to confirm this. There was less good agreement for the Dmean of the pituitairy and the coclea, probably due to their small sizes.

Conclusion
Knowledge based planning provides good prediction of the dose-sparing effect of protons for brain-CTV and Hippocampii and it saves time and resources in selection of patients for proton therapy.

15. 14:25-14:35: Camilla Panduro Nielsen, Odense, Denmark

Consistency in contouring of organs at risk by AI and radiation oncologists in head and neck cancer patients

Nielsen CP1,2, Lorenzen EL1,2, Sarup N1, Brink C1,2, Jensen K3, Johansen J1, Zukauskaite R1,2, Eriksen JG5,9, Farhadi M6, Andersen M7, Andersen E8, Overgaard J9, Grau C3,5, Friborg J3,4, Hansen CR1,2,3

1Dept of Oncology, Odense University Hospital, DK 2Institute of Clinical Research, University of Southern Denmark, DK 3Danish Center of Particle Therapy, Aarhus University Hospital, DK 4Dept of Oncology, Rigshospitalet, DK 5Dept of Oncology, Aarhus University Hospital, DK 6Dept of Oncology, Zealand University Hospital, Naestved, DK 7Dept of Oncology, Aalborg University Hospital, DK 8Dept of Oncology, University Hospital Herlev, DK 9Dept of Experimental Clinical Oncology, Aarhus University Hospital

Introduction
In the DAHANCA 35 trial patients are selected for proton treatment based on the NTCP benefit for proton compared to photon treatment at the referring departments. Immobilisation, scanning, contouring and planning are then repeated at the national proton centre. Variation in normal tissue contouring among radiation oncologists translates into inconsistencies in the expected NTCP and may result in a lower quality of the selection process. The study evaluated the consistency in the delineation of 12 OARs performed by AI and radiation oncologists, respectively.

Materials and Methods
The study used a convolutional neural network (nnUNet), to contour OARs for 63 patients from the DAHANCA 35 pilot trial. Each patient had a CT from the local referring DAHANCA centre and one from the proton centre. Deformable image registration, using MIM software, was used to transfer local AI and oncologist contours to the proton centre scans to compare contours from AI to AI, and oncologist to oncologist, respectively. Consistency was calculated using the Dice index and Mean Surface Distance (MSD). Two NTCP models from the trial were used to calculate NTCP for xerostomia and dysphagia.

Results
The AI contours showed significantly better consistency than the contours by the oncologists. The median Dice index was 0.85 (interquartile range [0.78,0.90]) and 0.68 [0.51,0.80] for AI and oncologist contours, respectively. The median MSD was 0.9mm [0.7,1.1] and 1.9mm [1.5,2.6] for AI and oncologist contours, respectively. There was no difference in ΔNTCP for xerostomia. The median difference in ΔNTCP for dysphagia was 1%-point (interquartile range [-0.1,4]) and 1%-point [-1,4] for AI and oncologist contours, respectively.

Conclusions
The study showed that the contours made by the AI algorithm were more consistent than those made by oncologists for 12 OARs in H&N cancer patients. However, no significant effect on the ΔNTCP calculation for xerostomia and dysphagia could be discerned.

16. 14:35-14:45: Emma Riis Skarsø, Aarhus, Denmark

Multi-center auto-segmentation model for internal mammary nodes using clinical data: A DBCG study

Skarsø ER1, Refsgaard LH2, Saini A3, Lorenzen EL4, Maae E5, Yates E6, Jensen I7, Andersen K8, Boye K9, Matthiessen LW8, Maraldo M9, Berg M5, Nielsen MH10, Møller M7, Al-Rawi SA3, Offersen BV1,2,6, Korreman SS1,6

1 Danish Center for Particle Therapy, AUH, Aarhus, DK, 2 Department of Experimental Clinical Oncology, AUH, Aarhus, DK, 3 Department of Clin Oncology and Palliative Care, SUH, Naestved, DK, 4 Laboratory of Radiation Physics, OUH, Odense, DK, 5 Department of Oncology, SDU, Vejle, DK, 6 Department of Oncology, AUH, Aarhus DK, 7 Department of Oncology, AAUH, Aalborg DK, 8 Department of Oncology, HGH, Herlev, DK, 9 Department of Oncology, RH, Copenhagen, DK, 10 Department of Oncology, OUH, Odense, DK

Purpose
We developed a deep learning (DL) based segmentation model for internal mammary lymph nodes (CTVn_IMN) for left-sided breast cancer (BC) pts. The model was trained on clinical delineations from all seven RT centres in DK.

Material
We included CT scans and clinical CTVn_IMN delineations from 778 high-risk left-sided BC pts from the Danish Breast Cancer Group (DBCG) RT Nation database, treated with adjuvant RT in DK during 2015-16. Delineations were crudely sorted to eliminate obvious deviations from DBCG guidelines and delineations beyond intercostal room 3. Pts were randomly split into a training (90%) and test set (10%).
CT scans were cropped to the posterior and caudal part of the heart and cranial part of the lungs and were used as input along with CTVn_IMN in a 3D full resolution nnUNet with five-fold (1000 epochs) cross-validation and default parameters.
The test-segmentations were evaluated with Dice coefficient (DSC), Hausdorff distance 95th (HD95) and mean surface distance (MSD) and compared to clinical ground truth (CGT) delineations. Difference in cranial and caudal (cc) extension was measured.

Results
In total 424 pts were excluded during the sorting process, leaving 319/35 pts to train/test the model. The model performed with median DSC=0.70, HD95=4.83mm and MSD=1.45mm. The largest variation between CGT and predictions were in caudal extension, varying up to 18 slices. The two lowest DSC scored pts, showed large disagreements in both cranial and caudal part of the CTVn_IMN. However, from a clinical perspective, these two DL-based delineations adhere better to the DBCG guidelines than the CGT.
Median scored pts showed minor disagreements in the cc extension, varying 1-2 slices.

Conclusion
We demonstrated the feasibility of developing a DL model for CTVn_IMN based on real world clinical delineations. The model exhibited minor for most pts. In pts with major deviations, model predictions were closer to DBCG guidelines than clinical ground truth.

17. 14:45-14:55: Maximilian Konrad, Odense, Denmark

An automatic open-source approach to organs at risk and target structure segmentation for T2 MR-guided brachytherapy of cervical cancer patients using nnU-Net

Konrad M, Lorenzen EL, Hazell I, Brink C, Knudsen AØ, Nyvang GB

Laboratory of Radiation Physics, Department of Oncology, Odense University Hospital, Odense Denmark; Department of Oncology, Odense University Hospital, Odense Denmark

Introduction
In MR-guided brachytherapy, organs at risk (OAR) are manually segmented by doctors during the planning process while the patient waits for the treatment to start. AI segmentation has the potential to support this manual work by providing fast and consistent segmentations.

Materials and Methods
A nnU-Net was trained and tested for segmenting bowel, bladder, sigmoid, rectum, GTV, and HR-CTV for cervical cancer patients. T2 MR scans acquired between June 2019, and September 2022 were used (n=291). 251 studies were used for the training of nnU-Net, and the 40 most recent for testing, comparing manual results with the AI segmentation using the dice similarity coefficient (DSC) and the mean surface distance (MSD). Only the part of the organ relevant to the treatment planning was used in the comparison (cropped with a margin of 40mm around the HR-CTV). Points outside 1.5 times the IQR of the DSC were labeled as outliers and reviewed by a doctor. All delineations were done according to the Embrace II protocol.

Results
The DSC and MSD (median±IQR) for OARs and targets were: GTV 0.73±0.29 and 1.3±2.7mm, HR-CTV 0.82±0.11 and 1.6±1.6mm, Bladder 0.93±0.04 and 0.6±0.4mm, Rectum 0.75±0.26 and 1.9±3.4mm, Sigmoid 0.79±0.16 and 1.8±2.7mm and Bowel 0.72±0.24 and 2.4±4.4mm. Out of 240 contours, 13 were marked as outliers. Most outliers were in the bowel (8) due to incompleteness of the AI segmentation. Other outliers were due to errors in the transition between rectum and sigmoid (2), non-conclusive differences in GTV (2), and both AI and manual being incomplete for the sigmoid (1).

Conclusion
Good performance of the trained network was observed in the testing cohort in terms of both accuracy and precision. This indicates that clinical use of the network would speed up the delineation process and potentially reduce the risk of errors. Clinical implementation is therefore undergoing. The trained network will be made publicly available after the work's publication.

Session 4: Clinical radiotherapy – CNS, head and neck, breast cancer

18. 16:20-16:30: Alice Clarke, Aarhus, Denmark

Radiation dose-escalation for Glioblastoma: who may benefit?

Clarke AM (1,2), Lukacova S (2,3), Dahlrot RH (1,4), Haslund CA (5), Muhic A (1,6), Bibby BM (7), Trip AK (1)

(1) Danish Center for Particle Therapy, Aarhus Univ Hospital, Aarhus, Denmark (2) Dept. of Clin Med, Aarhus Univ, Aarhus, Denmark (3) Dept. of Oncol, Aarhus Univ Hospital, Aarhus, Denmark (4) Dept. of Oncol, Odense Univ Hospital & Dept. of Clin Research, Univ of Southern Denmark, Odense, Denmark (5) Dept. of Oncol, Aalborg Univ Hospital, Aalborg, Denmark (6) Dept. of Oncol, Copenhagen Univ Hospital, Copenhagen, Denmark (7) Dept. of Biostatistics, Aarhus Univ, Aarhus, Denmark

Introduction
Glioblastoma (GBM) is known for its highly infiltrative nature as well as its high local recurrence rate. GBM patients with local-only disease, may potentially benefit the most from local radiation dose-escalation. The aim of this retrospective national study was therefore, to identify subgroups of patients with a high chance of local-only disease using patient, tumour, and treatment variables.

Methods
All adults with newly diagnosed GBM between 2014-2019 who started long-course (chemo)radiotherapy and had a RT-planning & follow-up MRI, were included. To assess local-only disease, first radiographic (RANO) progression was scored as: local-only (connected to GTV), non-local (new lesion without connection to GTV), or combined (connected and unconnected).
To evaluate the association of patient, tumour, and treatment variables to local-only progression, logistic regression was used. To assess the probability of local-only progression in subgroups, we used a multivariate additive model with MGMT-status and the top 3 explanatory variables.

Results
We included 831 patients, of whom 760 (91.5%) had radiographic progression. Progression was local-only in 69%, non-local in 16%, and combined in 15% of recurrences.
When comparing methylated to unmethylated MGMT tumours, there was no significant difference in local-only progression probability (.67, 95%CI .62-.73 vs. .73, 95%CI .69-.78, p=.08). In the multivariate model (MGMT-status, tumour focality & location at diagnosis, and extent of surgery), the local-only probability (95%CI) was minimum .56 (.40-.73) and maximum .82 (.74-.90) in respective subgroups.

Conclusion
In all subgroups of GBM patients, the probability of local-only progression was above .50. Based on this, all patient subgroups, independent of MGMT-status, could potentially benefit from radiation dose-escalation within clinical trials. To enrich study populations, the cut-off for local-only progression probability should be higher.

19. 16:30-16:40: Jørgen Johansen, Odense, Denmark

Accelerated Loss of Lean Body Mass in Head and Neck Cancer Patients During Cisplatin-based Chemoradiation

Lønbro S (1), Hermann P (2,3), Gam S (4), Hansen CR (3,5) & Johansen J (3,6)

1. Dept of Public Health, Section for Sports Science, Aarhus University, Denmark. 2. Dept. of Endocrinology, Odense University Hospital, Denmark. 3. Dept of Clinical Research, University of Southern Denmark, Odense, Denmark. 4. Dept. of Endocrinology, IRS-Sydvestjysk Sygehus, University of Southern Denmark, Denmark. 5. Laboratory of Radiation Physics, Odense University Hospital, Odense, Denmark. 6. Dept. of Oncology, Odense University Hospital, Denmark

Introduction
Weight loss is common following radiotherapy (RT) of HNC due to dysphagia from RT-induced mucositis. This study investigated the decline in total body weight (BW), lean body mass (LBM), and fat mass (FM), as well as functional performance, during RT, and the potential effect modification of cisplatin and RT-dose to the Pharyngeal Constrictor Muscles (PCMs).

Materials and methods
48 HNC patients in WHO PS 0-1 were included, receiving RT alone (n=16) with 66-68 Gy/33-34 Fx, 5-6 Fx/wk or CRT (n=32), adding 40 mg/m2 cisplatin weekly plus nimorazole. Dual X-ray Absorptiometry assessed BW, LBM and FM pre-RT and bi-weekly until 2 wks post-RT. Leg and chest press muscle strength and functional performance tests were evaluated pre-RT and 2 wks post-RT.

Results
BW and LBM declined significantly already at wk 2, i.e., before onset of RT side effects, and declined till the end of RT. LBM declined every two weeks until wk 6 by 1.2±0.4 kg, 2.0±0.4 kg, and 1.4±0.4 kg, respectively (p-values ≤0.001). FM declined with a two-week delay with significant, continuous reductions from wk 2 to 8. Leg press and chest press muscle strength both declined by 12.5%, 7.2±1.4 kg ($p<0.0001$) and 5.0±1.1 kg ($p=0.0001$) from pre-RT to post-RT. Functional performance was unchanged. Total loss of LBM was significantly associated with muscle strength impairment, but not to change in functional performance. Dose to the PCMs correlated significantly with weight loss. CRT patients lost 3.1±0.8 kg of LBM more from pre-RT to post-RT compared with RT alone ($p=0.0001$; 95% CI 1.5;4.7). Analyses adjusted for mean dose to the PCMs, tumor site, disease stage, nimorazole, and baseline BMI confirmed this effect.

Conclusions
BW and LBM declined significantly during RT, even before onset of RT-induced mucositis. LBM loss was more pronounced after CRT compared with RT alone even after effect modification of PCM radiation dose. Overall, LBM loss was significantly associated with loss of muscle strength.

20. 16:40-16:50: Lene Haldbo-Classen, Aarhus, Denmark

Is radiation dose to sleep-relevant brain structures associated with lower sleep quality in adults with primary non-glioblastoma brain tumours?

A. Amidi1+2, L. Haldbo-Classen2, J.F. Kallehauge3, L. M. Wu1+4, S. Lukacova2, Y. Y Lassen-Ramshad3, R. Zachariae1+2, M. Høyer3.

1Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Sciences, Aarhus University, 2Department of Oncology, Aarhus University Hospital, Aarhus. 3Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus.

Introduction
Poor sleep is associated with impaired cognitive functioning and reduced quality of life. In the present study, we investigated if radiation dose to sleep/wake-relevant brain structures is associated with poorer patient-reported sleep quality in primary non-glioblastoma brain tumour patients.

Methods
Seventy eight patients who had received radiation therapy (RT) for their brain tumour between 2006 and 2016 were included. They completed the Pittsburg Sleep Quality Index (PSQI) and mean radiation doses (Dmean) to sleep/wake-relevant structures; brainstem, thalamus, hypothalamus, and the pituitary and pineal glands were calculated. Dmean to these structures were compared between patients with and without impaired sleep outcomes using bootstrapped independent t-tests. Differences with effect sizes (ES, Cohen's d) exceeding ± 0.3 are reported.

Results
Median time since RT was 4.6 years. No differences were observed between tumour types, $F(3,74) = 0.37$, $\eta 2 = .02$. Clinical sleep disturbance (PSQI > 5) was reported by 37.2% (n=29). Those with sleep disturbance had received a higher radiation dose to the pituitary gland when compared to patients without sleep disturbance; Dmean = 26.11 Gy, SE = 2.59, versus 34.57 Gy, SE = 3.43, ES(d) = - 0.46, 95% CI [-0.93, 0.003]. Patients with low sleep efficiency had received a higher radiation dose to the thalamus and the pineal gland, Dmean = 18.11 Gy, SE = 2.36, versus 24.55 Gy, SE = 4.43, ES(d) = -0.35, 95% CI [-0.83, 0.15], and Dmean = 16.20 Gy, SE = 2.48, versus 23.10 Gy, SE = 4.25, ES(d) = -0.36, 95% CI [-0.85, 0.13]. Patients with poorer sleep latency had received higher dose to the pituitary gland and brain stem. Results not shown.

Conclusions
The prevalence of clinical sleep disturbances in patients with primary brain tumors was high (37%). Our results indicate that higher radiation doses to sleep/wake-relevant structures may contribute to poor sleep quality in patients with a primary brain tumour.

21. 16:50-17:00: Maja Olsen, Copenhagen, Denmark

Socioeconomic differences in the pre-diagnostic interval among patients diagnosed with head and neck squamous cell carcinoma - a nationwide, population-based study from DAHANCA, Denmark, 2008-2019

Olsen, M.H.(1,2), Maltesen, T.(3), Lassen, P.(1), Kjaer, T.K.(2), Johansen, J.(5), Primdahl, H.(6), Andersen, E.(7), Kristensen, C.A.(8), Andersen, M.(4), Farhadi, M.(9), Overgaard, J.(1), Dalton, S.O.(2,9)**
**shared last authorship*

1. Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark, 2. Survivorship and Inequality in Cancer, Danish Cancer Society Research Center, Copenhagen, Denmark, 3. Statistics and Data Analysis, Danish Cancer Society Research Center, Copenhagen, Denmark, 4. Department of Oncology, Aalborg University Hospital, Aalborg, Denmark, 5. Danish Centre for Particle Therapy, Aarhus University Hospital, Denmark, 6. Department of Oncology, Odense University Hospital, Denmark, 7. Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, 8. Department of Oncology, Herlev University Hospital, Denmark, 9. Department of Oncology, Rigshospitalet, Copenhagen, Denmark, 10. Department of Clinical Oncology & Palliative Care, Zealand University Hospital, N'stved, Denmark

Introduction
The socioeconomic differences in survival are pronounced for patients diagnosed with head and neck cancer. To identify targets for intervention, this nationwide, population-based study investigates socioeconomic differences in the pre-diagnostic interval and stage at diagnosis.

Materials and methods
Information on patient-reported symptom onset, symptoms, comorbidity, and disease-specific factors was obtained from the nationwide population-based Danish Head and Neck Cancer Group (DAHANCA) database for patients diagnosed with squamous cell carcinoma (SCC) in the head and neck region between 2008 and 2019. Information on consultations in primary care and socioeconomic position (SEP) was obtained from administrative registers. Differences in the interval from symptom onset to diagnosis were estimated in general linear models with 95% confidence intervals (CIs). Consultation patterns in primary care were examined using methods for change-point detection and associations with advanced-stage disease were estimated in logistic regression models.

Results
Overall, patients with low, medium and high SEP had a similar interval from patient-reported symptom onset to diagnosis of 10 weeks. Despite this interval varied according to primary symptom and anatomical subsite (range: 7-15 weeks), minor socioeconomic differences was observed. A distinct increase in consultation rates was observed close to reported symptom onset at 9 weeks (95% CI [9.3;10.7]) prior to diagnosis for patients with low SEP, and at 7 weeks (95 % CI [4.8;9.2]) for patients with high SEP. Patients with low compared to high SEP had increased odds for advanced-stage glottic, HPV+ oropharyngeal, and oral cavity SCC (OR range: 1.5-1.8 95% CI [1.0-2.3]), but not non-glottic laryngeal, HPV- oropharyngeal, and hypopharyngeal SCC.

Conclusion
Despite socioeconomic differences in stage at diagnosis for some subsites, minor socioeconomic differences in the pre-diagnostic interval were observed.

22. 17:00-17:10: Morten Horsholt Kristensen, Aarhus, Danmark

Cancer stem cell expression and tumor volume as prognostic markers for radioresistance in HNSCC

Kristensen MH(1);Alsner J(1);S›rensen BS(1,2);Hansen CR(2,3,4);Zukauskaite R(5);Samsøe E(6);Maare C(7);Johansen J(5); Primdahl H(8);Bratland Aa(9);Kristensen CA(10);Andersen M(11);Lilja-Fischer JK(1);Tramm T(12);Overgaard J(1);Eriksen JG(1)

(1)Dep Exp Clin Onc, AUH, Aarhus, DK; (2)DCPT, AUH, Aarhus, DK; (3)Lab Rad. Phys., Odense Univ Hosp, Odense, DK; (4)Dep Clin Res, Univ. of Southern Denmark, Odense, DK; (5)Dep Onc, Odense Univ Hosp, Odense, DK; (6)Dep Onc, Zealand Univ Hosp, Næstved, DK; (7)Dep Onc, Herlev Hosp, Herlev, DK; (8)Dep Onc, AUH, Aarhus, DK; (9)Dep Onc, Oslo Univ Hosp, Oslo, Norway; (10)Dep Onc, Rigshospitalet, Copenhagen, DK; (11)Dep Onc, Aalborg Univ Hosp, Aalborg, DK; (12)Dep Pathol, AUH, Aarhus, DK

Purpose/Objective
Radioresistance is assumed to be the main reason for failure after primary curative (chemo-)radiotherapy ((C-)RT) for HNSCC. We aimed to identify if putative cancer stem cell (CSC) markers and tumor volume could identify patients (pts) with more or less radioresistant tumors following primary (C-)RT.

Material/Methods
The DAHANCA 19 cohort from 2007-12 was included. Treatment was primary curative IMRT-based (C-)RT (66-68Gy/33-34fx 6 fx/wk (+/- cisplatin 40mg/m2 weekly)) and nimorazole. Total GTV (GTVTot) was extracted from planning-CTs. RNA qPCR from formalin-fixed paraffin embedded tumor tissue was used to analyse gene expression of putative CSC markers. The absolute number of CSC was estimated as the sum of the products of tumor volume and expression of CSCs. Radioresistant tumors were defined as failure in the high-dose region following (C-)RT within 3 years. Analyses were conducted separately on groups of pts with p16-positive oropharyngeal (OPSCCp16+) and non-HPV-driven tumors. Variables were categorized group-vice in tertiles based on the absolute number of CSC.

Results
Of 600 pts, 545 pts with sufficient tumor tissue and valid volumes were included: OPSCCp16+ (n=282) and non-HPV-driven (n=263 (OPSCCp16- (n=100); oral cavity (n=20); hypopharynx (n=65); larynx (n=78))).
For non-HPV-driven tumors, large volume was a poor prognostic factor, whereas the absolute number of CSC increased the ability to distinguish more radiosensitive tumors (HR=0.3 (0.1-0.7) for low vs. high number of CSC).
Total volume was not prognostic for pts with OPSCCp16+. The number of CSC was able to identify pts with more radioresistant tumors, where high number of CSCs had a higher risk (HR=9.7 (2.2-41.7)) of high-dose failure compared to low and intermediate CSC.

Conclusion
Tumor volume was prognostic for the non-HPV-driven tumors only. In contrast to volume, the level of CSC was prognostic in OPSCCp16+, which may benefit in selection of pts for individualized treatment.

Wednesday June 21

Session 5: Proton radiobiology

23. 08:40-08:50: Esther Troost, Dresden, Germany

Multi-parametric MRI for unraveling radiation-induced changes in primary brain tumor patients

Troost, EGC1-3; Witzmann1,2, K; Dünger1, L; Raschke, F1,2.

1 OncoRay - National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany; 2 Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany; 3 Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany.

Introduction
Many primary brain tumor patients are being offered photon and proton beam irradiation, based on contracts with insurance companies or the model-based approach. While neurocognitive function tests are being collected as subjective outcome measures, objective indicators of the possible benefit from protons in terms of normal tissue toxicity are thus far scarce. Therefore, we assessed prospectively and repeatedly obtained, multi-parametric MRI data obtained in two clinical studies to unravel changes in normal appearing brain.

Materials and methods
Multi-parametric MRI data of primary brain tumor patients were obtained prior to radio(chemo)therapy (RT) and at three-monthly intervals thereafter. All MRI scans were acquired on the identical 3 Tesla Philips Ingenuity TF PET/MRI-Scanner using an 8-channel head coil. Grey and white matter (WM) was segmented in the T1w images using SPM12 and rigidly registered to specific MR-contrasts with ANTs. Abnormal tissue regions were manually contoured in the FLAIR images and excluded from the analyses. Imaging findings were correlated with radiation dose and time, and with MRI data obtained in healthy volunteers.

Results
The cerebellar volume decreased significantly and irreversibly after RT as function of time, time×dose and age[1]. Hippocampus, amygdala, thalamus, putamen and pallidum showed significant atrophy after RT depending on time and dose, but not on radiation modality[2]. The perfusion in brain tissue remained unaltered after proton beam RT[3]. Assessing DWI-MRI, RT led to a significant mean diffusivity (MD) reduction in WM, increasing with both radiation dose and time[4]. In DTI-MRI, MD, radial diffusivity, axial diffusivity and T2* in low dose WM regions were found to be significantly reduced, worsening with the dose and time[5].

Conclusions
Multi-parametric MRI may serve as objective response measure following photon and proton beam radiotherapy.

24. 08:50-09:00: Fredrik Kalholm, Stockholm, Sweden

Modeling RBE with Qeff significantly improves prediction of cell survival for proton therapy compared to LET

Fredrik Kalholm[1,2], Leszek Grzanka[3], Iuliana Toma-Dasu[1,2], Niels Bassler[4,5]

1. Medical Radiation Physics, Department of Physics, Stockholm University, Stockholm, Sweden. 2. Department of Oncology and Pathology, Medical Radiation Physics, Karolinska Institutet, Stockholm, Sweden. 3. Institute of Nuclear Physics Polish Academy of Sciences, Krakow, Poland. 4. Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. 5. Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Introduction
For proton therapy, a relative biological effectiveness (RBE) of 1.1 has been widely applied clinically. However, since unexpected toxicities occasionally are observed near proton track ends, several variable proton RBE models have been proposed for optimizing and/or evaluating treatment plans. For these models, dose averaged linear energy transfer (LETd) is the most commonly used radiation quality descriptor, but whether or not other metrics correlate better with RBE has so far not been thoroughly investigated. We compare consistently calculated LETd with other quantities as input variables for a novel RBE model and benchmark their performances.

Methods
Protocol consistent high-throughput in vitro cell survival studies' experimental set-ups for proton RBE determination were simulated using the Monte Carlo particle transport code SHIELD-HIT12A. LET, Q and $z^*2/\beta 2$, here called effective Q (Qeff) are scored for both dose and track-averaging, while the scoring includes all secondaries, all protons or only primaries. A linear-quadratic based phenomenological RBE model is then fitted, with the different beam quality quantities used as input variables, with the goodness of fit determined using a bootstrapping approach. The corresponding NTCP values produced by the various models are also investigated for patients experiencing unexpected toxicities.

Results
Versions of Qeff and Q predicts RBE more accurately than LET, with the best linear fit having a relative root-mean-square-error (RMSE) for RBE2 Gy ± one standard error of 2.76 ± 0.07 (Qeff_(d, primary)), compared to 3.33 ± 0.08 For LET_(d, protons). Welch's t-test for comparing the calculated RMSE of RBE2 Gy resulted in two-tailed p-values of <0.002 for all Q and Qeff quantities compared to LET_(d, protons), indicating a statistically significantly better performance.

Conclusion
Q or Qeff might be a better choice than LET as an input parameter for proton phenomenological LQ based RBE models.

25. 09:00-09:10: Maksym Fritsak, Villigen, Switzerland

On the role of treatment uncertainties in the onset of radiation-induced optic neuropathy after proton therapy

Fritsak M, De Angelis C, Safai S, Weber DC, Lomax AJ, Fattori G

Department of Chemistry and Applied Biosciences, ETH, Zürich, Switzerland. Center for Proton Therapy, Paul Scherrer Institute, Villigen, Switzerland; University Hospital Zürich, Zürich, Switzerland; University Hospital of Bern (Inselspital), University of Bern, Bern, Switzerland.

Purpose
Radiation-induced optic neuropathy (RION) is a rare but critical complication of skull and brain radiation. The role of advanced age, hypertension (HT), and tumor involvement (TI) in the onset of RION finds confirmation in several clinical studies, whereas no direct correlation with treatment dose has been found. In this study, we examined the impact of treatment uncertainties on RION occurrence and explored the potential effects of different models of proton biological efficacy.

Methods
216 meningioma (93.1%) and chordoma/chondrosarcoma (6.9%) patients treated with at least 45 GyRBE1.1 to the optic apparatus were studied. The dataset is from a single institute with a 6.5% RION incidence. Next to common dose metrics (D2, DMean), worst-case dose due to setup uncertainties (2.25mm) and HU calibration (3%) were considered. In addition, LET distribution, approximate proton fluence maps, LET-weighted dose, DxLET, and DxRBEMcNamara have been studied as possible RION predictors. These were combined with established clinical parameters in univariate and multivariate analyses on bootstrapped data to search for evidence of causality. Diverse statistical methods were used to identify the most robust predictive factors and fit NTCP logistic model.

Results
Older age ($p=0.001$), HT ($p<0.001$), and TI ($p=0.04$) were significantly correlated with RION, and their importance over any other dose-derived metric was confirmed in multivariate statistics. The best-performing NTCP model (AUC-ROC 0.87) was well calibrated on the dataset (Hosmer-Lemeshow $p=0.94$). No dosimetric parameter among the studied was strongly associated with the RION incidence.

Conclusion
The statistical power of dose metrics including variable RBE, LET, and treatment robustness was not sufficient for inclusion in NTCP modeling. Neither uncertainties nor biological effects were found to be better predictors than the aforementioned clinical parameters, confirming these as primary risk factors on our dataset.

Session 6: Clinical radiotherapy - Genito-urinary cancer

26. 09:30-09:40: Anders Frederiksen, Aarhus Denmark
Presented by Kari Tanderup, Aarhus, Denmark

Peripheral neuropathy in cervix cancer patients: a trajectory analysis

Frederiksen A.T.1, Pelizzola M.1, Kirchheiner K.2, Jürgenliemk-Schulz I.M.3, Nout R.A.4, Schmid M.P2, Tanderup K.1, Tan L.T.5, Spampinato S.1

1: Danish Center for Particle Therapy, Aarhus University Hospital, 2: Department of Radiation Oncology-Comprehensive Cancer Center, Medical University of Vienna, 3: Department of Radiation Oncology Utrecht, University Medical Centre Utrecht, 4: Department of Radiation Oncology Rotterdam, Erasmus MC, 5: Oncology Centre, Cambridge University Hospitals NHS Foundation Trust

Objective
Peripheral neuropathy (PN) is a common side-effect after chemoradiation. Previous studies found that persistent patient-reported PN has major impact on long-term quality of life (QoL) among patients treated for locally advanced cervical cancer (LACC). This analysis evaluates persistency and identifies time development patterns of patient-reported PN among LACC patients.

Materials and methods
The analysis was conducted within the prospective international EMBRACE-II study which enrolled LACC patients (2016-2021) treated with EBRT, concomitant weekly cisplatin, and brachytherapy.
PN was scored with the EORTC CX24 questionnaire by patients at baseline and regular follow-ups. This analysis included patients with reporting at baseline and >=3 follow-ups (FUPs) at 3 months after end of treatment and up till 24 months.
Late persistency (LAPERS) of PN was calculated based on the median score of PN across FUPs. Late persistency of PN was defined if patients scored “a little or worse” and “quite a bit or worse” in at least of half of FUPs, respectively. Trajectory analysis (TJA) was used to group patients based on their longitudinal time patterns of PN development over the observation period and identify relevant clusters.

Results
Of the EMBRACE II cohort, 804 patients fulfilled the criteria at the time of longitudinal analysis. “A little or worse” late persistent PN was experienced by 42.7% (n=343) and “quite a bit or worse” by 9.7% (n=78) of patients. Within these two groups 8.5% and 1%, respectively, did not experience any worsening compared to baseline. TJA found three major clusters of patients with similar time development patterns: progressing to “a little”, progressing to “very much”, and transient PN.

Conclusion
Patient-reported tingling and numbness in hands and feet was experienced frequently after treatment by LACC patients in EMBRACE II. TJA allowed to identify clusters of patients with clear worsening of PN, most of them reporting “a little”.

27. 09:40-09:50: Anne Cobussen, Maastricht/Aarhus, The Netherlands/Denmark

Clinical outcomes using a 3D printed tandem-needle-template and the EMBRACE-II planning aims for image guided adaptive brachytherapy in locally advanced cervical cancer.

Cobussen A (1,2), Petric P (1,3), Wulff CN (1), Buus S (1), Spejlborg H (1), Nielsen SK (1), Traberg A (1), Meisner B (1), Hokland S (1) and Lindegaard JC (1)

1Department of Oncology, Aarhus University Hospital, Denmark 2Department of Radiation Oncology, MAASTRO clinic, the Netherlands 3Department of Radiation Oncology, Zürich University Hospital, Switzerland

Introduction
Extensive local disease or narrow vagina may compromise brachytherapy (BT) in patients with cervical cancer. This is the first study to analyze clinical feasibility and long-term outcomes of using 3D printed vaginal tandem-needle templates (3DP TNT) for transvaginal insertion of needles in parallel (P) or parallel and oblique (P&O) direction to the tandem.

Material and methods
All patients treated with BT using 3DP TNT from 2015-2020 were included. Decision to use a 3DP TNT and pre-planning of its optimal geometry were made after 4-5 weeks of external beam radiotherapy, based on gynecological examination and MRI with a tandem-ring applicator in situ. The TNT was 3D-printed in house, using biocompatible autoclavable material and consisted of a circular template and shaft fitting a uterine tandem and with P and O holes for guidance of plastic needles. Thus, the radioactive source was never in direct contact with the 3DP TNT. The TNT was 3D printed in a standard or individualized configuration. Planning aims were based on the Embrace II protocol.

Results
101 patients with a median age of 63 years were included: 49 with P needles only and 52 with both P&O needles. Individualized TNT was used in 19 patients in the P&O group. Performance status (WHO) was > 0 in 48%. FIGO2018 stage III-IV was present in 78%. T-score at diagnosis and BT was 9.1 and 6.5 respectively, with a significantly higher T-score in the P&O compared to P group. The mean high-risk CTV D90 was 93 Gy with no significant difference between the two groups. Three-year local control rates were 85%, 95%, 75% for the overall, P- and P&O group respectively and 68%, 80% and 56% for cancer specific survival. Grade ≥3 treatment related complications were observed in 10 patients.

Conclusions
The use of 3DP TNT for BT in cervical cancer provides successful management of very extensive local disease and/or unfavorable anatomy with the possibility for treatment individualization.

28. 09:50-10:00: Ingerid Knudtsen, Trondheim, Norway

PSMA-PET of prostate cancer patients with biochemical recurrence

Knudtsen IS1, Abrahamsen BS1, Selnæs KM2, Elschot M1,2, Langørgen S2, Keil TM2, Johansen H2, Bertilsson H3,4, Halvorsen DL3, Tandstad T5,4, Bathen TF1,2, 180°N-prostate consortium

1Department of Circulation and Medical Imaging, Norwegian University of Science and Technology, Trondheim, Norway. 2Department of Radiology and Nuclear Medicine, St. Olavs hospital, Trondheim, Norway. 3Department of Urology, St. Olavs hospital, Trondheim, Norway. 4Department of Clinical and Molecular Medicine, Norwegian University of Science and Technology, Trondheim, Norway. 5The Cancer Clinic, St. Olavs hospital, Trondheim, Norway

Introduction
We have investigated how a combined PSMA (prostate specific membrane antigen)-PET/MRI/CT-protocol affected treatment of patients referred as candidates for salvage radiotherapy (RT) after biochemical recurrence (BCR).

Materials/methods
Patients included had undergone radical prostatectomy (+/- ePLND) and presented with BCR in accordance with the European Association of Urology. The imaging protocol consisted of MRI (chin to thighs), 18F/68Ga-PSMA PET/CT (vertex to thighs) and PET/mpMRI of the pelvic region, performed sequentially. The PET/CT, PET/mpMRI and mpMRI were evaluated separately by specialists in nuclear medicine and radiology and then in consensus. Imaging recurrence was defined as local/loco-regional/metastatic disease according to consensus. This was compared to corresponding readings of mpMRI only.
Change of treatment due to PSMA-PET was defined as cases where a) detected lesions according to consensus differed from mpMRI and b) these lesions resulted in upgrading of disease necessitating other treatment than observation or standard salvage RT of the prostate bed +/-/ elective RT of the pelvic region.

Results
Of the 116 patients (median PSA 0.36 ng/ml) eligible for analysis, recurrence was detected in 47% based on PET/CT/mpMRI. Recurrence was detected in 20% based on mpMRI only. For 21% of the patients, PET uncovered more advanced disease leading to change of treatment. 8% had metastatic disease incompatible with curative treatment and initiated hormone therapy only. 9% had recurrence in loco-regional lymph nodes and were referred to standard treatment consisting of hormone therapy and RT of the pelvic region, but including dose escalation to affected lymph nodes. 4 % had single metastatic skeletal lesions compatible with stereotactic RT or dose escalation within the elective RT volume.

Conclusions
In this low-level PSA patient group, 22% of the patients presented with advanced disease demanding change of treatment based on PSMA-PET.

29. 10:00-10:10: Marta Pelizzola, Aarhus, Denmark

Identification of syndromes from temporal evolution of symptoms in cervix cancer patients

Pelizzola M, Spampinato S, Chopra S, Jürgenliemk-Schulz I M, Nout R, Kirchheiner K, Tanderup K

Dept of Clinical Medicine - DCPT - Danish Center for Particle Therapy, Aarhus, Denmark, Dept of Radiation Oncology, Advanced Centre for Treatment Research and Education in Cancer, Tata Memorial Centre, Navi Mumbai, India, Dept of Radiation Oncology, University Medical Centre Utrecht, The Netherlands, Department of Radiation Oncology, Erasmus University Medical Center, Utrecht, The Netherlands, Department of Radiation Oncology- Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria

State of the art treatment for locally advanced cervical cancer (LACC) has shown excellent disease control and survival. However, treatment is still associated with a wide spectrum of late symptoms. The aim of this study was to identify clusters of co-occurring symptoms over time in LACC patients, focusing particularly on multifactorial symptoms with a strong impact on quality of life.

EMBRACE I is a multicenter prospective observational study with 1416 LACC patients enrolled from 2008 to 2015. Information on physician-assessed morbidity and patient reported outcome (PRO) has been prospectively assessed at regular follow-ups (median 48 months) with the CTCAE v.3 and EORTC-C30/CX24, respectively. Patients with more than 25% missing entries were removed from the analysis.

Factor analysis was used to determine clinical syndromes (or clusters), which are groups of co-occurring symptoms. Clusters of symptoms were identified on both EORTC and CTCAE data with symptoms and follow-ups as observations.

The analysis included 509 and 1182 patients for EORTC and CTCAE, respectively. Despite the differences in CTCAE and EORTC reporting, similar factors are identified by the two assessment methods. Three main organ-related factors are recognized for urinary (frequency, incontinence and cystitis), gastro-intestinal (diarrhea, abdominal cramps and flatulence) and vaginal (bleeding and stenosis) morbidity.

Furthermore, a factor where fatigue, pain, insomnia, neuropathy and hot flashes have high importance is found and can be interpreted as a factor of general symptoms.

This analysis on both PRO and physician-assessed morbidity found syndromes associated with general and organ-related symptoms after treatment. Organ-related factors for urinary, gastro-intestinal and vaginal morbidity and a factor including general symptoms were identified. These results point towards a multifactorial nature of these radiotherapy induced symptoms and shows that they often occur together.

30. 10:10-10:20: Simon Buus, Aarhus, Denmark

Clinical outcome of MRI based high-dose-rate brachytherapy combined with EBRT for prostate cancer

S. Buus 1, HAS Hansen 1, S. Rylander 2 , S. Hokland 1, K. Tanderup 1, L. Bentzen 3

1. Dept, of Oncology, Aarhus University Hospital, Denmark 2. Dept of Oncology, Aalborg University Hospital, Denmark, 3. Department of Oncology Vejle Hospital, Denmark

Introduction
The purpose of this study was to evaluate the clinical outcome of combined EBRT and MRI based high-dose-rate brachytherapy (HDR BT) boost in a single institution prostate cancer patient cohort.

Materials/methods
The study included 113 consecutive prostate cancer patients; 11 D´Amico intermediate-risk (IR), 99 high-risk (HR), and three lymph node positive (N1) patients. EBRT was given as 46 Gy in 23 fractions to the pelvis followed by two separate 8.5 Gy boosts of HDR BT to the prostate gland. Patients were evaluated at baseline, after EBRT and at 6 weeks, 3, 6, 12, 24, 36, 60 and 96 months after HDR BT. Evaluation included clinical examination, blood samples, CTCAE v.4.0 toxicity assessment, EORTC QLQ C30, and patient-reported- outcomes consisting of items from the RT-ARD score, DAN-PSS, and EPIC-26 questionnaires.

Results
The included patients had a PSA of median 16 ng/ml (range 4 -108). The ISUP grade distribution in the cohort was; 3% ISUP grade 1, 35% grade 2, 20% grade 3, 27% grade 4, and 15% grade 5. The follow-up period was median 5 years. 5-year RFS was estimated by Kaplan Meier method to 95%. Six patients experienced a recurrence of prostate cancer; of which one was a local recurrence, one was a nodal recurrence, and four were distant recurrences. There were six recorded deaths during the follow-up period, none of which were related to prostate cancer. Grade 2 or greater CTCAE GI toxicity was 4%, 10% and 11% at baseline, 12 months and 60 months, respectively. Similarly, CTCAE urinary toxicity grade 2 or higher was reported at 1%, 18% and 13% at baseline, 12 months and 60 months, respectively. (Figure 2). Finally, the mean global health score (GHS) was 82, 78 and 77 at baseline, 12 months and 60 months after HDR BT, respectively. No significant decrease in GHS was observed from baseline to 12 months (p=0.50) or from baseline to 60 months (p=0.47).

Conclusions
Combined EBRT and MRI based HDR BT provides excellent clinical outcomes.

31. 10:20-10:30: Sofia Spampinato, Aarhus, Denmark

Patient-reported persistent symptoms after radiotherapy and association with quality of life for prostate cancer survivors

Spampinato S1, Waskiewicz JM2, Avuzzi B3, Garibaldi E4, Faiella A5, Villa E6, Magli A7, Cante D8, Girelli G9, Gatti M10, Noris Chiorda B3, Rago L11, Ferrari P2, Piva C8, Pavarini M12, Rancati T13, Valdagni R3, Vavassori V6, Munoz F4, Sanguineti G5, Di Muzio N14, Kirchheiner K15, Fiorino C12, Cozzarini C16

1)DCPT, Aarhus University Hospital, Aarhus, Denmark 2)Radiotherapy, Azienda Sanitaria dell'Alto Adige, Bolzano, Italy 3) Radiotherapy,Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy 4) Radiotherapy, Ospedale Regionale Parini-AUSL Valle d'Aosta, Aosta, Italy 5)Radiotherapy, Istituto Nazionale dei Tumori "Regina Elena", Rome, Italy 6)Radiotherapy, Cliniche Gavazzeni-Humanitas, Radiotherapy, Bergamo, Italy 7)Radiotherapy, Azienda Ospedaliero Universitaria S. Maria della Misericordia, Udine, Italy 8) Radiotherapy, ASL TO4 Ospedale di Ivrea, Ivrea, Italy 9) Radiotherapy, Ospedale degli Infermi, Biella, Italy 10)Radiotherapy, Istituto di Candiolo - Fondazione del Piemonte per l'Oncologia IRCCS, Candiolo, Italy 11)Radiotherapy, IRCCS CROB, Rionero in Vulture, Italy 12) Medical Physics, IRCCS San Raffaele Scientific Institute, Milan, Italy 13)Data Science, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy 14)San Raffaele Scientific Institute, Milan; Università Vita Salute San Raffaele, Milan, Italy 15) Dpt of Radiation Oncology- Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria 16)Radiotherapy, IRCCS San Raffaele Scientific Institute, Milan, Italy

Purpose

To evaluate persistence of symptoms after radiotherapy (RT) for prostate cancer (PCa) and association with quality of life (QoL).

Material and methods

Prospective patient-reported outcome (PRO) from a multi-institutional study on PCa treated with radical RT (2010-2014) was analyzed. Data was collected at baseline (BL) and regular follow-ups (FUPs) up to 5 years. Patients with BL and ≥3 late FUPs (≥6 months) were analyzed. PRO was scored with the IPSS and ICIQ-SF (urinary, GU), LENT-SOMA (gastrointestinal, GI) and EORTC-C30 (pain, fatigue and QoL) questionnaires. Symptoms were defined "persistent" if the median score over late FUPs was >2 (for GU) or ≥2 (for GI, pain and fatigue), and worse than BL. QoL was linearly transformed in a continuous scale (0-100). Linear mixed models were used to identify significant differences (p-value adjusted for multiple testing <0.05) between groups with and without persistent symptoms including also age, smoking status and diabetes as confounders. Mean QoL differences between groups were evaluated longitudinally over late FUPs.

Results

The analysis included 293 patients. Persistent GU symptoms ranged from 2% (straining) to 12% (weak stream and nocturia). GI symptoms ranged from 7% (rectal pain and fecal incontinence) to 30% (fecal urgency). Proportions of pain and fatigue were 6% and 18%, respectively. Urinary incontinence, frequency, urgency, weak stream and nocturia showed significant differences in QoL (12 to 15 points). Among GI symptoms, rectal pain and fecal incontinence showed significant differences (14 and 15 points). Persistent fatigue was associated with the largest difference (16 points).

Conclusion

The analysis showed that symptoms after RT for PCa occur with different persistence and their association with QoL varies in magnitude. A number of persistent GU and GI symptoms showed differences in QoL in a comparable range. Persistent fatigue was also prevalent and significantly associated with worse QoL

32. 10:30-10:40: Trine Tramm, Aarhus, Denmark

T-lymphocytes and hypoxia predicts survival after brachytherapy in locally advanced cervical cancer

Tramm T (1), Alsner J (2), Nielsen PS (1), Georgsen JB (1), Overgaard J (2), Lindegaard JC (3)

1) Dept. of Pathology, Aarhus University Hospital, Aarhus , Denmark; 2) Dept. of experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark; 3) Dept of. Oncology, Aarhus University Hospital, Aarhus, Denmark

Introduction
Presence of CD8 positive (CD8+) intratumoral T-lymphocytes has been found to predict benefit of radiotherapy (RT) in breast cancer with improved distant tumor control translating into superior survival. Following employment of chemoradiation (CRT) and image guided adaptive brachytherapy (BT), loco-regional control in locally advanced cervical cancer (LACC) has improved considerably and systemic relapse is now the dominant problem. We aimed to investigate, if presence of tumorinfiltrating T-lymphocytes is a prognostic factor in LACC.

Materials and Methods
In tumor-biopsies from 189 consecutive patients with squamous cell LACC treated 2005-2016, subsets of T-lymphocytes were visualized by immunohistochemistry (CD4, CD8, FOXP3). Hypoxic status was reported previously. All patients received pelvic external beam RT of 45-50 Gy/25-30 fx and were treated with BT with mean CTVHR volume of 35 cm3 and D90 of 92 GyEQD2. Endpoints were extra-pelvic control (EPC), disease free survival (DFS), and overall survival (OS). Statistical analysis included Aalen-Johansen estimator, Cox regression and Kaplan-Meier estimator.

Results
Median observation times were 5.1 years (EPC) and 7.1 years (OS). EPC was obtained in 140/189 (74%). High levels of CD8+, CD4+, and FOXP3+ cells, and a ‘less’ hypoxic profile was significantly associated with improved OS. Similar trends were observed for EPC and DFS but only association between hypoxia and DFS was significant. On continuous scales, CD4 and CD8 were correlated. ‘Less’ hypoxia was significantly associated with high levels of CD4, CD8 (p values < 0.0001) but not with FOXP3.

Conclusions
Tumor-infiltrating T-lymphocytes and hypoxic status are prognostic factors for OS for squamous cell LACC after BT. High infiltration of CD4+ and CD8+ T-cells correlated with a ‘less’ hypoxic profile. Evaluation of immune cell infiltration and hypoxia may assist in selecting high risk patients for adjuvant systemic treatment following CRT and BT.

Session 7: Clinical radiotherapy – Gastro-intestinal and lung cancer

33. 12:10-12:20: Karen Wind, Aarhus, Denmark

Pre-treatment immune-inflammation-related biomarkers and relation to disease-free survival in anal cancer

Wind KL (1), Kronborg C (2), Jakobsen AV (1), Spindler KGS (1)
1) Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark 2) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Introduction
Cancer development is highly correlated to the immune system, and inflammation is one of the hallmarks of cancer. Hence measurement of neutrophile-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR) and systemic inflammatory index (SII) in pre-treatment blood samples have been proposed as easy-to-measure biomarkers related to the prognosis of different cancer types, including anal cancer (AC). This study aimed to investigate if these biomarkers were prognostic for disease-free survival (DFS) in AC.

Material and methods
From pre-treatment blood samples of 339 patients with AC treated with curative (chemo)radiotherapy, the NLR, PLR and SII (platelet x neutrophil/lymphocyte) were calculated. The most optimal cut-off values for NLR, PLR and SII were estimated by computing receiver operating characteristic (ROC) curves and the area under the curves (AUC) using the method by Liu. The primary endpoint was DFS, estimated by the Kaplan-Meier method.

Results
AUC for NLR was 0.63, and the best cut-off value was 2.98 (sensitivity 62 %, specificity 73 %). The AUC for PLR was 0.57 with a cut-off value of 145.31 (sensitivity 56 %, specificity 60 %), and the AUC for SII was 0.62 with a cut-off value of 679.86 (sensitivity 66 %, specificity 55 %). DFS was significantly worse in patients with values above the calculated cut-off for all three biomarkers, with a hazard ratio (HR) of 2.05 (95%CI 1.43;2.94), $p < 0.001$ for NLR, 1.76 (95% CI 1.23;2.53), $p = 0.002$ for PLR, and 1.97 (95%CI 1.36;2.86), $p < 0.001$ for SII. In multivariate cox regression analysis, NLR above cut-off showed a non-significant trend towards a poorer DFS (HR = 1.56 (95%CI 0.96;2.55), $p = 0.08$).

Conclusions
All three immune-inflammation-related markers were prognostic for DFS in AC. These easy-to-measure biomarkers could be relevant, potentially in combination with other emerging biomarkers, and international collaboration would be highly relevant in future investigations.

34. 12:20-12:30: Lise Bech Jellesmark Thorsen, Aarhus, Denmark

National consensus based automatic delineation of thoracic organs at risk

Thorsen LBJ 1, Mortensen HR 2, Hoffmann L 1, Aagaard T 1, Knap MM 1, Nyeng TB 1, Szejniuk WM 3, Persson G 4, Pøhl M 5, Nordsmark M 1, Weber B 2, Kristiansen C 6, Land LH 7, Borissova S 4, Larsen ID 3, Korreman SS 1,2, Kyndt M 8, Møller DS 1

1) Dept. of Oncology, Aarhus University Hospital, Aarhus, DK 2) Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, DK 3) Dept. of Oncology, Aalborg University Hospital, Aalborg, DK 4) Dept. of Oncology, Herlev-Gentofte Hospital, Copenhagen, DK 5) Department of Oncology, Rigshospitalet, Copenhagen, DK 6) Dept. of Oncology, Vejle Hospital, Vejle, DK 7) Dept. of Oncology, Odense University Hospital, Odense, DK 8) MIM Software Inc., Cleveland OH

Introduction
Manual delineation of organs at risk (OAR) in radiation therapy (RT) planning is time-consuming and subject to variation. We aimed to develop an algorithm for automated delineation of thoracic OAR based on national consensus.

Materials and methods
Ten oncologists and two radiographers from different RT departments reached national consensus on delineation of nine thoracic OAR (trachea, bronchi, heart, aorta, left/right lung, esophagus, spinal cord and canal). Ground truth OAR sets were manually delineated on contrast enhanced 4D-CT scans from 10 lung cancer patients: five independent sets per patient, resulting in 50 sets of OAR. Subsequently, a training set of thoracic OAR was delineated on 100 patients with lung cancer. A U-Net AI algorithm (AI) was trained in collaboration with MIM software. The AI auto-delineated OAR on the initial 10 CT scans with ground truth delineations. Dice Similarity coefficient (DSC) and mean Hausdorff distance (mHD) were calculated to compare manual to AI delineations. For both DSC and mHD we report median[range] values for all observers and all 10 patients. For manual delineation, all observers are intercompared, while the algorithm is compared to each observer.

Results
Median DSC varied between 0.77/0.78 (spinal cord) and 0.99/0.97 (lungs) for manual/AI delineations. For manual delineations, median DSC were 0.83[0.71-0.91] for esophagus, 0.85[0.69-0.94] for bronchi and 0.95[0.91-0.97] for heart, while similar DSC was seen for AI with 0.86[0.76-0.89], 0.87[0.72-0.93] and 0.95[0.91-0.96], respectively. mHD were generally small with median mHD for manual/AI delineations of 0.9mm[0.6-1.7]/0.8mm[0.6-1.3] for esophagus, 0.9[0.4-2.0]/0.8[0.6-4.9] for bronchi and 1.4mm[0.7-3.1]/1.4mm[0.9-2.8] for heart.

Conclusions
We produced an algorithm fit for OAR delineation from national consensus. This paves the way for development of national standards for and implementation of consistent and fast OAR delineation in clinical practice.

35. 12:30-12:40: Nina Levin, Trondheim, Norway

Dose response relationship of acute esophagitis for patients with limited stage small cell lung cancer treated with chemoradiotherapy in a randomized phase II trial

Levin N.(1,2), Killingberg K. (1,2), Grønberg B. H. (1,2), Halvorsen T. O. (1,2), Redalen K. R. (3), Danielsen S. (2,3)

(1) Dept. of Clinical and Molecular Medicine, NTNU, Trondheim, Norway (2) Cancer Clinic, St. Olavs Hospital, Trondheim, Norway (3) Dept. of Physics, NTNU, Trondheim, Norway

Introduction
Dose escalation with a twice daily thoracic radiotherapy (TRT) schedule for patients with limited stage small cell lung cancer (LS SCLC) has raised concerns about severe radiation induced acute esophagitis, as the esophagus is often positioned within the planning target volume (PTV) and thus will receive high doses. In a randomized phase II trial, we showed a significant increase in survival of high-dose twice daily TRT of 60 Gy in 40 fractions compared with the standard schedule of 45 Gy in 30 fractions. Interestingly, the higher dose did not cause more toxicity, and more data is needed to predict severe esophagitis. Collected treatment plans from patients in this trial are used to investigate the dose-response relationship for acute esophagitis.

Materials and methods
170 patients from 22 Scandinavian hospitals received platinum/etoposide chemotherapy and were randomized between 2014 and 2018 to twice daily TRT of 60 or 45 Gy. Radiotherapy treatment plans were collected for all the 166 patients who started radiotherapy and toxicity was scored using the CTCAE v.4. Doses to the esophagus were recalculated to 2-Gy equivalent doses (EQD2) and equivalent uniform dose (EUD) was then calculated with parameters that reflected the mean and maximum doses. These EQD2-corrected EUDs were then used as an independent variable in ordinal logistic regression models to predict outcome probabilities.

Results
A difference in the dose volume histograms for patients scored with grade 1, 2 and 3 esophagitis were seen for a large range of doses. The ordinal logistic regression model showed a correlation between mean dose and toxicity. More data on the correlation will be presented at the meeting.

Conclusions
Our results implies that mean dose to the esophagus seems to be the most important predictor for radiation induced acute esophagitis, and we have implemented a dose-response model also enabling clinical parameters to be considered.

Session 8: Preparing for the future

36. 14:10-14:20: Katia Parodi, Munich, Germany

First in-silico demonstration of a novel platform for small animal image-guided, intensity modulated proton therapy

Parodi K[1,2], Belka C[2,3], Bortfeldt J[1], Dash PK[1], Dedes G[1], Englbrecht FS[1§], Evangelista F[1], Haghani R[1,§], Holthoff G[1], Hu G[1], Huang Z[1], Kalunga R[1,§], Kurichiyanil N[1,§], Gebhard J[1,§], Gerlach S[1], Gerlei M[1], Gianoli C[1], Lascaud J[1], Lämmer P[1,§], Lauber K[2,3], Lovatti G[1], Meyer S[1,§], Nitta M[1], Noto A[1], Palaniappan P[1], Palmans H[4], Pinto M[1], Poulsen P[5], Rädler M[1], Riboldi M[1], Rösch T[1,§], Safari M[1,§], Schnürle K[1,§], Schreiber J[1], Sharifi B[1], Sitarz MK[5], Steinbrecht C[1], Thirolf PG[1], Wieser HP[1,§], Würl M[1,§]*

[1] *Department of Medical Physics, Ludwig-Maximilians-Universität München (LMU Munich), Munich, Germany*
[2] *German Cancer Consortium (DKTK), Partner Site Munich, Munich, Germany* [3] *Department of Radiation Oncology, University Hospital, LMU Munich, Germany* [4] *MedAustron Ion Therapy Center, Wiener Neustadt, Austria and National Physical Laboratory, Teddington, The United Kingdom of Great Britain and Northern Ireland.* [5] *Danish Centre for Particle Therapy (DCPT), Denmark*
** Corresponding author, email: Katia.Parodi@lmu.de*
[§] *Work done during past affiliation with LMU Munich*

Introduction
In the project SIRMIO we developed a modular and portable system for precision image-guided irradiation of small animals at clinical proton facilities [1].

Materials and methods
SIRMIO features a dedicated beamline to degrade and focus a low energy clinical proton beam and deliver it to a target on motorized stages. Different imaging solutions are implemented for alignment, planning and in-vivo range verification. For treatment planning we rely on a validated RayStation research system.

Results & conclusion
In the just concluded experiments at the Danish Centre for Particle Therapy we showed the ability to degrade and focus the incoming lowest energy (70 MeV) proton beam and perform intensity modulated delivery to homogenous and murine-like [2] phantoms. Image guidance based on proton radiography and proton tomography, also in comparison to prior X-ray CBCT from a SARRP system, was successfully deployed, along with on-line monitoring with a dedicated in-beam positron-emission-tomography scanner. The entire workflow of image-guided planning and delivery controlled by a dedicated beam monitor was demonstrated. Future work will aim at automation/acceleration to pave the way for physics and biology experiments with the developed system.

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37. 14:20-14:30: Morten Busk, Aarhus, Denmark

Development of preclinical orthotopic lung tumor mouse models generated by CRISPR/CAS9 in vivo gene knockout

BUSK M1, 2, OVERGAARD J1, BERTELSEN MF3, THOMSEN MK4, VENDELBO MH4,5

1Department of Experimental Clinical Oncology, Aarhus University Hospital (AUH), Denmark; 2Danish Centre for Particle Therapy, AUH; 3Department of Clinical Medicine, Aarhus University, Denmark (AU); 4Department of Biomedicine, AU; 5Department of Nuclear Medicine and PET Centre, AUH

Introduction
Dual-tracer PET using 11C-acetate and FDG may improve detection rate and refine assessment of aggressiveness in lung cancers. In addition, hypoxia-selective tracers, like FAZA, may guide treatment decision-making. Hypoxia and elevated glucose metabolism are linked to poor outcome, but are coupled through aerobic glycolysis. The spatial relationship between FDG and hypoxia and 11C-acetate PET remains unresolved in lung cancer patients, possibly due to the technical complexity of such trials. Rodent models that faithfully recapitulate carcinogenesis, metabolism and microenvironment may improve our understanding on the coupling of various PET tracers, and serve as an experimental tool for treatment development.

Methods
Orthotopic lung tumors were induced in CRISPR/Cas9 knock-in mice by inhalation of adeno-associated virus vectors to generate loss of function mutations in p53, KRAS and then either LKB1 or PTEN. Tumor growth was monitored by FDG-PET/MRI. When ready for experiments, mice were administered the hypoxia marker pimonidazole and then either FDG + 14C-acetate or FAZA + 14C-2DG and subsequently sacrificed. Lung/tumor tissue was cryosectioned and analyzed for 18F and 14C using dual-tracer autoradiography, and pimonidazole and selected proteins using immunohistological methods. Reference tissue sections for normalization of FDG/14C-2DG or 14C-acetate (brain) and FAZA (muscle) were included.

Results/discussion
Tumors with a size suitable for experiments typically developed in 3-6 months and could be identified reliably using FDG-PET/MRI. Typically, mice presented with several lesions of different sizes. Autoradiographic analysis revealed inter- and intratumoral differences in FDG and 14C-acetate retention patterns, with a more peripheral uptake of 14C-acetate in large lesions, and the presence of small, non-avid FDG, lesions with high 14C-acetate uptake. FAZA and 14C-2DG distributed differently. Updated results will be presented at the meeting.

38. 14:30-14:40: Signe Winther Hasler, Odense, Denmark

A multicenter study of geometric accuracy of clinical MR sequences used for radiotherapy in Denmark

Hasler SW 1,2, Kallehauge JF 3,4, Hansen RH 5, Nilsson CM 6, Arp DT 7,8, Nissen HD 9, Edmund JM 10,11, Bernchou U 1,2, Mahmood F 1,2

1 Lab. of Rad. Phys., Dept. of Oncol., OUH, Odense, DK, 2 Dept. of Clin. Res., SDU, Odense, DK, 3 DCPT, AUH, Aarhus, DK, 4 Dept. of Clin. Med., AU, Aarhus, DK, 5 Sec. for Rad. Therapy, Dept. of Oncol., RH, Copenhagen, DK, 6 Rad. Therapy Dept., SUH, Næstved, DK, 7 Dept. of Med. Phys., Aalborg UH, Aalborg, DK, 8 Dept. of Clin. Med., AAU, Aalborg, DK, 9 Dept. of Med. Phys., VH, Vejle, DK, 10 Radiotherapy Res. Unit, Dept. of Oncol., HGH, Herlev, DK, 11 Niels Bohr Inst., KU, Copenhagen, DK

Introduction
As RT becomes dependent on MR images used directly for treatment planning, geometric distortion in MRI has implication for accurate dose delivery. Lack of harmonization across centers results in a vast catalog of MR sequences used in RT, and multicenter studies comparing quality are sparse. This study investigated geometric distortion of clinical MR sequences, and found relations to specific sequence settings, for seven RT centers in Denmark.

Methods
In total 11 MRI/MRL systems were investigated. A benchmark sequence tested the inter-center distortion variation, and clinical MR sequences were acquired with a large field-of-view phantom. In-house distortion analysis was performed reporting 95th percentile max distortion. Dependence of distortion on receiver bandwidth, echo time, 2D/3D acquisition, and contrast (T1w/T2w) was investigated.

Results
In total, 78 clinical sequences were analyzed for four anatomical sites: brain, head/neck (HN), abdomen and pelvis. We found that 2D/3D acquisitions (median distortion = 1.2/0.9 mm) influenced the distortion level. Minor distortion dependence on echo time and bandwidth was seen, but investigations with larger susceptibility effects are warranted. No influence from contrast was found. Brain and abdomen sequences showed lower distortion than HN and pelvis. The number of 2D/3D sequences could account for variation between anatomical sites, as fewer brain and abdomen sequences were 2D sequences. A large variation for similar sequences was seen, e.g. pelvic T2w sequences had a distortion range of 0.5-2.6 mm (σ = 0.7 mm) which exceeds the baseline distortion variation between centers (σ = 0.2 mm).

Conclusion
We recommend using 3D MRI sequences for RT planning as this has a minimizing effect on distortion levels. Across centers, large variation in geometric accuracy was seen for similar sequences. Harmonization across sites to ensure overall low distortion level would increase the accuracy of dose delivery on a national basis.

39. 14:40-14:50: Simon Vindbæk, Aarhus, Denmark

Motion-induced proton dose change measured by 3D deformable dosimeters in an anthropomorphic phantom

Vindbæk SH (1,2), Ehrbar S (3), Worm E (4), Muren LP (1,2), Tanadini-Lang S (3), Petersen JBB (2,4), Balling P (5,6), Poulsen PR (1,2)

(1) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark (2) Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (3) Department of Radiation Oncology, University Hospital Zürich and University of Zürich, Zürich, Switzerland (4) Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark (5) Department of Physics and Astronomy, Aarhus University, Aarhus, Denmark (6) Interdisciplinary Nanoscience Center, Aarhus University, Aarhus, Denmark

Introduction
Intra-fractional motion in proton therapy typically requires motion mitigation (e.g. respiratory gating), especially in the thoracic and abdominal regions. Planar and 2.5D dose measurements have limitations in terms of spatial resolution when investigating the effects of motion. In this study, a deformable abdominal phantom is combined with an embedded 3D liver dosimeter to measure the effects of intra-fractional motion and gating on clinically relevant pencil beam scanning (PBS) proton treatments in the liver.

Material and methods
A deformable abdominal phantom with a liver cavity was produced to hold an anthropomorphic 3D liver dosimeter. A 3-field PBS proton plan was made for a clinically realistic clinical target volume (CTV) on the exhale phase of a 4DCT scan using multi-field robust optimization (±5 mm shift along each axis including ±3.5 % range uncertainty). Two batches, each with two radiochromic silicone-based 3D liver dosimeters, were made. In both batches, one dosimeter was irradiated in a stationary position in the abdominal phantom. The second dosimeter was irradiated while the abdominal phantom moved sinusoidally with a 10 mm peak-to-peak amplitude without gating (Batch 1) and with optically guided (Batch 2) respiratory gating using a 50% duty cycle around the exhale phase (Varian RPM system). The dosimeters were read out using an optical CT scanner which provided a 3D distribution of the radiation-induced change in optical attenuation coefficients ($\Delta\alpha$).

Results
The gamma pass rates for the motion experiments, using the stationary experiments as reference, were 68% (3%/3 mm) and 44% (2%/2 mm) without gating and 96% (3%/3 mm) and 85% (2%/2 mm) with gating. Furthermore, $\Delta\alpha$-volume histograms showed that gating improved the CTV coverage.

Conclusion
An anthropomorphic 3D dosimeter was for the first time embedded in a deformable abdominal phantom, and successfully measured the motion-induced dose perturbation of liver proton PBS treatments.

ABSTRACTS - POSTER DISCUSSION GROUPS

Poster discussion group 1: Preclinical studies

Chairs: Gabriel Adrian, Per Poulsen

40. Anders Tobias Frederiksen, Aarhus, Denmark

Evaluating in vitro setup designed for horizontal beamline irradiation at the Danish Centre for Particle Therapy

A.T. Frederiksen 1,3,4, M.B. Jensen 1,2, P.R. Poulsen 1, N. Bassler 1, B.S. Sørensen 1,3, M. Sitarz 1
1 Danish Centre for Particle Therapy. 2 Department for Medical Physics, Aarhus University. 3 Department of Experimental Clinical Oncology Aarhus University Hospital. 4 Aarhus University.
AndersTFrederiksen@gmail.com

Introduction
Radiobiological irradiation setups are challenged with precise sample positioning along depth dose profile, scattering conditions, and potential practical difficulties that must be addressed in individual designs. The aim of this study was to evaluate a new dosimetrically advantageous setup for in vitro cell line irradiation. An important feature of the setup is its utility with different irradiation modalities. We here present the setup as well as obtained Relative biological effectiveness (RBE)values from V79 cell irradiations using this setup.

Materials and methods
The setup consists of a water phantom constructed for in vitro irradiations in a horizontal beam line using V79 Chinese hamster lung fibroblasts. The cells were irradiated and clonogenic cell survival was determined. Cells were placed at 2.0 cm depth along the beam axis for MV photons. For protons, the depth can be varied to examine the increasing Linear Energy Transfer (LET)along the Spread-out brag peak (SOBP). Cell survival-curves were produced using biological triplicates for 50 keV photons, 280 keV photons, 6 MeV photons, and 85-111 MeV protons.
For all irradiation modalities dosimetric uncertainties were kept at +/- 2 %, except for 50 keV and 280 keV. Survival curves with fitting uncertainties were used to calculate RBE-values with 6 MeV LINAC photons as reference modality.

Results
RBE was found to be 1.1 [0.90; 1.2] for protons at the proximal SOBP position, 0.95 [0.77; 1.1] at the middle SOBP position and 0.96 [0.78; 1.1] at the semi-distal SOBP position. RBE for 280 keV photons was 0.99 [0.88; 1.1] and RBE for 50 keV photons was 1.2 [1.1; 1.3].

Conclusion
The laboratory workflow showed to be robust within variations expected from biological systems and the workflow was suitable for future in vitro studies. However, the overall uncertainties (cell-handling, biological variation, fitting errors etc.)might render subtle LET differences difficult to detect.

41. Charlemagne A. Folefac, Aarhus, Denmark

Targeting Solid Tumors with the combination of Stereotactic Radiation combine with hyperthermia

Charlemagne A Folefac 1, Priyanshu M. Sinha1, Mateusz K. Sitarz 2, Niels Bassler 2, Michael R. Horsman 1.

1. Experimental Clinical Oncology-Dept. Oncology and 2. Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Introduction
Higher Stereotactic (SBRT) dose irradiation also damages tumors blood vessels, contributing to hypoxia, increase extracellular acidity, and low glucose which exists within most solid tumors. These cell population are sensitive to heat Hence, therapeutic benefits can be obtained from combining SBRT with heat.

Objectives
To determine fractionated doses of SBRT and optimum temperature to treat solid tumors with less toxicity.

Materials and methods
C3H mammary carcinoma tumor volume of around 200 mm3 grown in the leg of CDF1 mice are treated over a week with three fractions each of 5, 10, 15, and 20 Gay irradiation using Photon and proton for control animals group. Experimental animals received same irradiation fractions plus heat treatment at 41.50C for 1-hour at 30 minutes after last irradiation fraction.

Endpoints include tumor growth delayed (time to grow to 3x starting treatment volume; TGT3). Repeating the same treatments above on a non-tumor bearing leg of animals, acute toxicity in terms of moist desquamations(MD) are observed with scores from 0, 0.5 1, 1.5, 2, 2.5, 3, 3.5 based it severity. RESULTS: Early results of P Values calculated from mean TGT3 of photon treatment are 0.004, 0.002. 0.07 for 5, 10 and 15Gy irradiation animals groups respectively. P Values for protons treatment groups are 0.0493, 0.007, 0.04 for 5,10,15 Gy irradiation animals groups respectively. Preliminary acute skin score results of irradiation dose in 50% of animals with the maxi-mum cut-off score of 2.5 showeed MD of animals' legs (MD50 dose) to be 47Gy and 45Gy for photon and photon plus heat groups, respectively, and with thermal enhancement ratio (ER) of 1.04. For Proton irradiation in animals with or without heat groups, the MD50 dose value is 47Gy and 44Gy respectively with ER of 1.07.

Conclusion
Combining hyperthermia with SBRT shows optimum beneficial effect. Ongoing normal tissue studies are to determine the optimum treatment with minimal toxicity.

42. Ingunn Hanson, Oslo, Norway

TGF-β3 injections increases severity of radiation induced oral mucositis and salivary gland fibrosis in a mouse model

Hanson I [1], Juvkam I S [2], Zlygosteva O [1], Edin N F J [1] "[1]Department of Physics, University of Oslo, Oslo, Norway; [2] Institute of Oral Biology, University of Oslo, Oslo, Norway

Side effects from radiotherapy (RT) of head and neck cancers may include acute oral mucositis and chronic salivary gland fibrosis. The transforming growth factor (TGF)-β family of cytokines are key players in the fibrotic response. While TGF-β1 is known to be pro-fibrotic, TGF-β3 has mainly been considered anti-fibrotic. In addition, TGF-β3 has been shown to alleviate chemotherapy-induced oral mucositis in preclinical studies.

30 female C57BL/6 mice were randomly assigned into three treatment groups. The RT group received local head and neck irradiation in 10 fractions à 6.6 Gy of 100 kV x-rays over 5 days. The RT + TGF-β3 group received identical irradiation, in addition to 5 TGF-β3 injections à 0.25 µg, at 24-hour intervals with the first injection 24 hours before the first RT fraction. The control group was sham-irradiated according to the same RT schedule as the other two groups. In the follow-up period, mice were weighed frequently, subjected to blinded anesthetized oral examinations every three days, and saliva was sampled at five time points. After termination of the experiment, oral tissues were collected for histological analysis.

Mice in the RT + TGF-β3 group displayed increased severity of oral mucositis, increased weight loss, and increased mortality compared to mice in the RT group. The surviving mice in the RT + TGF-β3 group demonstrated increased collagen deposition in the submandibular and sublingual gland compared to controls, while mice in the RT group showed increased collagen deposition in the submandibular gland only.

We conclude that when repeatedly administered in concurrence with fractionated RT at the current dose of 0.25 µg per fraction per mouse, TGF-β3 increased acute side effects of oral irradiation in a subset of animals to the point of increased mortality, and increased salivary gland fibrosis in surviving animals.

43. Line Kristensen, Aarhus, Denmark

Skin toxicity of FLASH proton radiation within the Spread-out Bragg Peak

Kristensen L (1,2), Rohrer S (1), Kanouta E (1), Ankjærgaard C (3), Andersen CE (3), Johansen JG (1), Poulsen P (1,2), Sørensen BS (1,2)

(1) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, (2) Department of Experimental Clinical Oncology, Aarhus University Hospital, (3) DTU Health Tech, Roskilde, Denmark

Introduction
The promising new radiation modality of FLASH radiotherapy has gained the interest of many within the field for both electron and proton radiation. Most proton FLASH experiments so far have been using the entrance of the proton beam and not the most beneficial property of proton radiation; namely the Spread-out Bragg peak (SOBP). We present the first study of skin reaction to proton FLASH radiation within the SOBP. The aim was to investigate whether the use of FLASH dose rates reduced radiation-induced acute skin toxicity compared to conventional dose rates when the skin was placed within an SOBP.

Materials and methods
Healthy female CDF-1 mice were restrained in a jig with the right hindleg placed within a water bath, and plates of solid water placed in front of the water bath to induce the desired depth within the beam. The SOBP was obtained from a single beam energy using a Ridge filter placed in front of the solid water plates. The Ridge was designed to scatter the incoming beam in order to create a broad energy distribution, thereby creating a SOBP. Mice were irradiated with a single dose ranging between 20-55 Gy for conventional dose rates of 0.4 Gy/s or between 35-70 Gy for FLASH dose rates of 60 Gy/s. The dose groups were spaced with increments of 5 Gy for full range of the dose-response curves for each acute score. Dosimetry included alanine pellets, scintillators, and pre-experimental measures of the depth-dose curve with a Marcus chamber and calibrated EBT-XD Radiochromic film.

Results
Final acute scores have yet to be collected for all treatment groups, however, a preliminary evaluation of early-stage acute skin toxicity shows indications of a reduced radiation-induced toxicity in mice radiated with FLASH compared to conventional dose rate.

Conclusion
We here illustrate the first use of FLASH radiation within the SOBP performed on a skin-toxicity in vivo model.

44. Olga Zlygosteva, Oslo, Norway

Normal tissue response following proton and photon fractionated irradiation of the head and neck in a murine model

Zlygosteva O (1), Juvkam IS (2)*, Sitarz M (3), Sørensen BS (3,4), Galtung HK (2), Søland TM (2,5), Edin NJ (1)†, Malinen E (1,6)† (*Joint first authors, †Joint senior authors)*

(1)Department of Physics, University of Oslo, Oslo, Norway (2)Institute of Oral Biology, University of Oslo, Oslo, Norway (3)Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark (4)Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark (5)Department of Pathology, Oslo University Hospital, Oslo, Norway (6)Department of Medical Physics, Oslo University Hospital, Oslo, Norway

The aim of this study was to investigate differences in acute and late normal tissue responses following proton or photon irradiation of the head and neck (H&N) in a murine model.

Female C57BL/6J mice were irradiated with photons or protons, with Bragg peak stopping either in the middle (midplane plan) or outside the mouse (transmission plan). The radiation field covered the oral cavity and the major salivary glands. Delivered doses ranged from 40 to 66 Gy given in up to 10 fractions. Acute tissue responses in the oral cavity and surrounding tissues were investigated by clinical examination. To assess the influence on salivary gland function, saliva was sampled before and after irradiation. To study late responses in the major salivary glands, histological analysis was performed on tissues collected at day 105 after onset of irradiation.

Oral mucositis appeared earlier, had a higher severity score and was found in a higher percentage of mice after protons compared to photons. Skin dermatitis, on the other hand, had a similar appearance after protons and photons. The estimated RBE values with 95% confidence intervals for acute damage was 2.2 (1.3, 3.6) for midplane plan and 1.8 (1.1, 3.0) for transmission plan relative to photons. Saliva production was significantly reduced after completion of both proton and photon irradiation and remained reduced until day 105. However, a higher trend of saliva production recovery was seen after photons compared to protons by day 105. This was in line with a more extensive acinar atrophy observed in the major salivary glands after proton compared to photon irradiation.

We observed differences between proton- and photon-induced acute and late normal tissue responses in the H&N. Estimated RBE-values for protons were high, although large confidence intervals prevent firm conclusions. Still, our results indicate a need for further investigations of the biological effectiveness of protons in normal tissue.

45. Toralf Husevåg, Oslo, Norway

Predicting saliva production and fibrosis in mice post-irradiation using T2-weighted MRI-based radiomic features

Toralf Husevåg, Olga Zlygosteva, Inga S. Juvkam, Hilde Galtung, Tine M. Søland, Nina F. J. Edin, Eirik Malinen

Department of Physics and Institute of Oral Biology, University of Oslo, and Oslo University Hospital

Background
Radiotherapy of cancer in the head and neck region can induce late effects such as xerostomia and fibrosis in the salivary glands. Medical imaging biomarkers may predict such effects is therefore of clinical interest for pre-emptive mitigation. This work uses MRI-based radiomics on longitudinal data from irradiated mice to predict xerostomia and fibrosis.

Materials and methods
Female C57BL/6J mice were irradiated with a total of 10 fractions (7.5 Gy / fraction) or control. The radiation field covered the oral cavity and the major salivary glands. Stimulated saliva was collected after intraperitoneal pilocarpine injection, and fibrosis in the submandibular gland (SMG) was scored in mice post-termination by histologic evaluation. T2-w MR-images were acquired at baseline and after irradiation (days 5 - 105).

The SMG was segmented manually. 107 first-order, shape-based, and textural radiomic features were extracted from each VOI.
Control group, saliva production, or fibrosis scores was predicted and evaluated by leave-one-out cross-validation. Feature selection was done for each held-out observation by an iterative correlation method.

Results
Irradiated mice had lower saliva production at late time points (> 35 days) and higher percentage fibrosis covering the SMG ($p < .001$). Saliva production was negatively correlated to SMG fibrosis ($\rho=-.595$, $p = .002$). Predicting whether an animal belonged to the control group using a logistic model scored a ROC-AUC of 1.0 and a Brier score of 0.013. A linear regression model (LRM) predicted saliva production or fibrosis scoring with the coefficient of determination (R2) being 0.178 and 0.155 on unseen data, respectively. Among the top-performing models the first-order feature 90th_percetile, and shape- and textural features were frequently selected.

Conclusion
T2w-MR based radiomic features in the irradiated salivary gland seem to have some predictive ability on saliva production and fibrosis post-irradiation.

Poster discussion group 2: Biology, biomarkers and adaptation

Chairs: Jørgen Johansen, Katia Parodi

46. Ana Ureba, Solna, Sweden

Biologically-guided automated treatment planning and evaluation: potential for treatment adaptation in head and neck cancer

Ureba A, Toma-Dasu I, Lazzeroni M

Department of Physics, Stockholm University, Stockholm, Sweden; Department of Oncology and Pathology, Karolinska Institute, Stockholm, Sweden

Introduction
A biologically guided dose painting (BGDP) strategy and automated treatment planning (TP) pipeline are presented. Information extracted from hypoxia-PET and FDG-PET images is synergistically combined pre-optimization to drive a dose prescription strategy, and post-optimization to assess the radiobiological response. This workflow aims at identifying failure-prone sub-volumes to be monitored and targeted within an adaptive radiation therapy (ART) framework.

Material and Methods
An automated TP workflow assisted via scripting in RayStation was developed and tested on H&N cases of different complexities. FDG and FMISO PET/CT images were available. The automated pipeline consisted of the following steps:

1.Calculation of the prescribed dose distribution to be delivered as BGDP accounting for the radiosensitivity due to the oxygen (pO2) and the clonogenic cell number (CCN) distributions and aiming at 95% tumour control probability (TCP) in the clinical target volume.

2.Optimisation :
2.1 Pre-optimization: algebra combinations of the volumes of interest based on a template.
2.2 Optimization for obtaining a reference dose distribution for targets and OARs based on the prescribed dose calculated in (1); minimax optimisation that mimicked doses obtained in (2.1).
3.Treatment plan dosimetric and radiobiological evaluation.

Results
Treatment plans aiming at 95% TCP with an integrated boost were generated. The plans were evaluated post-optimisation in terms of target coverage and OAR constraints and in terms of radiobiological response by calculating the actual TCP. The failure-prone sub-volumes were identified based on 3D distributions of EQD2 and the number of surviving cells calculated considering underlying radiosensitivity and CCN derived from the FDG- and FMISO-PET images.

Conclusions
BGDP automated treatment planning and evaluation pipeline allows identifying volumes that may be prone to treatment failure and hence should be targeted within ART.

47. Demet Özcan, Aarhus, Denmark

Exploring the analytical validity of CD20 as a potential biomarker for benefit of post-operative radiotherapy in breast cancer patients

Özcan D[1], Nielsen PS[1], Alsner J[2], Tramm T[1]

[1] Dept. of Pathology, Aarhus University Hospital, [2] Dept. of Experimental Clinical Oncology, Aarhus University Hospital

Background
Subsets of intratumoral immune cells are being investigated as predictors of benefit from radiotherapy (RT). Yet, clinical utility of a biomarker depends on clinical as well as analytical validity. As part of a large study of the DBCG82bc-cohort (Danish Breast Cancer Group), results from tissue microarrays (TMA) have indicated issues with the analytical validity of the B-lymphocyte marker CD20.

We aimed to test the use of TMA as compared to whole-slide sections (WS) in evaluation of CD20 using digital image analysis (DIA).

Material and Methods
Immunohistochemistry for CD20 was performed on TMA (1 core/patient) and corresponding WS from 221 DBCG82bc patients. DIA based on the convolutional neural network U-Net automatically quantified the CD20-index of WS and TMA within four regions: 1) in direct contact with tumor-epithelial cells; 2) in tumor-related stroma, 3) in the whole lesion, and 4) in stroma margin (20 µm) of tumor-epithelial cells. Bland-Altman analysis and Wilcoxon signed-rank tests compared CD20-indices of WS and TMA.

Results
CD20 B-lymphocytes was heterogeneously distributed in the tumor and often forming nodules in the tumor-periphery. For all four regions, a higher CD20-index was detected on WS as compared to TMAs ($p<0.001$). The variation in CD20-indices was widest in the tumor-related stroma and most narrow in the tumor-epithelium. The mean difference between CD20-indices of WS and TMA were 0.15% (95% limits of agreement: -0.74; 1.0)% for tumor-epithelium contact; 1.3% (-5.9; 8.5)% for tumor-related stroma; 1.0% (-4.7; 6.7)% for whole lesion and 0.65% (-3.6; 4.9)% for stroma margin of tumor-epithelium.

Conclusion
Low CD20-indices were predominantly observed on TMAs and high CD20-indices on WS. The results indicate that TMAs can underestimate presence of CD20 cells in BC presumably due to formation of nodules. This tumor-intraheterogeneity must be taken into account, when exploring the use of CD20 as a potential biomarker for RT-benefit

48. Eleni Kanouta, Aarhus, Denmark

Scintillation imaging for in vivo monitoring of pre-clinical mouse treatments with conventional and FLASH proton pencil beam scanning

Kanouta E (1), Bruza P (2), Johansen JG (1), Sørensen BS (1,3), Kristensen L (3), Poulsen PR (1)

1) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, 2) Thayer School of Engineering, Dartmouth College, Hanover, NH, United States, 3) Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

Introduction
Dosimetry in pre-clinical studies is essential for the developing field of FLASH radiotherapy(RT). The ultra-high dose rates in FLASH RT require high temporal resolution for time-resolved dosimetry. In this study we propose a novel camera-based system for time-resolved 2D in vivo dosimetry and present the first in vivo tests of the system during pre-clinical conventional and FLASH proton pencil beam scanning (PBS) irradiations.

Materials and methods
The right hind leg of non-anaesthetized mice was placed in the middle of a Spread-out Bragg Peak, in a water bath, and irradiated with either conventional or FLASH dose rates. A 1mm thick transparent scintillator sheet was placed either perpendicular to the beam, in front of the mouse leg or parallel to the beam, next to the mouse leg, for measuring the lateral or depth dose profile respectively. The scintillating light from the sheet was reflected through a mirror setup and captured with a fast CMOS camera. The frame rate was 4fps for conventional and 500fps for FLASH. The raw images were corrected for geometrical distortions and variations in spatial sensitivity. The measured total field intensity was found by summing the intensity of all frames, after background subtraction and spatial filtering.

Results
A clear visualization of the mouse leg position relative to the lateral or depth profile was obtained with 0.5mm spatial resolution. For conventional irradiations, leg movement during beam delivery exceeding 2mm was observed. For FLASH irradiations, the positions of the individual spots relative to the mouse leg were found.

Conclusions
A scintillating sheet dosimetry system was successfully applied in pre-clinical proton PBS treatments with conventional and FLASH dose rates. Preliminary results indicate the potential of the system in measuring the time-resolved dose rate in 2D as well as tracking of the target within the scanning field. Characterization of the system's response will be conducted next.

49. Guillermo Garrido Hernandez, Trondheim, Norway

FDG-PET-based mid-treatment dose escalation of proton therapy in head and neck cancer

Garrido-Hernandez G, Henjum H, Winter R M, Danielsen S, Alsaker M D, Boer C G, Ytre-Hauge K S, Redalen K R

1. Department of Physics, Norwegian University of Science and Technology, Trondheim, Norway, 2. Department of Physics and Technology, University of Bergen, Bergen, Norway, 3. Department of Oncology, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway, 4. Department of Radiotherapy, Cancer Clinic, St. Olav's Hospital, Trondheim University Hospital, Trondheim, Norway, 5. Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway

Introduction
Image-driven dose escalation to tumor subvolumes has been proposed to improve treatment outcome in head and neck cancer (HNC). We used 18F-FDG-PET acquired at baseline and two weeks into treatment (interim) to identify boost target volumes (GTVboost). We then assessed the feasibility of interim adaptation of proton therapy by dose escalation to the GTVboost and its effects to organs at risk (OARs).

Materials/Methods
We used the semiautomated just-enough-interaction (JEI) method to segment GTVboost from planning 18F-FDG-PET/MR images on nine HNC patients in treatment position. Between baseline and interim FDG-PET all patients received photon radiotherapy. We assumed a correlation between tumor radioresistance and remaining standardized uptake value (SUV) at interim to identify the GTVboost. Using Eclipse (Varian Medical Systems), we simulated and compared proton therapy plans with a 10% (6.8 Gy) dose escalation to the prescribed GTVboost with standard proton plans.

Results
There was a spatial overlap between high SUV regions at baseline and interim scans, although treatment-induced reductions of the regions were seen in interim PET scans. The smaller GTVboost can potentially be used to more precisely target radioresistant tumor regions. Proton planning revealed that, compared to standard proton plans, median and max dose increases to OARs were on average below 3.0 Gy and 0.5 Gy, respectively, when performing interim 10% dose escalation to the GTVboost.

Conclusions
The JEI method could potentially be used to identify GTVboost on interim FDG-PET. Proton therapy adaptation by dose escalation based on interim FDG-PET seems feasible and may give more precise and efficient treatment to HNC with radioresistant tumor subvolumes without compromising treatment safety. Further studies in larger cohorts are required to determine the full potential for mid-treatment FDG-PET-guided dose escalation of proton therapy in HNC.

50. Jacob Lilja-Fischer, Aarhus, Denmark

HPV subtype not prognostic in p16+ oropharyngeal squamous cell carcinoma

Lilja-Fischer JK (1,2), Kristensen MH (1), Steiniche T (3), Tramm T (1,3), Lassen P (1), Eriksen JG (1), Stougaard M (4), Overgaard J (1).

1) Department of Experimental Clinical Oncology, Aarhus University Hospital, Denmark. 2) Department of Otolaryngology – Head & Neck surgery, Aarhus University Hospital, Denmark. 3) Department of Pathology, Aarhus University Hospital, Denmark. 4) Danish Life Science Cluster, Aarhus, Denmark.

Introduction
Treatment response and prognosis after primary (chemo-)radiotherapy for oropharyngeal squamous cell carcinoma (OPSCC) is affected by Human Papillomavirus (HPV) status, with a markedly better prognosis in HPV-positive OPSCC. There are numerous HPV subtypes, and it is still debated if prognosis depends on this. Purpose of this study was: 1) Validation of a custom-made targeted HPV next generation sequencing (NGS) panel in OPSCC; 2) determine correlation with p16 immunohistochemistry (IHC) 3); assess impact on outcome in a contemporary cohort treated in a rigorous protocol.

Materials and methods
We included a total of 194 patients with OPSCC treated with primary (chemo-)radiotherapy according to DAHANCA guidelines. Of these, 160 (82%) were p16-positive, and 34 (18%) p16-negative.
HPV-status was determined by targeted HPV next generation sequencing (NGS), using a custom-made genotyping panel covering all 25 carcinogenic, probably carcinogenic, and possibly carcinogenic HPV types.

Results
HPV was detected in 154 tumor samples. p16 IHC and NGS HPV status were concordant in 188 (97%) of 194 patients, whereas we did not detect HPV DNA in 6 p16+ tumors (See table).
HPV16 accounted for 135 of 154 HPV-positive cases (88%). HPV33 was found in 11 patients (7%). HPV types 18, 31, 35 and 59 were also detected.
Overall survival was similar whether patients were separated by p16 IHC, or HPV DNA status ($p<0.0001$ for both). Overall survival did not depend on HPV type ($p=0.3$).

Conclusion
We successfully validated use of a targeted HPV NGS panel in HNSCC, with very high concordance with p16 IHC. HPV type hold no prognostic information after primary (chemo-)radiotherapy, in a contemporary cohort treated to a uniformly high standard. p16 IHC still remains a valid and sufficient prognostic biomarker in OPSCC.

51. Marie Tvilum, Aarhus, Denmark

Using image biomarkers to predict pattern of failure for patients with locally advanced NSCLC

TVILUM M (1), LUTZ C.M. (2), KNAP M.M. (2), HOFFMANN L. (2), KHALIL A.A. (2), APPELT A. (3), GRAU C. (1), ALBER M. (4), Schmidt H.H. (2), Kandi M. (5), Holt M.I. (6), Mortensen L.S. (2), MØLLER D.S. (2)

(1) Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, DK, (2) Dept. Of Oncology, Aarhus University Hospital, Aarhus, DK, (3) Institute of Medical Research at St James's, University of Leeds, Leeds, UK, (4) Dept. Of Radiation Oncology, Heidelberg University Clinic, Heidelberg, DE, (5) Dept. of Oncology, Gødstrup Regional Hospital, Herning, DK, (6) Dept. of Clinical Genetics, Sygehus Lillebaelt, Vejle, DK

Introduction
Concurrent chemo-radiotherapy (cCRT) is standard of care for patients with locally advanced NSCLC. Regardless, recurrence rates are high, and 5-year overall survival poor. This study evaluates whether initial radiologic and metabolic image features could be prognostic of pattern of failure, hereby enabling new tools for treatment optimization.

Materials and methods
Patients with NSCLC treated with curatively intended concomitant chemo-radiotherapy (>60Gy total dose) at a single institution from 2012-2018 were included for analysis (n=278). Radiotherapy was delivered as normofractionated IMRT with 5 weekly fractions. Planning PET/CT (pPCT) with target structures of tumour and lymphnodes were included for analysis. Measurements included volume and SUVpeak. Time was measured from pPCT to event. First site of failure was defined as loco-regional (LR), distant (M) or simultaneous (LR+M). Fine and Gray competing risk modelling was performed including baseline characteristics of histology (squamous vs. non-squamous), performance status (PS) and stage, in addition to image features including tumour volume, tumour SUVpeak, lymphnode volume and SUVpeak.

Results
Median follow-up was 60 months (95%CI [52;68]). For LR-failure, both histology and tumour SUVpeak showed significant subdistributed hazard rates (sHR) of 2.43 (95%CI [1.34;4.42], p<0.01) and 1.08 pr. increase in SUVpeak (95%CI [1.01;1.1], p=0.02), respectively. Squamous cell histology had a significant lower risk of M-failure (sHR: 0.25, 95%CI [0.13;0.51], p<0.01) while a trend towards higher risk of M-failure pr. mL increase in lymphnode-volume (sHR=1.01, 95%CI [0.99;1.03], p=0.07) was found. For LR+M, no clear correlation was observed.

Conclusions
Histology and tumour SUVpeak at baseline are strong prognostic factors of LR failure for patients with locally advanced NSCLC treated with cCRT. For distant failure, histology endured its significant prognostic power.

52. Sara Linde, Aarhus, Denmark

Early radiologic and metabolic response to chemotherapy in patients with limited disease small cell lung cancer

Linde S (a), Hoffmann L (a,b) , Knap MM (a), Schmidt HH (a), Tvilum M (c), Lutz CM (a), Møller DS (a,b)

a: Department of Oncology, Aarhus University Hospital, Aarhus, Denmark b: Department of Clinical Medicine, Faculty of Health Sciences, Aarhus University, Aarhus, Denmark c: Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Introduction
The standard treatment for limited disease small cell lung cancer (LD-SCLC) is combined chemo-radiotherapy. However, frequent local and distant recurrences are present. This study evaluates the radiologic and metabolic response to the initial chemotherapy treatment measured as changes in tumor volume and highest standard uptake value in 1cm3 (SUVpeak). Hereby making it possible to predict more persistent tumors.

Materials and Methods
20 patients (pts) with LD-SCLC treated in 2015-2016 were retrospectively examined. Chemotherapy regimen consisted of platinum/Etoposide. Radiotherapy (RT) was delivered as 45Gy/30fx/10week. The stage distribution was IB (1 pt), IIA (5 pts), IIIA (4 pts), and IIIB (10 pts). All pts had diagnostic PET/CT-scans (dPCT) and planning PET/CT scans (pPCT) acquired for RT planning. Median time between dPCT and pPCT was 1.5 months [1;4], during which, 1-4 series of chemotherapy were administered. Gross tumor volumes for tumor (GTV-T) and lymph nodes (GTV-N) were delineated at pPCT and deformably transferred to dPCT followed by visual inspection and correction. Volume and SUVpeak of GTVs were determined on all scans and changes were calculated.

Results
On dPCT, median GTV-T and GTV-N volumes were 112.0ml, [minimum; maximum] [1.7;452.2] and 42.9ml [2.3;247.8], and median SUVpeak were 10.8 [1.9;16.4] and 9.1 [2.8;15;4], respectively. The median decrease in volume was 40.9% [1.0;93.3] for GTV-T and 42.6% [5.2;91.3] for GTV-N. The median decrease in SUVpeak was 41.2% [10.8;83.0] for GTV-T and 57.0% [17.7;85;1] for GTV-N. The study is planned to be extended to a cohort of 200 pts with LD-SCLC.

Conclusion
All patients had a decrease in volume and SUVpeak, for both GTV-T and GTV-N, as a response to initial chemotherapy. The individual patient response may be used to deliver individualized RT with increased doses to patients with more persistent tumors.

53. Tiril Hillestad, Oslo, Norway

Early microenvironmental changes to radiation therapy in cervical cancer patients

Hillestad T, Hompland T, Lund KV, Lyng H

Department of Core Facilities, Oslo University Hospital, Oslo, Norway; Department of Radiation Biology, Oslo University Hospital, Oslo, Norway; Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway; Department of Radiation Biology, Oslo University Hospital, Oslo, Norway

Introduction
Radiotherapy (RT) is a successful treatment of cervical cancer (CC), but due to tumor radiation resistance some patients are not cured, and so there is need for better understanding of the biological mechanisms. CC patients are treated with fractionated external RT (2 Gy x 25), followed by brachy therapy. An early response evaluation may provide a window of opportunity to change the treatment for patients with suboptimal response. The aim of this study was to explore early RT induced changes to the microenvironment using magnetic resonance (MR) imaging.

Methods
MR-imaging, including anatomical T2w imaging and DCE was performed in 25 CC patients before RT and again after receiving a total dose of 10 Gy. From DCE MR data the Tofts parameters Ktrans , reflecting perfusion, and Ve, reflecting the extracellular volume fraction, were derived. Tumour volume was obtained from T2w images. Furthermore, a biopsy was obtained at the same time points, and cell density (CD) was estimated from immunohistochemistry slides.

Results
After 10 Gy all patients had a decrease in CD ($p<0.001$), however this was not reflected in tumor volume as no significant reduction was found ($p=0.95$). Ve, which has been shown to negatively correlate with CD, increased by 19% but this was not statistically significant ($p=0.067$). Reperfusion is thought to be an important factor of fractionated RT and median Ktrans increased by 28% ($p=0.011$). 4 patients experienced tumor recurrence and was classified as non-responders. Responders had a significantly higher increase in Ktrans than non-responders ($p=0.008$). There was no difference in CD, Ve or tumor volume between responders and non-responders.

Conclusion
After 10 Gy significant changes were observed in parameters reflecting the tumor microenvironment that were independent of tumor volume changes. An increase in tumor perfusion, Ktrans, was higher in responders than non-responders and may be a promising biomarker for tumor response to RT.

Poster discussion group 3: Clinical studies A

Chairs: Slavka Lukacova, Mette van Overeem Felter

54. Daniella Østergaard, Copenhagen, Denmark

Dose-accumulation analysis of target and organs at risk with clinical outcome after re-irradiation of diffuse midline glioma.

Daniella Elisabet Østergaard, Morten Jørgensen, Mimi Kjærsgaard, Rene Mathiasen, Karsten Nysom, Astrid Sehested, Isak Wahlstedt, Ivan Richter Vogelius and Maja Vestmø Maraldo

Diffuse midline glioma (DMG) is the most common brainstem cancer among children, and it has a dismal prognosis. Only radiotherapy (RT) has demonstrated tumour control – unfortunately only transient. Re-irradiation (reRT) has been has increasingly been studied the last decade, but cumulated dose to organs at risk is, however, unaddressed. We analysed dosimetric and clinical data of reRT patients with DMG using EQD2 sum plans.

We retrospectively reviewed health records for demographic, clinical, and RT data of patients with DMG at Rigshospitalet from Jan 2011 to May 2021. We screened for toxicity and clinical status after reRT. RT treatment plans were collected, and we used $EQD2=D(d+\alpha/\beta)/(2+\alpha/\beta)$ to recalculate biologically equieffective dose volume histograms for all contoured structures for both primary RT and reRT ($\alpha/\beta = 2$). Assessment of overlap of primary RT target and reRT target was done with sum plans, and cumulated biologically equieffective Dmax and Dmin to selected structures was measured from sum plans.

We found 7 re-irradiated patients with DMG . Median age at diagnosis was 6 years (2y;13y). All patients were initially treated with 54Gy/30F and median time between treatments was 10months (8;17m). Median survival time was 20m (9m; 30m) and median time from reRT to death was 4m (3m;10m). The observed toxicity from reRT was reported to be mild for all patients. For 6 out the 7 patients, the dose summation demonstrated complete overlap of target in the primary and reRT plan. Median cumulated Dmax for brainstem (89Gy (79-91Gy)), chiasm (70Gy (56-87Gy)), and optic nerves (left: 36Gy (11-53Gy), right: 43Gy (14-50Gy)) exceeded internationally, recommended dose constraints. Though limited by the number of patients, reRT offers a relevant palliative treatment for DMG patients upon progression. Although cumulated doses to the brainstem, chiasm, and optic nerves violated dose constraints the observed toxicity was mild and no radionecrosis was reported in this study.

55. Hendrik Hansen, Maastricht, the Netherlands

Automated plan quality monitoring for patient cohorts using dashboards: demonstration for a 'RapidPlan introduction' use case

Hansen HHG, Bogowicz M, Fick P, Kubica J, Veugen J, Merk G, de Rooy M, Canters R, van Elmpt W

Department of Radiation Oncology (MAASTRO), GROW School for Oncology and Reproduction, Maastricht University Medical Center, the Netherlands

To quantify the impact of changes in the planning workflow (e.g. updating OAR constraints, introduction new planning techniques), we developed an automated framework for plan quality monitoring on a patient cohort level. In this abstract we introduce this framework and use it to quantify changes in plan quality between cohorts of lung patients planned before (n=74) and after (n=60) introduction of RapidPlan (RP) (Varian Medical Systems).

Plans (30x2 Gy) were planned using Eclipse (Varian Medical Systems). After plan approval, a custom-made tool, PlanQA (a calculation core in Matlab wrapped by a Spring Boot microservice), automatically read out DICOM structure, dose, and plan data and extracted dose-volume-histogram (DVH) parameters. PlanQA also predicted DVH-values per patient based on previously validated reference dose falloff maps per OAR. Achieved and predicted values were stored in an SQL database and imported and presented in predesigned graphs in a Microsoft Power BI dashboard to facilitate fast quantification and visualization of possible changes in plan quality.

The percentage of achieved DVH values exceeding predicted values reduced by 5-18% for all OARs, indicating more optimal plans with RP. Dmax to the spinal cord was 7.5 Gy lower with RP than without ($P<0.01$, Mann-Whitney U-test). For the heart, Dmean dropped by 0.6 Gy and average values for V30Gy, V45Gy, and Dmax were similar, while their range reduced by 5-12% indicating more constancy of plans with RP. Finally, DVH metrics improved for the contralateral lung (V5Gy: -5.7%, Dmean: -1.1 Gy, Dmax: -3.0 Gy), whereas overall lung dose increased slightly (V5Gy: +0.9%, Dmean: +1.2 Gy) with RP.

In summary, an automated plan quality monitoring framework was developed and it quantified advantages of using RapidPlan for lung patients. The framework is now in use for longitudinal plan quality monitoring and to quantify the impact of RapidPlan introduction for other treatment sites.

56. Hjørdis Hjalting Schmidt, Aarhus, Danmark

Do changes in treatment over time affect survival and pattern of failure in 177 consecutive patients treated with chemoradiotherapy for limited disease small-cell lung cancer (LD-SCLC)?

Schmidt HH (a), Knap MM (a), Khalil AA (a), Mortensen LS (a), Kandi M (d), Tvilum M (c), Lutz CM (a), Hoffmann L (a,b), Moeller DS (a).

A: Department of Oncology, Aarhus University Hospital, Aarhus, Denmark B: Department of Clinical Medicine, Faculty of Health Sciences, Aarhus University, Aarhus, Denmark C: Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark D: Department f Oncology, Gødstrup Hospital, Gødstrup, Denmark

Introduction
The standard treatment for LD-SCLC is concurrent platinum-based chemotherapy (Ctx) and hyperfractionated radiotherapy (RT) followed by prophylactic cranial irradiation (PCI). Despite treatment with curative intent, relapse is frequent and associated with a dismal prognosis.

Material and Methods
From 2012-2020, 177 consecutive patients (pts) with LD-SCLC were treated with curative intent. Median [range] age was 66 years [40-83] and performance status was 0-1 (84%) and 2-3 (16%). Disease stage was I-II (17%), IIIa + IIIb (each 31%) and IIIc (21%). Ctx consisted of 1-4 cycles of platinum and etoposide. All pts underwent planning PET/4D-CT scan. Tumor and pathological lymph nodes received 45 Gy/30F/10w. Patients were set up based on daily conebeam CT.

Pts were divided into two groups, group A (treated in 2012-2016) and group B (treated in 2017-2020). Kaplan-Meier curves (KM) were plotted for overall survival (OS) and compared using log-rank test. OS was defined from RT start until death. First failure was characterized as either loco-regional (LR), distant metastasis (M) or simultaneous (LR+M).

Results
With a median follow-up of 72 months (reverse-KM), the median OS (mOS) was 22 months for the entire group with a 2-year (5-year) survival rate of 48% (24%). There was no difference in survival between Group A and Group B, only stage had an impact on OS in a multivariate analysis. In Group A pts were more frequently treated with cis- than carboplatin (52% vs. 20%) and PCI (84% vs. 47%) than in Group B. The first relapse was equally distributed in Group A and B at two years with 10% LR, 32% M and 24 % LR+M. However, 17 patients in Group B, with less frequent use of PCI, had brain metastases as first failure compared to 10 patients in Group A.

Conclusion
Even though fewer pts received PCI over time and more pts developed brain metastasis, it had no influence on OS. Relapses are frequent and call for improvements in the treatment of LD-SCLC.

57. Ida M. H. Borgen, Oslo, Norway

Assessing cognitive functioning in patients with diffuse glioma grade 2 and 3 in the PRO-GLIO trial – advantages and disadvantages of a cognitive screening battery versus a full neuropsychological assessment

Borgen IMH, Nordenmark TH, Heggebø LC, Rylander H, Ledal RJ, Werlenius K, Blomstrand M, Brandal P

1 Department of Oncology, Oslo University Hospital, Oslo, Norway, 2 Department of Physical Medicine and Rehabilitation, Oslo University Hospital, Oslo, Norway, 3 The Skandion Clinic, Uppsala, Sweden, 4 Representative from the Norwegian Brain Tumor Alliance, Norway, 5 Department of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden, 6 Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Introduction
PRO-GLIO is a multicenter phase III randomized controlled trial of proton versus photon therapy for diffuse grade 2 and 3 gliomas. Radiation therapy may contribute to cognitive decline in such patients, thus exacerbating cognitive deficits expected with this disease. Cognitive assessments are important to evaluate the extent of cerebral dysfunction and identify rehabilitation needs. Brain tumor user organizations emphasize the need for cognitive assessment in diffuse glioma patients, however, neuropsychologists are a scarce resource in the field of oncology. The PRO-GLIO trial will evaluate different cognitive assessment approaches.

Materials and methods
PRO-GLIO will include 224 patients with IDH-mutated oligodendroglioma and astrocytoma grade 2 and 3. Cognitive assessments take place at baseline (pre-radiation), 5 months, 2, 5, 10, and 15 years post-radiation. All 224 patients will be assessed using four iPad-based tests (cognitive screening battery). All Norwegian and some Swedish patients (estimated n=100) will undergo a full neuropsychological assessment at the same time points.

Results
The full test batteries will be presented at BiGART, with an overview of potential advantages and disadvantages related to the use of a cognitive screening battery versus a full neuropsychological assessment.

Conclusion
The two-fold assessment planned in PRO-GLIO will enable a comparison between a low-cost cognitive screening battery and an in-depth standard neuropsychological examination in diffuse grade 2 and 3 gliomas patients. PRO-GLIO will also reveal the degree of cognitive deficits which over time often develops in these patients. The comprehensive neuropsychological data collected will pave the way for exploratory research on the consequences of low-dosage radiation to radiotherapeutic organs at risk, such as the hippocampi, for cognitive functioning.

58. Liv Cathrine Heggebø, Oslo, Norway

Quality of life, perception of treatment, and life perspectives in diffuse low-grade glioma patients – initial presentation of a qualitative sub-study in the PRO-GLIO trial

Heggebø LC (1), Borgen IMH (1), Kiserud CE (1), Hellebust TP (2), Ledal RJ (3), Werlenius K (4), Blomstrand M (4), Brandal P (1), Lie HC (5)

1) Depart. Oncol., Oslo University Hospital (OUH), Oslo, Norway, (2) Dep. Me. Physics, OUH, Oslo, Norway, (3) Norwegian Brain Tumor Alliance representative, Norway, (4) Depart. Oncol., Sahlgrenska University Hospital, Gothenburg, Sweden, (5) Depart. Behavioural Med., Faculty of Medicine, University of Oslo, Oslo, Norway

Introduction
PRO-GLIO is a multicenter phase III trial in which patients with isocitrate dehydrogenase (IDH)-mutated oligodendroglioma or astrocytoma grade 2 or 3 are randomized to photon or proton therapy. Primary endpoint is first intervention free survival and key secondary endpoints are fatigue and cognitive status, all at 2 years. As little is known about the patients' perceptions of the two different treatment modalities, we explore patients' perceived impact of disease, treatment and care on their quality of life in this sub-study.

Materials and methods
This is a longitudinal, qualitative, semi-structured interview study of 20 patients (10 receiving proton and 10 photon therapy) recruited at PRO-GLIO inclusion by the sub-study investigator. Interviews are conducted at baseline, five months, two years and five years. Comparisons between the two study arms and a longitudinal analysis of patient's perspectives will be performed. User representatives were consulted in the interview guide development to ensure study relevance.

Results
To date, 19 patients (n=7 females) have been invited, of which all consented, and 27 interviews are completed (n=18 baseline, n=9 five months). Preliminary analysis of interviews at baseline and five months has identified main themes including severe impact of the cancer on everyday life and relationships, changes in identity, information needs, and ways of coping with the new situation. Several pros and cons with either treatment alternative were discussed.

Conclusion
Being diagnosed with diffuse glioma brings about severe life challenges, but the patients demonstrate a range of strengths and coping strategies. The patients' experiences add valuable insight into how information, treatment, and clinical trial participations are perceived, useful to improve future patient care pathways and anti-neoplastic and supportive treatment.

59. Michael Ruben Teindl Laursen, Copenhagen, Denmark

Protocol: OLIGO-DK - Local ablative therapy of oligometastatic disease

Michael Ruben Teindl Laursen (1), Mette van Overeem Felter (1), Nicklas Juel Spindler (1), Gitte Fredberg Persson (1,2)

(1) Dept of Oncology, Copenhagen University Hospital – Herlev and Gentofte, Copenhagen, Denmark (2) Dept of Clinical Medicine, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark

Introduction
Local ablative therapy (LAT) of oligometastatic disease (OMD) is considered standard of care in several diagnoses and metastatic sites, and is clinically implemented in daily practice. Evidence is emerging supporting this notion, but phase III trials are lacking support, as lack of equipoise is a concern. Most studies focus on a single treatment modality or cancer diagnosis.
Within the frame of a national centre for radiotherapy research, we aim to develop 1) SBRT based regimens for all metastatic sites and 2) a prospective clinical umbrella trial for all patients who are treated with LAT for OMD regardless of modality.

Materials and methods
To evaluate feasibility, two prospective, multicentre, phase 2 trials were completed. The BONY-M trial and SOFT trial evaluated SBRT of bony metastases and infradiaphragmatic soft tissue metastases, respectively. Accrual was faster than anticipated, underlining the demand for SBRT for OMD.
The OLIGO-DK trial will prospectively include Danish patients who are referred for LAT of OMD. We will evaluate all LAT modalities, including surgery, thermal ablation, and stereotactic radiotherapy. The aim is to assess efficacy, safety, and quality of life, the primary endpoint being time to failure of LAT strategy. We aim to build a model for prospective selection of patients who will benefit from a LAT strategy, and map the longitudinal treatment trajectory of individual patients.
The trial will be initiated in the Capital Region and then expanded. After 50 patients, an interim analysis will assess accrual and protocol adhesion. After 100 and 200 patients, further interim analyses will adjust the power calculation to the primary endpoint.

Perspectives
The pragmatic design of the trial will increase our knowledge of OMD through evaluation of all local ablative treatment modalities, while safely implementing SBRT to several metastatic sites at all radiotherapy centres in Denmark.

60. Sandy Mohamed, Aarhus, Denmark

The value of MRI in response evaluation after primary (chemo-) radiotherapy for head and neck squamous cell carcinoma

Mohamed S 1-2, Lilja-Fischer JK 3, Madsen MH 4, Eriksen JG1.

1Dept of Experimental Clinical Oncology, AUH, Aarhus 2Dept of Radiotherapy and nuclear medicine, NCI, Cairo University. 3Dept of ENT surgery, AUH, Aarhus. 4Dept of Radiology, AUH, Aarhus.

Aim
To evaluate the value of MRI, in addition to standard clinical evaluation for head and neck squamous cell carcinoma (HNSCC) 2 months after end of primary (chemo-)radiotherapy, (C-)RT.

Material & method
394 consecutive patients (pts) treated with primary (C-)RT for HNSCC of the larynx (not T1 glottic cancer), pharynx, and oral cavity from 2016 to 2019 were retrospectively analyzed. Result of clinical evaluation 2 months after (C-)RT (clinical examination and flexible laryngoscopy), imaging reports and MDT decisions (3 months after (C-)RT) and pathology reports were collected.

Results
Tumor sites were larynx (17%), pharynx (77%) (Oropharynx 59%, Non-oropharynx 18%), and oral cavity(6%). Clinical evaluation at 2 months after (C-)RT found group A: 302 pts in complete remission (CR). Of those, 5% had suspected lesion by MRI, with subsequent positive pathology. Group B: 58 pts had clinically suspicious residual tumor at clinical evaluation. 24% of them had persistent disease by MRI, with subsequent positive pathology. Group C: 14pts were not fully evaluated clinically but did MRI, 21% of them had a suspected lesion by MRI and positive pathologically confirmed disease. Group D: 20 pts did not undergo clinical evaluation nor MRI. In the total cohort, 20, 8, and 5 pts had treatment failure at nodal site (N), primary tumor (T), or combinations of T, N or distant, respectively. At 1-year follow up, 10 pts with T-site failure were dead of disease in contrast to 2 pts with N-site failure. MRI negative predictive value was 91%.

Conclusion
Follow up with MRI after (C-)RT identified 5% of the pts with treatment failures despite estimated CR by clinical examination and endoscopy. Most of the early failures not suspected clinically were N failures. N failures had a better 1-year outcome after salvage surgery than other treatment failures.
MRI is useful to evaluate treatment response after primary curative (C-)RT of the larynx, pharynx and oral cavity

61. Slavka Lukacova, Aarhus, Denmark

Examining clinical patterns in the referral of brain tumor patients to proton therapy: A single center retrospective study

Lukacova S (1,2), Høyer M (2,3), Byskov CS (2) Kallehauge JF (1,3)

(1) Dept. of Clinical Medicine, Aarhus University, Aarhus, Denmark (2) Dept. of Oncology, Aarhus University Hospital, Aarhus, Denmark (3) Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Introduction
In Denmark, patients with primary brain tumors and expected survival > 5 years are considered for proton treatment (PT). The decision for referral to PT is based on the dosimetric comparison between photon and proton plan for each individual patient. The aim of this retrospective single center study was to identify clinical parameters associated with the referral to PT.

Methods
Patients with primary brain tumor and candidates for PT at Aarhus University Hospital between 01.01.2019 and 31.12.2022 were included. The clinical (age, diagnosis, radiation dose, target volume, date of photon-proton comparison and treatment modality selection) and dosimetric (mean dose difference to the healthy brain, Dmean diff) parameters were collected. The association of predefined parameters and the selection of treatment modality (PT vs. photons) was analyzed using univariate and multivariate logistic regression.

Results
The cohort consisted of 104 patients, of whom 44 had meningioma and 38 glioma. Patients selected for PT (n=51) were significantly younger (median age 44 years (23-72) vs. 53 years (39-74), $p < 0.001$), had larger targets (median target volume 112 cc (3 -363) vs. 11 cc (0.2 – 206), $p < 0.001$) and higher Dmean diff (5.9 Gy (-2 – 11.5) vs. 2.3 Gy (-0.6 – 10.6), $p < 0.001$). Age was independently associated with PT referral ($p < 0.001$). For glioma and meningioma patients 79% and 24% were referred to PT, respectively. Glioma and meningioma PT subgroup was younger (median age 39 and 54 years vs. 54.5 and 64 years, $p < 0.05$) and had larger targets (median target volume 180 cc and 16 cc vs. 71 cc and 8 cc, $p < 0.05$) compared to photons. In glioma, target volume and in meningioma, Dmean diff were independently correlated with PT referral ($p < 0.05$).

Conclusion
Patients with glioma are more likely referred to PT. Age and for glioma patients target volume are independently associated with PT referral.

Poster discussion group 4: Clinical studies B

Chairs: Einar Dale, Camilla Kronborg

62. Anders W. Mølby Nielsen, Aarhus, Denmark

Difference between planned and delivered dose to the internal mammary nodes in high-risk breast cancer patients

Nielsen AWM(1),Spejlborg H(2) Lutz CM(2),Poulsen PR(3,4) Offersen BV(1,3,4)

1Dept. of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark. 2Dept. of Medical Physics, Aarhus University Hospital, Aarhus, Denmark. 3Danish Center for Particle Therapy, Aarhus University Hospital, Denmark. 4Dept. of Oncology, Aarhus, Denmark

Introduction
This study examines the delivered dose coverage of the internal mammary nodes (IMN) in high-risk breast cancer patients using continuous portal images (cine MV) of tangential breast fields.

Material and methods
A prospective single-center quality assurance study was conducted in a consecutive cohort of left-sided node-positive breast cancer patients treated with image guided radiotherapy (IGRT) during 2021. During treatment, cine MV images were recorded at every fraction for the medial and lateral tangential main fields. On the final frame of each cine MV recording the chest wall was matched with the Digitally Reconstructed Radiograph (DRR) from the treatment plan. The match was performed at the chest wall level closest to the IMN target. The geometrical errors were rounded to integer millimeters and binned. For each 1 mm bin, an isocenter-shifted treatment plan was recalculated assuming that the 2D error observed in the cine MV image was caused by an anterior-posterior chest wall shift in the IMN region. A weighted plan sum yielded the IMN clinical target volume receiving at least 90% dose (V90_CTVn_IMN). The primary outcome was the difference between delivered and planned V90_CTVn_IMN.

Results
In total, 39 breast cancer patients were included for analysis. The mean number of cine MV observations per patient was 36 (range 26-55). Most patients (67%) had on average a lowered chest wall position on cine MV images compared to the plan DRR. This translated into a change in the delivered median V90_CTVn_IMN of -0.7% (range, -11.9-2.9%; p=0.0002). The V90_CTVn_IMN reduction was >9% in three patients. No clinically relevant differences were found for the mean lung dose or mean heart dose.

Conclusion
Using cine MV images, we found that the delivered V90_CTVn_IMN was significantly lower than planned. In 8% of the patients, the V90_CTVn_IMN reduction exceeded 9%.

63. Anne Lindegaard, Copenhagen, Denmark

A systematic review on clinical adaptive radiotherapy for head and neck cancer

Lindegaard AM, Håkansson K, Specht L, Vogelius IR, Friborg J

Department of Oncology, Centre for Cancer and Organ diseases, Copenhagen University Hospital - Rigshospitalet, Copenhagen Denmark

Introduction
Head and neck cancer (HNC) patients' anatomy may undergo significant changes during radiotherapy (RT). This potentially affects dose distribution and compromises conformity between planned and delivered dose. Adaptive radiotherapy (ART) is a promising modality to overcome this problem but requires a significant workload. This systematic review aims to estimate the clinical and dosimetric benefits and highlight some of the challenges of implementing ART.

Material and methods
A PubMed search according to the PRISMA guidelines was made on Feb 6, 2023. Search string used was: "adaptive radiotherapy head neck cancer". English and Danish language filters were applied. All studies were screened for inclusion on title and abstract, and the full text was read and discussed in the research group in case of uncertainty. Inclusion criteria were a prospective ART strategy for HNC investigating clinical and dosimetric outcomes.

Results
A total of 1128 articles were identified of which 14 met inclusion criteria. All included studies were published between 2010 and 2022 and characterized by a substantial diversity in design, endpoints, and nomenclature. The number of patients treated with ART was small with a median of 21 patients per study (range 4 to 86). Mean dose to the parotid glands was reduced by 0.6-7.12 Gy. Maximum dose to the spinal cord was reduced by 0.5-4.6 Gy. Five studies (36%) reported clinical outcomes whereas 3 had a control group (one was randomized). Clinical outcome data were mixed but one study claimed improved disease control and quality of life with ART. Median follow-up time was reported in 4 out of 14 studies (range 6-31 months).

Conclusion
The literature on clinical ART in HNC is limited. ART is associated with a small reduction in dose to OARs but toxicity data is sparse. There is a clear need for larger, prospective trials with a well-defined control group.

64. Camilla Kronborg, Aarhus, Denmark

Organ specific secondary cancer risk after radiotherapy for seminoma. Comparison of robust intensity modulated proton therapy (IMPT) vs IMRT and VMAT photon plans

Kronborg CJS 1, R›nde HS1, Høyer M1, Hansen J2, Bak ME3, Agergaard SN4, Als AB2, Agerb'k M2, Lauritsen J3, Petersen PM3, Dysager L4, Kallehauge JF1

1 Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, 2 Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, 3 Department of Oncology, Rigshospitalet, Copenhagen, Denmark, 4 Department of Oncology, Odense University Hospital, Odense, Denmark

Introduction
Several studies have documented an increased risk of secondary cancer after radiotherapy in patients with seminoma. The patients are young with favorable prognosis and the extent of treated volumes results in a large dose bath to surrounding organs at risk (OAR). Thus, optimizing radiotherapy with the aim of reducing secondary cancer risk is pertinent.
We compared Robust Optimized Intensity Modulated Proton Therapy (IMPT) to opposing IMRT fields and VMAT, assessing organ specific secondary cancer risk.

Materials and methods
Comparative dose planning was done using planning CT-scans from ten patients with seminoma, treated with photons and traditional "dog-leg" field. The CTV-E (Elective) volume doses ranged from 20-25 Gy with a 10 Gy sequential boost to pathological lymph nodes.
Photon plans were either opposing 3-4 field IMRT (Eclipse, Varian Medical Systems) or 2 arc VMAT (Pinnacle, Philips Healthcare). IMPT used robust (5 mm setup error; 3.5% range uncertainty) multi field optimization planning with 3 posterior fields supplemented by 2 anterior fields at the level of the iliac vessels (Eclipse, Varian Medical Systems).
The risk of secondary cancer was calculated according to the model described in Schneider et al., 2011, using excess absolute risk (EAR, per 10.000 persons per year) for full body (FB), stomach, duodenum, pancreas, bowel and bladder. Wilcoxon's signed rank test with Holm-Bonferroni corrected p-values was used for comparison.

Results
A total of 30 plans were generated. The FB secondary cancer risk was reduced from 51 for VMAT and 31 for IMRT to 17 for IMPT. For bowel the corresponding calculations went from 56 and 51 to 21, for stomach from 3.2 and 2.7 to 0.5 and for bladder from 3.1 and 2.6 to 0.9.
For duodenum EAR increased from 0.9 and 1.1 to 1.3, for pancreas changed from 1.2 and 1.5 to 1.3, all comparisons were statistically significant ($p<0.05$) with lower EAR for IMPT except for pancreas and duodenum IMPT vs IMRT. VMAT had significantly lower EAR than IMPT for duodenum.

Conclusion
The reduced OAR dose obtained with proton therapy resulted in modelling a reduced risk of secondary cancer compared to both IMRT and VMAT. However, for the duodenum and pancreas the difference was less pronounced and with a lower absolute excess incidence of secondary cancer compared to other OAR . Finally, VMAT had a lower EAR for duodenum than IMPT.

65. Camilla Skinnerup Byskov, Aarhus, Denmark

Facility questionnaires from the European multicentre PROTECT phase III trial randomising proton vs. photon beam therapy in oesophageal cancer

Byskov CS1,2, Ehmsen ML2, Shamshad M3, Canters R4, Defraene G5, Mortensen HR2, Møller DS1,2,6, Vilches-Freixas G4, Hoffmann L1,2,6

1 Dept of Oncology, Aarhus University Hospital, Aarhus N, Denmark 2 DCPT, Aarhus University Hospital, Aarhus N, Denmark 3 EBG MedAustron GmbH, Marie Curie-Straáe 5, Wiener Neustadt, Austria 4 Dept of Radiation Oncology (Maastro), GROW School for Oncology

Introduction
The European randomized phase III PROTECT-trial investigates the clinical effect of proton therapy (PT) versus photon therapy (XT) for oesophageal cancer patients treated with chemoradiotherapy followed by surgery. To ensure high quality of the trial, strict mandatory quality assurance (QA) guidelines have been developed. As part of the QA procedure, facility questionnaires (FQ) have been distributed to gain insight in the patient treatment workflow across the centres. The FQs are collected and updated yearly. For each centre, there will be an onsite RTQA visit with a checklist to be followed once the first two patients are included. The aim of this study was to review treatment planning data from the FQs, however data exist on the full treatment procedure.

Materials and methods
A FQ was circulated to 29 European centres to collect information about facilities and methodologies concerning treatment preparation, -planning, -verification, -delivery, -adaptation and -interruptions for both trial arms.

Results
Twenty FQs were returned (10 XT/10 PT). The prescribed dose was 41.4 Gy/23 fractions (Fx) (13) and 50.4 Gy/28 Fx (7). For XT the treatment technique was IMRT (3), VMAT (6) or Tomotherapy (1). For PT IMPT (6), SFUD (3) and IMPT/SFUD (1) were used. PT repainting was used in five centres. Beam angles were class solutions (1 XT, 4 PT), variable arcs (3 XT), variable beams (2 XT, 6 PT), two full arcs (3 XT) and Tomotherapy (1 XT). A PTV/other margin is used for all XT centres and in four PT centres. No robust evaluation scenarios were used in two centres. For the remaining centres it varied between 6-14 (XT) and 12-70 (PT) with setup uncertainties of 3-8 mm and PT range uncertainties of 3-5%.

Conclusion
All centres used intensity modulated treatment with beam angles, dose prescription, treatment planning margins and range uncertainties for PT according to guidelines. Two XT centres violated the RTQA requirement of at least six robust evaluation scenarios.

66. Faisal Mahmood, Odense, Denmark
Presented by Maja Bruvo Lazovic, University College Absalon, Næstved, Denmark

Potential early predictors of permanent xerostomia following head and neck radiotherapy

Bruvo M, Behrens CP, Samsøe E, Pedersen AML, Maare C, Hansen RH, Johannesen HH, Mahmood F

Dept. of Radiography, University College Copenhagen, DK; Dept. of Oncology, Copenhagen University Hospital - Herlev and Gentofte, DK; Dept. of Clinical Oncology and Palliative Care, Zealand University Hospital, DK; Dept. of Odontology, University of Copenhagen, DK; Dept. of Oncology, Copenhagen University Hospital – Rigshospitalet, DK; Dept. of Clinical Physiology and Nuclear Medicine, Copenhagen University Hospital -Rigshospitalet, DK; Dep. of Oncology, Odense University Hospital, DK.

Introduction
Xerostomia is one of the most prominent side effects of radiotherapy (RT) for head and neck cancer (HNC). The aim of this exploratory study was to identify potential early predictors of permanent xerostomia following HNC RT.

Materials and methods
Twenty-four prospectively included patients with HNC were examined prior to the first RT fraction (Baseline), immediately after the RT course (End RT) and one year after the RT course end (Follow up). Examinations included measurements of saliva flow rate, total protein concentration, α-amylase activity and the apparent diffusion coefficient (ADC) of the ipsilateral parotid gland under unstimulated and stimulated conditions. Moreover, the severity of xerostomia was assessed according to standard radiation morbidity scoring criteria. Permanent xerostomia was defined as grade 2-3 at Follow up.

Results
Six patients were diagnosed with permanent xerostomia. For these patients, significant changes were observed in the ADC and saliva flow rate in the stimulated condition between Baseline and End RT, and between End RT and Follow up ($p<0.001$). For the total protein concentration, significant changes were observed in the unstimulated condition between Baseline and End RT ($p=0.004$). No significant changes were observed for the α-amylase. Mean radiation dose to the parotid gland(s) was not significantly different between patients with no xerostomia and patients with permanent xerostomia.

Conclusion
The ADC, saliva flow rates and total protein concentration are potential early predictors of permanent xerostomia in patients with HNC following RT. Validation in large patient cohorts is warranted.

67. Johannes Tjelta, Bergen, Norway

Radiation exposure to parent-in-treatment-room during pencil beam scanning pediatric proton therapy

Tjelta J, Ytre-Hauge K, Lyngholm E, Handeland A, Henjum H and Stokkevåg C

Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway. Department of Physics and Technology, University of Bergen, Bergen, Norway

Introduction
Radiation protection regulations do not allow caretakers to remain near their children during radiotherapy treatment. However, new treatment modalities such as pencil beam (PB) scanning proton therapy (PT) may open possibilities due to reduced radiation exposure in the treatment room. This study examines the radiation environment in the treatment room from PB scanning PT and the concept of exposure to a parent in the treatment room.

Method
The PT treatment room under construction at Haukeland university hospital was modeled in the FLUKA Monte Carlo (MC) code, together with a patient and a whole-body CT of a male representing a parent located in the treatment room at variable distances (1-3 meters) from the patient's isocenter. A treatment plan for a 10-year-old pediatric patient with a brain tumor (low-grade glioma; volume 4.4 cc, 54 Gy(RBE) prescribed) was optimized in the Eclipse treatment planning system (Varian Medical Systems) using a vertex (90°) field, combined with two lateral fields (80° and 280°). The treatment plan was further recalculated in FLUKA and the radiation exposure of the parent was scored, including neutrons (ICRP 103 weighting for equivalent doses), photons, and protons.

Results
The whole body of the parent received an average absorbed dose of 27 µGy and a equivalent dose of 50 µSv per treatment Gy at 1 m. At 3 m, the average absorbed dose was 7 µGy and the equivalent dose was 20 µSv per treatment Gy. For the whole treatment, the parent would receive 1.5 mGy (2.7 mSv) at 1 m, reduced to 0.4 mGy (1.1 mSv) at 3 m.

Conclusion
When the parent was close enough to hold the child's hand at 1 m the estimated doses would be comparable to a chest CT (1.5-6.1 mSv) or equivalent to 6-12 months of background radiation. The dose at 3 m including the whole treatment would be similar to 3 months of background radiation. There is therefore opportunity to further examine whether parents can occupy the treatment room for comforting their children.

68. Tine Bisballe Nyeng, Aarhus, Denmark

Risk of large intra-fractional target shift during stereotactic treatment of peripheral lung lesions

Nyeng TB (1), Thomsen SN (1,2), Møller DS (1,2), Hansen R (1), Khalil AA (3), Hoffmann L (1,2)

1: Department of Oncology, Medical Physics, Aarhus University Hospital, Aarhus, Denmark. 2: Dept. of Clinical Medicine, Faculty of Health Sciences, Aarhus University, Denmark. 3: Dept. of Oncology, Aarhus University Hospital, Aarhus University, Denmark

Introduction
Treatment of small peripheral lung lesions with stereotactic radiotherapy (SRT) is critically sensitive to geometrical shifts during RT delivery. We investigated the intra-fraction target displacement and the impact of resting time after patient positioning.

Materials and methods
Fifty-one lung lesions were treated with SRT of 45-67.5Gy in three fractions, with a planning target volume (PTV) margin of 4mm. Patients were positioned in the treatment room (End of positioning, Time: T0). A cone-beam CT (CBCT) image was acquired and used for online position correction through a soft tissue target match to the planning CT (pCT), before (Acquisition start, Time: T_CBCT0), and after treatment (Acquisition start, Time: T_CBCT1). Retrospectively, CBCT0 and CBCT1 were matched to pCT on both the target and the vertebral column, and the resulting 3D vector shifts between CBCT0 and CBCT1 were calculated. Correlation between target and vertebra shifts was tested by calculating the Spearman's rank correlation coefficient. The resting time, defined as the time interval from T0 to T_CBCT0 was calculated.

Results
The median [range] target and vertebra shifts were 2.2mm [0.2;16.1] and 0.9mm [0;5.7], respectively. In 54 of the 153 fractions, target shifts of more than 3mm were seen, three of these above 8mm. Vertebral column shifts were generally small and were uncorrelated to target shifts (ρ=0.4566). The median T0 to T_CBCT0 time was 133s [52;1478]. The median resting time of fractions with target shifts below and above 3mm was 143s [52;1478] and 119s [65;405], respectively. Except for a few outliers, when the resting time was at least 3min30sec all intra-fractional target shifts were below 4mm, corresponding to the total PTV margin.

Conclusions
For some lesions, large intra-fractional shifts were observed. In most cases, this effect was reduced by allowing a longer patient resting time. The observed target shifts were uncorrelated to the shifts of the vertebra.

69. Veera Ahtiainen, Helsinki, Finland

Concept of individual dosing of Lu-177-PSMA radionuclide treatments based on prediction of tumor control and kidney tolerance

Ahtiainen V. (1, 4), Reijonen V. (1), Vaalavirta L. (2), Utriainen T. (3) and Tenhunen M. (1)

(1) Molecular radiotherapy unit, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland (2) Department of Oncology, Kymenlaakso Central Hospital, KYMSOTE, Kotka, Finland (3) Department of Oncology, Helsinki University Hospital Comprehensive Cancer Center, Helsinki, Finland

Introduction
Systemic radionuclide treatments are usually administered using fixed activities. We need better knowledge about effective absorbed doses (Gy) in normal and tumor tissue. We modelled prostate-specific antigen (PSA) responses of patients receiving Lu-177-PSMA-617/I&T ([177Lu]PSMA) for metastatic castration-resistant prostate cancer (mCRPC), combining it with kidney dosimetry results to test the optimization concept.

Materials and Methods
Patients (n=91) with mCRPC received four 6-8 GBq administrations of [177Lu]PSMA at 8-week intervals. PSA was recorded before each cycle and up to 6 months after treatment. The mean kidney dose was determined after each cycle from 1-2 SPECT-CT images, with a cumulative tolerance limit of 28 Gy for the whole course. We developed a radiobiological model for tumor response (PSA as a surrogate), considering the PSA response of an individual cycle and tumor repopulation rate. This was combined with the kidney doses to maximize the probability of response without complications = TCP(1-NTCP), with conditions TCP = probability that PSA<0.2 ng/ml (as a surrogate for complete response, CR) and NTCP = probability that cumulative mean kidney dose ≤28 Gy, or ≤40 Gy. This was repeated after each [177Lu]PSMA dose to increase prediction accuracy and avoid overdosing.

Results
Modelling PSA<0.2 ng/ml as a CR could be achieved with 29/91 (32%) patients if the given activities were increased to 28 Gy mean kidney dose in four cycles. It requires the activity increase from the start value in the following cycles based on PSA response and kidney dosimetry data on the earlier administrations. If the kidney tolerance level were 40 Gy, 46/91 (51%) patients would achieve CR.

Conclusions
For a large proportion of patients, treatment could have been intensified within a safe therapeutic window for kidney complications. Verifying these results in a prospective clinical trial, with modelling of bone marrow toxicity, should be considered.

Poster discussion group 5: Imaging

Chairs: Anne Vestergaard, Mikko Tenhunen

70. Anne Bisgaard, Odense, Denmark

Longitudinal DWI for response assessment in patients with rectal cancer treated on MRI-linac

Bisgaard, A (a,b), Kensen, CM (c), Betgen, A (c), Zijlema, S (c), Tanaka, MD (c), Marijnen, CAM (c), Mahmood, F (a,b), van der Heide, UA (c), van Houdt, PJ (c)

a: Laboratory of Radiation Physics, Department of Oncology, Odense University Hospital, Odense, Denmark b: Department of Clinical Research, Odense University Hospital, Odense, Denmark c: Department of Radiation Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands

Introduction
The apparent diffusion coefficient (ADC) derived from diffusion-weighted magnetic resonance imaging (DWI) is a potential biomarker for radiotherapy (RT) response. The aim of this study was to investigate if ADC obtained on a 1.5 T MRI-linac changes during short-course RT for patients with rectal cancer.

Materials and methods
This study included 24 patients with rectal cancer treated with 5x5 Gy on a 1.5 T MRI-linac (Unity, Elekta, Stockholm, Sweden). T2-weighted (T2W) MRI and DWI scans with b-values 0, 80, 150 and 500 s/mm2 were acquired at each fraction before irradiation. All images were visually inspected for artifacts. The gross tumour volume (GTV) was delineated on T2W scans and propagated to DWI and ADC maps using rigid registration. If necessary, the GTV was adjusted to match the tumour shape on DWI. ADC maps were calculated using b-values of 150, 500 s/mm2 using in-house software. To estimate the rectum ADC repeatability, the (un-irradiated) prostate was delineated on scans from fraction 1 and propagated to fraction 2 for all male patients (17), as no ADC change in healthy prostate is expected during the treatment. The repeatability coefficient (%RC) was calculated as 2.77 times the within subject coefficient of variation.

Results
The median [range] change (%) in the median ADC within the GTV relative to fraction 1 was 5.1 [-9.7, 31.6], 7.2 [-3.0, 33.8], 11.8 [-11.9, 33.8] and 9.7 [1.6, 37.1], for fraction 2, 3, 4 and 5, respectively. The estimated ADC %RC was 6.8. Some patients showed large ADC fluctuations between fractions, which may be explained as sensitivity to delineation.

Conclusion
ADC changes during RT were larger than the estimated repeatability, indicating that the observed ADC changes reflect biological changes induced by RT. However, the true repeatability coefficient of the tumour may be larger, due to delineation uncertainties. The ADC changes differed between the patients, potentially reflecting different responses to RT.

71. Anne Vestergaard, Aarhus, Denmark

Image changes after proton therapy of low and high grade gliomas

Vestergaard A, Kallehauge JF, Muhic A, Carlsen JF, Dahlrot R, Lukacova S, Haslund CA, Worawongsakul R, Høyer M

1 Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, 2 Department of Oncology, Rigshospitalet, Copenhagen, Denmark, 3 Department of Radiology, Rigshospitalet, Copenhagen, Denmark, 4 Department of Oncology, Odense University Hospital, Odense, Denmark, 5 Institute of Clinical Research, University of Southern Denmark, Odense, Denmark, 6 Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, 7 Department of Oncology, Aalborg University Hospital, Aalborg, Denmark, 8 Department of Diagnostic and Therapeutic Radiology, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Introduction
Contrast enhanced brain lesions on T1 MRI-scans have previously been reported after proton therapy of brain tumours. It has been suggested that the incidence of image changes (IC) is associated with high prescribed dose and with proximity to the periventricular zone. This study seeks to confirm these findings.

Materials and Methods
91 patients with low and high grade gliomas treated with proton therapy at DCPT from January 2019 to December 2021 were included (median age 41.3 and IQR 32.1 to 50.6 years). Prescribed dose was 50.4 to 60 GyRBE. All patients were treated with 3 beams using Pencil Beam Scanning and multi field optimization. Periventricular zone was delineated on treatment planning MRI-scans, for all patients. Follow-up MR-scans were acquired in the referring region. Patients with contrast enhanced lesions outside the GTV on MR-scans were registered and the follow-up scans with first sign of IC were used for the analysis. When a biopsy was possible it was used to distinguish between tumour progression and necrotic tissue. Monte Carlo calculations (Perl, Shin et al. 2012) of dose and LET were performed for all treatment plans. McNarama model was used to calculate variable RBE (RBEvar). The groups with and without IC were compared using Wilcoxon Rank-Sum test for D5cc for brain and periventricular zone for constant and variable RBE ($p<0.05$).

Results
13 patients (14%) had ICs on the follow up scans. 5 of the 13 patients had symptoms. The incidence of IC in the high dose (≥ 54 GyRBE prescribed) was similar to the low dose group (<54 GyRBE). The median D5ccRBEvar for the brain were higher in the IC group compared to the no IC group, but the difference was not statistical significant. No difference was seen using D5cc for constant RBE.

Conclusion
The incidence of IC was comparable to recent studies. In this preliminary study we could not confirm the correlation to high prescribed dose nor to high dose in the periventricular zone.

72. Kim Hochreuter, Aarhus, Denmark
Presented by Jesper Folsted Kallehauge, Aarhus, Denmark

National Quality Assurance of Quantitative Diffusion Tensor MR Imaging in Patients with Glioblastoma Multiforme

Hochreuter K.M(1,2), Jespersen S(3,4), Hansen A.E(10,11), Hansen R.H(9), Mahmood F(8), Hansen C.R(8), Arp D.T(7), Nielsen M.S(7), Muhic A(9), Dahlrot R(5,8), Guldberg T.L(7), Lukacova S(2,6), Kallehauge J.F(1,2)

(1) DCPT, AUH, Aarhus, Denmark (2) Dept. of Clin. Med., AU, Aarhus, Denmark (3) CFIN, Dept. of Clin. Med., AU, Aarhus, Denmark (4) Dept. of Physics and Astronomy, AU, Aarhus, Denmark (5) Dept. of Clin. Research, SDU, Odense, Denmark (6) Dept. of Onc., AUH, Aarhus, Denmark (7) Dept. of Onc., AAUH, Aalborg, Denmark (8) Dept. of Onc., OUH, Odense, Denmark (9) Dept. of Onc., RH, Copenhagen, Denmark (10) Dept. of Diag. Rad., RH, Copenhagen, Denmark (11) Dept. of Clin. Med., KU, Copenhagen, Denmark

Introduction
Diffusion Tensor Imaging (DTI) is an MRI technique that can be used to probe white matter (WM) tracts in the brain. A national study seeks to investigate the hypothesis that glioblastoma multiforme(GBM) spread primarily follows the WM tracts. The prospective cohort includes DTI as part of standard imaging during the therapy scan. This study aimed to evaluate the quality and the comparability of DTI sequences performed on MRI-scanners with different field strengths and from different vendors.

Materials and method
In total 4 centers were included with scanners of field strength 1.5T and 3T, from 2 different vendors. In each center the DTI sequence intended for clinical use was optimized on a healthy subject. A Quantitative Imaging Biomarker Alliance diffusion phantom was scanned using a specific benchmark sequence and subsequently with the DTI sequence for clinical use. Both benchmark and clinical scans were repeated four times on the phantom to assess repeatability.

The measured Mean Diffusivity (MD) in the phantom was calculated by averaging voxel values within vials with known diffusion values. In the clinically relevant vials, we calculated the difference between measured and phantom-specific reference values (bias) and an estimate of short-term repeatability using a within-subject coefficient of variation (wCV). This was done for both the benchmark and clinical sequence.

Results
For the benchmark sequences, the median(range) bias in MD across all centers was 2.2x10-6 mm2/s (-19.1–39.6x10-6 mm2/s), and the measured MD had a median(range) wCV of 4.2%(2.4–6.3%).
The results for the clinical sequence were median(range) bias of 4.3x10-6 mm2/s (-104.1–31.3x10-6 mm2/s) and median(range) wCV was 5.8%(5.3 – 7.3%).

Conclusion
The DTI sequences in each center produced consistent results across varying field strengths and vendors. Based on the quality assurance protocol, each scanner has been approved for patient inclusion in the investigation of GBM growth patterns.

73. Laura Toussaint, Aarhus, Denmark

A framework for quantifying longitudinal MRI changes after pediatric brain irradiation

Laura Toussaint (1), Simon Eskildsen (2), Oscar Casares-Magaz (1), Yasmin Lassen-Ramshad (1), Louise Tram Henriksen (3), Ludvig Muren (1)

(1) Danish Centre for Particle Therapy, Aarhus, Denmark. (2) Center of Functionally Integrative Neuroscience, Aarhus University, Aarhus, Denmark. (3) Department of Pediatrics, Aarhus University Hospital, Aarhus, Denmark.

Introduction
Systematic brain magnetic resonance imaging (MRI) at follow-up after radiotherapy (RT) allows for longitudinal analysis of neuroanatomical changes. However, assessing RT-related brain changes in pediatric patients is challenged by their ongoing normal growth. This study explored a framework to identify longitudinal changes in MRIs of pediatric brain tumor survivors.

Materials and methods
The framework was explored on longitudinal MRI series (median of eight non-contrast T1 scans per patient) from seven pediatric brain tumor patients previously treated with RT. After pre-processing, a subject-specific template was generated by iteratively aligning all MRIs in a template space, providing a common voxel-space to all time-points. RT data (i.e. CT, dose and masks) were registered to the subject-specific template space. Voxel-based morphometry was used to classify all voxels as white matter (WM), gray matter (GM) or cerebrospinal fluid. The cerebral lobes and 45 regions of interest from an established atlas were automatically segmented. The hippocampus was segmented by patch-based method. The above-mentioned features allow for longitudinal assessment at a structure-specific level of volumetric and cortical GM thickness changes, as well as RT dose metrics.

Results
The median volume of WM at baseline was 253.4 cm3 vs. 246.2 cm3 after three years, with a median WM dose of 11.2 Gy. Of the four lobes, the occipital lobe received the highest Dmean (median left/right of 17.6/20.9 Gy). Patch-based hippocampus contours were in good agreement with the clinical contours dose-wise, with a median Dmean 26.2 vs. 27.6 Gy for the left hippocampus.

Conclusion
We described the use of an automatic segmentation and classification framework on longitudinal MRIs from pediatric brain tumor patients. Applied to a large cohort of pediatric brain tumor survivors, this framework will help untangling the relations between delivered RT dose and neuroanatomical changes.

74. Marte Kåstad Høiskar, Trondheim, Norway

Quantitative dynamic contrast-enhanced MRI in head and neck cancer: a systematic comparison of different modelling approaches

Høiskar MK, Sæther O, Alsaker MD, Redalen KR, Winter RM

Department of Physics, Norwegian University of Science and Technology, Trondheim, Norway
Department of Radiology and Nuclear Medicine, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway
Cancer Clinic, St. Olavs hospital, Trondheim University Hospital, Trondheim, Norway

Introduction
Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a promising method for describing the tumour microvasculature and has the potential to become a prognostic tool for head and neck cancer (HNC) treatment. Three pharmacokinetic models used in quantitative analysis of DCE-MRI are the Tofts model (TM), the extended Tofts model (ETM) and the Brix model (BM). The TM and ETM require an arterial input function (AIF), which can be obtained for each patient individually, or from a collection of patients (population AIF). We investigated the accuracy and robustness of the population AIF, the correlation between parameters from different models and their association to T stage.

Materials and methods
DCE-MRI was acquired in 56 HNC patients, with a total of 45 malignant lymph nodes and 38 primary tumours. Population AIFs with six different approaches were calculated. DCE-MRI was analysed with the TM using both the population AIFs and the individual AIF, the ETM with the individual AIF, and the BM. In addition, model-free areas under the curve (AUCs) were calculated. The resulting model parameters were compared using the Pearson correlation coefficient.

Results
The population AIF was robust but differed from the individual AIFs. There was significant correlation between Ktrans and ve, and Ktrans and Kep from both TM and ETM over all lesions. A from BM and AUC60 correlated for lymph nodes. Kep from BM correlated with A from BM and Ktrans and Kep from both TM and ETM for primary tumours. All the parameters decreased with increasing T stage. This was most prominent for HPV negative patients.

Conclusion
Individual AIF is preferred for accurate pharmacokinetic modeling of DCE MRI. There were few correlations between parameters from different models and the correlations varied for primary tumors and lymph nodes. The consistent correlation between the parameters and T stage indicate the potential clinical value of quantitative DCE MRI.

75. Minea Jokivuolle, Odense, Denmark

Mapping tumor microstructure with time dependent diffusion MRI on a clinical 1.5 T MRI system

Jokivuolle MM (1,2), Lundell H (3), Madsen KH (3,4), Mahmood F (1,2)

(1) Laboratory of Radiation Physics, Dept. of Oncology, Odense University Hospital, Odense, Denmark. (2) Dept. of Clinical Research, University of Southern Denmark, Odense, Denmark. (3) Centre for Functional and Diagnostic Imaging and Research, Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital Amager and Hvidovre, Hvidovre, Denmark. (4) Dept. of Applied Mathematics and Computer Science, Technical University of Denmark, Copenhagen, Denmark

Introduction
Non-invasive methods for characterization of tumor microstructure are required to improve radiotherapy individualization for example in glioblastoma, which is notorious for its heterogeneity and poor prognosis. Time dependent diffusion MRI (TDD-MRI) provides quantitative estimates of tissue microstructure, but has been investigated mainly on pre-clinical systems. Here, we introduce a TDD-MRI acquisition, usable for imaging glioblastoma, on a clinical 1.5 T MR sim, and demonstrate its ability to estimate clinically relevant cell sizes using asparagus as a model tissue.

Materials & Methods
The TDD-MRI acquisition consisted of two scans acquired with differing diffusion times (26 and 44 ms), but with the same b-values (0, 1250, 2500 s/mm²). The total scan time was 12:24 (mm:ss). Asparagus stems (N = 16), submerged in water, were scanned on a 1.5 T MR sim (Ingenia, Philips) with 45 mT/m gradient strength and 50 T/m/s slew rate. For validation, Monte Carlo simulations of MRI signal were performed for varying cell radii. Analytical model for diffusion in cylinders [1] was fitted to the data to estimate cell radius and diffusivity.

Results
The measured diffusion signals showed a clear time dependence with an 8.0 %-points signal increase as a function of diffusion time, in agreement with the simulations. The analytical model estimated a cell radius of 19.3 µm and diffusivity of 1.34*10^-3 mm²/s. The difference to microscopy reference (18.52 µm in central asparagus) was ~4%.

Conclusions
We demonstrated the feasibility of TDD-MRI acquisition on a clinical 1.5 T MR sim with clinically relevant cell sizes and a clinically feasible scan time. The results show promise for differentiation of tissues by cell size, which could help in characterizing tumor sub-regions for example in glioblastoma, and thus allow improved targeting of radiation therapy.

[1] van Gelderen et al., J. Magn. Reson., Series B 103.3:255, 1994

76. Moritz Rabe, Munich, Germany

Accuracy and reproducibility of brain diffusion-weighted imaging at a 0.35 T MR-linac in volunteers

Rabe M [1], Dietrich O [2], Forbrig R [3], Niyazi M [1], Belka C [1,4], Corradini S [1], Landry G [1], and Kurz C [1]

[1] Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany. [2] Department of Radiology, University Hospital, LMU Munich, Munich, Germany. [3] Department of Neuroradiology, University Hospital, LMU Munich, Munich, Germany. [4] German Cancer Consortium (DKTK), Partner Site Munich, Munich, Germany

Introduction
Diffusion-weighted imaging (DWI) at MR-linacs could enable early treatment response assessment and biology-guided adaptive radiotherapy for brain cancer patients. We evaluated the accuracy and reproducibility of apparent diffusion coefficients (ADCs) in volunteers at a 0.35 T MR-linac.

Materials and methods
Six volunteers (age: 23-32 y) were imaged with an echo planar imaging DWI sequence with five b-values (0-800 mm2/s) before and after an outside-scanner break. Two sequence variants (acquisition times: 6.5 min) were compared: a high-resolution variant (HR; voxel size: 3×3×5 mm3), and a high-signal variant (HS; 3.5×3.5×7 mm3). The mean ADC values within the cerebrospinal fluid (CSF) and four regions-of-interest (ROIs) in homogeneous brain tissue at different locations were measured and compared to literature values to assess the ADC accuracy. The absolute relative deviation of the values before and after the break were computed to quantify the ADC reproducibility. The ADC-to-noise ratio (ADCNR) was estimated by the mean/σ ADC values for each brain tissue ROI.

Results
Averaged over all volunteers, the ADC values (in 10-3 mm2/s) for the CSF and brain tissue ROIs were 2.36, 0.53, 0.52, 0.66, and 0.74 for the HR, and 3.07, 0.68, 0.67, 0.81, and 0.80 for the HS variant, respectively. Compared to literature values (CSF: 2.73-3.02; white/gray matter: 0.69-0.91), the values were similar for the HS variant, but underestimated for the HR variant. The mean ADC deviations before and after the break averaged over all ROIs was 2.3% (range: 1.3-3.3%) for the HR variant and 2.8% (2.0-4.2%) for the HS variant. The average ADCNR was 61% higher for the HS (8.7) than for the HR (5.4) variant.

Conclusions
High ADC reproducibility was demonstrated with both variants. The HR variant was affected by high noise levels, leading to lower ADC accuracy and ADCNR than the HS variant. Analysis of additional volunteer cases and a diffusion phantom will be presented at the conference.

77. Nadine Vatterodt, Aarhus, Denmark

Cross-platform assessment of CBCT-based dose evaluations for head and neck cancer proton therapy

Vatterodt N[1,2], Elstrøm UV[2], Korreman SS[1,2]

[1]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark [2]Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Purpose
We investigated if CBCT-based dose evaluation is suitable to replace prescheduled repeat CTs(reCTs) to assess need for replanning with on-demand CT acquisition in head and neck cancer proton therapy. We performed a cross-platform and cross-methodology investigation of three commercially available synthetic CTs(synCTs) compared to evaluation on reCT.

Methods
The study included the first reCT and same-day CBCT of 20 patients with oropharyngeal cancer treated at our proton facility in 2020-2022. Structure sets transferred from the planning CT(pCT) in Eclipse(Varian Medical Systems) were used for reCTs. Artificial CTs were manually created with Velocity AI(Varian Medical Systems) by deforming the pCT to the CBCT(stitched with pCT). Within RayStation 12A R(RaySearch Labs) virtual CTs and corrected CBCTs were created fully automized, structures were mapped from the pCT to all synCTs and clinical treatment plans were recalculated on all images(MC dose engine). For each patient, images were compared by structural similarity index(SSIM). Absolute differences in D99% for CTV1 and dose to OAR were quantified. We report medians over all patients and methods with (min,max)-range for synCT-reCT and synCT-synCT comparisons.

Results
Highest SSIMs were found between synCTs with a median of 0.978(0.931,0.991) while synCT-reCT comparisons scored 0.955(0.901,0,976). The D99% difference for CTV1 was 0.09Gy(0.01Gy,0.30Gy) vs. 0.11Gy(0.00Gy,1.24Gy) for synCT-synCT vs. synCT-reCT comparisons, with even larger deviations between reCT and synCTs for OAR, e.g. for D0.03cc to spinal cord of 0.39Gy(0.05Gy,2.91Gy) vs. 1.38Gy(0.07Gy,8.35Gy).

Conclusion
We found better agreement between all synCTs than between synCTs and reCT, despite use of various platforms and methodologies. This is likely due to residual anatomical variations between CBCT and reCT. Hence, reCTs may not reflect the treatment situation adequately and synCTs be suited for triggering replanning with on-demand CT scans.

Poster discussion group 6: Proton therapy A

Chairs: Armin Lühr, Michael Horsman

78. Amit Ben Antony Bennan, Heidelberg, Germany

Impact of variable RBE models on jointly optimized (JO) photon – proton combined treatment plans

Bennan ABA, Wahl N

Department of Medical Physics in Radiation Oncology, German Cancer Research Center, Heidelberg, Germany; Department of Medical Physics in Radiation Oncology, German Cancer Research Center, Heidelberg, Germany

Combined radiotherapy treatments must take advantage of distinct physical and radiobiological characteristics of photons and protons by simultaneously optimizing both modalities, as opposed to conventional separately optimized combined treatments (REF plans). We optimize intensities of both modalities to achieve prescribed cumulative biological effects (LQ model) over all predefined unimodal fractions. Jointly optimized (JO) treatments exhibit 2 mechanisms: (1) flexibility from depth-dose properties and beam angles of both modalities (2) selecting dose per fraction in sub-volumes and protect healthy tissue through fractionation. Biological objectives are subject to uncertainty from underlying RBE models. We investigate impact of variable RBE models of protons on jointly optimized SBRT photon - proton plan.

Plans are generated for spinal metastasis patient case where the spinal cord is completely surrounded by CTV (prescribed 35Gy in 5 fractions). Dose objectives are translated to biological effect objectives using target α/β=0.5/0.05 and healthy tissue α/β=0.1/0.05. We compare REF plans, JO plans using the constant RBE model, Mcnamara model (MCN). Experiment: (1) recalculate REF const RBE plans using MCN, (2) recalculate JO const RBE plan using MCN.

Overall, the JO plans show 5-6% improvement in conformity index to REF plans. For similar target coverage(EQD7 to 5% volume), consider the spinal cord: (1) compared to REF-constRBE, JO-constRBE plans reduce by 2.2Gy. (2) Recalculation of REF-constRBE plans with the MCN leads to a 0.2Gy increase.(3) Recalculating JO-constRBE with MCN shows a similar effect. Compared to JO-constRBE, JO-MCN plan shows a 0.1Gy further reduction in dose as more photon fractions used to irradiate regions around spinal cord to avoid high LET.

Considering end of range toxicities in protons, JO plans potentially avoid this using photons to supplement dose in OAR-adjacent target subvolumes while still reducing integral dose to healthy tissue.

79. Evangelia Choulilitsa, Villigen, Switzerland

Dosimetric benefit of Online Daily Adaptive Proton therapy for Head and Neck cancer patients

Choulilitsa E 1, 2, Weber DC 1, 3, 4, Lomax AJ 1, 2, Albertini F 1

1 Center for Proton Therapy, Paul Scherrer Institute, Switzerland, 2 Department of Physics, ETH Zurich, Switzerland, 3Department of Radiation Oncology, University Hospital Zurich, Switzerland, 4 Department of Radiation Oncology, University Hospital Bern, Switzerland.

Introduction
This study aimed to evaluate the dosimetric benefit of daily online adaptive proton therapy for head and neck (H&N) cancer patients.

Materials & Methods
5 H&N patients with daily cone beam CTs (CBCT), treated with proton therapy, were included in this retrospective study. Intensity Modulated Proton Therapy (IMPT) plans were robustly optimized for range uncertainties on a 2mm expansion of the targets (CTVs) with a simultaneous integrated boost (SIB) approach following the clinical prescription. Synthetic CTs (synCTs) were created by deforming the planning CT to the anatomy of every daily CBCT. Targets were rigidly propagated, and OARs were deformed on each synCTs. IMPT plans were then recalculated (not-adapted) and reoptimized (adapted) on the daily synCTs using the online adaptive scheme used at PSI. That is, the beamlet position and fluences were fully re-optimized every day, while optimization constraints and beam configuration were maintained as per the initial treatment plan. The target coverage and dose to organs at risk (OARs) were evaluated on each daily fraction for the adapated and not-adapted approach.

Results
The target coverage of the daily adapted plans was always equal or slightly higher than the prescribed dose, with an average increase of 0.9% in the dose delivered to 98% of the CTVs (CTV D98%). In contrast, the not-adapted plans resulted in target underdosage for 75% of the fractions due to the day-to-day anatomical and set-up variations, with an average decrease of more than 5% in CTV D98%. Interestingly, while daily dose variations were observed for some OARs, an overall similar sparing of OARs was observed across all patients.

Conclusions
The analysis indicates that an online daily adapted proton therapy workflow is an effective approach to ensure target coverage for H&N patients, even in the presence of longitudinal anatomical changes.

80. Fardous Reaz, Aarhus, Denmark

Design and commissioning of a proton minibeam collimator at the Danish Center for Proton Therapy for experimental studies on Spatially Fractionated Radiotherapy - current status and need for standardized reporting

Reaz F[1,2], Traneus E[3], Bassler N[1,2]

[1] Danish Centre for Particle Therapy (DCPT), Aarhus, Denmark, [2] Department of Clinical Medicine, Aarhus, Denmark, [3] RaySearch Laboratories, Stockholm, Sweden

Proton minibeam radiotherapy (pMBRT) has the potential to augment the therapeutic ratio. A metal collimator with suitable apertures can produce a pMBRT profile. An optimized collimator is indispensable to validate and quantify the biological efficacy of pMBRT. At DCPT, we designed a working collimator for pre-clinical studies. However, the quantification and reporting of pMBRT fields are inadequately defined; we aim to precisely define some of the critical parameters involved in pMBRT.

We built a pMBRT collimator system based on Geant4 Monte Carlo simulations. Parameters influencing the dose profile of pMBRT, namely thickness, center-to-center distance (CTC), and throughput, were evaluated using a realistic DCPT beamline-specific treatment plan (using Eclipse TPS) to be used for planned in-vivo studies. The optimization procedure required achieving a homogeneous dose in the planning target volume (PTV), alongside a sharp dose contrast at the normal tissue prior to PTV.

We present the Grid Factor (GF) as a robust metric to characterize the biological effects of pMBRT. We use the valley-to-peak dose ratio (VPDR) to overcome the mathematical instability of PVDR at zero valley dose, while also providing a straightforward biological interpretation of SFRT's efficacy. We observed the CTC is dependent on both the lateral and longitudinal position and may differ from the geometric CTC of the collimator apertures. Moreover, the actual throughput of the collimator may differ from the geometric throughput. The scoring voxel size influences the VPDR evaluation. To ensure a reliable outcome with reasonable uncertainty, we recommend a voxel dimension between 20% to 40% of the size of the smallest structures to be resolved.

Establishing precise pMBRT parameters is crucial for developing a uniform reporting format. Such standardization would facilitate convenient comparison among disparate outcomes derived from a multitude of SFRT investigations.

81. Jacob Johansen, Aarhus, Denmark

Assessing the Effectiveness and Toxicity of Boron in Proton Therapy: Monte Carlo Simulations and In Vitro Clonogenic Assay

Jacobsen VL1,2, Johansen JG2, Sørensen BS3, Fynbo HOU4, Sitarz M2, Frederiksen A3, Bassler B1,2, Bønnelykke J5, Nielsen CS5

1 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. 2 Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark. 3 Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark. 4 Department of Physics and Astronomy, Aarhus University, Aarhus, Denmark. 5 Department of Chemistry, Aarhus University, Aarhus, Denmark.

Proton boron capture and proton boron neutron capture therapies have been proposed to increase the relative biological effectiveness (RBE) of proton therapy. However, their effectiveness and potential toxicity remain unclear. This study aimed to evaluate the effectiveness of boron in increasing RBE using Monte Carlo simulations and in vitro clonogenic assays.

Results from Monte Carlo simulations, using TOPAS and SHIELD-HIT12A, showed that the n + 10B capture reaction produced a factor of 177 +/-24 more high-LET particles than the p + 11B reaction for clinical relevant phantom and field sizes. The fluence of low energy neutrons required for the 10B reaction varied greatly depending on phantom and proton field sizes. The fluence of low energy neutrons (< 1 keV) can vary up to two orders of magnitude, confirmed by both MC simulations. Previous studies may have underestimated the neutron capture reaction channel due to non-clinical relevant conditions and problematic choices of physics packages for MC simulations.

In the in vitro experiments, no indication of an increased RBE in the presence of sodium borocaptate (BSH) was observed, but an apparent toxicity of the BSH affected colony growth and plating efficiency. Chemical analysis revealed that the procured BSH was contaminated with toxic oxidation products despite being stored in protective gas. A photon (6 MV linac) reference experiment further supported BSH toxicity but not radiosensitization.

Overall, the effectiveness of boron in increasing RBE may come from the n+10B reaction rather than the p+11B reaction for clinical relevant phantom and field sizes when natural boron is used. However, caution is warranted in using BSH due to its apparent toxicity and potential contamination.

82. Michael Horsman, Aarhus, Denmark

Using immunotherapy to enhance the response of a C3H mammary carcinoma to proton radiation

Nielsen S (1), Sitarz MK (2), Sinha PM (1), Folefac CA (1), Høyer M (2), Sørensen BS (2), Horsman MR (1)

(1) Experimental Clinical Oncology-Dept. Oncology and (2) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Introduction
The aim of this study was to investigate the potential anti-tumor effect of combining immunotherapy and protons.

Methods
A C3H mammary carcinoma, implanted in the right rear foot of male CDF1 mice, was used when tumors reached 200 mm3. Proton radiation was delivered to tumors only using an 83-107MeV pencil scanning proton beam in the center of a 3 cm spread out Bragg peak. Following irradiation (day 0), mice were intraperitoneal injected with either PBS, anti-CTLA-4, anti-PD-1, or anti-PD-L1 antibodies (10 mg/kg on days 1, 4, 7, and 10). Endpoints were tumor growth time (TGT3; time for tumors to grow to 3 times treatment volume) or local tumor control (percent tumor control at 90 days). A Student's T-test (tumor growth) or a Chi-squared test (tumor control) were used for statistical comparisons; significance level of $p<0.05$ for both.

Results
Mean (+ 1 S.E.) TGT3 for control tumors was 4.8 days (+ 0.1). No significant effect was seen with any checkpoint inhibitor; TGT3 values being 5.0 (+ 0.2), 5.2 (+ 0.3), and 5.2 (+ 0.2) days, for anti-CTLA-4, anti-PD-1, and anti-PD-L1, respectively. TGT3 linearly increased with increasing radiation doses (5-20 Gy), reaching 17.2 days (+ 0.7) with 20 Gy. Anti-CTLA-4 did not affect radiation doses up to 15 Gy, but significantly enhanced 20 Gy; TGT3 being 23.0 days (+ 1.3). Higher radiation doses were investigated by producing a tumor control dose-response curve (35 to 60 Gy). Following logit analysis of this curve, the TCD50 value (radiation dose causing 50% tumor control) with 95% confidence intervals, was 48 Gy (44-53) for radiation only. Anti-CTLA-4 significantly decreased this to 43 Gy (38-49), but anti-PD-1 or anti-PD-L1 had no significant effect; the respective TCD50 values being 48 Gy (44-53) and 49 Gy (41-59).

Conclusion
Immunotherapy enhanced the response of this C3H mammary carcinoma to proton irradiation. However, this enhancement depended on both the radiation dose and the checkpoint inhibitor.

83. Niels Bassler, Aarhus, Denmark

Variable Relative Biological Effectiveness in proton therapy is better described with experimentally obtained Qeff than LET

Niels Bassler1,2, Anne Vestergaard2, Liliana Stolarczyk2, Jeppe Brage Christensen3

1 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark 2 Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark 3 Department of Radiation Safety and Security, Paul Scherrer Institute, Villigen PSI, Switzerland

It is widely acknowledged that the RBE is variable and related to the linear energy transfer (LET) of the charged particles, even if clinical protocols foresee a fixed RBE of 1.1. Predictive RBE models are typically relying on dose-averaged LET as a radiation quality specifier. Advanced treatment planning may take the variable RBE into account, to further reduce tissue toxicity, e.g. by LET-painting to shift high-LET regions away from the distal edge of the incoming beam. To translate LET mitigation strategies to clinical practice, a way to verify the LET distribution of a plan is desirable. Alas, dose averaged LET is difficult to obtain experimentally and associated with large uncertainties. We show the alternative radiation quality Qeff can be measured with optically stimulated luminescence detectors (OSLDs) and can be linked to RBE.

Point-like OSLDs based on Al2O3:C were irradiated at DCPT in proton beams, and read-out with a pulsed stimulation technique to separate the UV and blue OSL emissions, whose ratio correlates with the radiation quality. The OSLDs were analyzed for estimation of LETd, LETt and Qeff including all secondaries, compared to MC simulations carried out with TOPAS and SHIELD-HIT12A.

For mono-energetic protons and 4He ions spanning the LETt range 0.4-6.7 keV/um, the standard deviation of the measured Qeff values is 4% in contrast to the 12% for LETt and 14% for LETd. In reference fields irradiated at DCPT with mono energetic protons the measured LETt and Qeff are within 5%. In a 10 cm SOBP, LETt is 20% off, whereas Qeff is only 15% off. Finally, at distal edge Qeff was within 5%, where LETt was 15-25% off.

Qeff is a quantity which can be measured by OSLDs, and can be determined with less uncertainty in mixed radiation fields than LETt. Qeff is also known to perform significantly better than LETt for estimating the RBE in proton fields, which makes Qeff an interesting candidate for patient specific validation of LET-painted radiation fields.

84. Peter Lægdsmand, Aarhus, Denmark

Relative Biological Effectiveness in Pencil Beam Scanning Proton Therapy of Pediatric Brain Tumors Near Brainstem

Lægdsmand P, Vestergaard A, Muren L, Lassen-Ramshad Y, Toussaint L

Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Introduction
The uncertainties associated with variation of Linear Energy Transfer (LET) and Relative Biological Effectiveness (RBE) of proton beams are a challenge for evaluating treatment plans for pediatric brain tumors — especially when the tumor is near critical organs such as the brainstem. We evaluated the distributions of LET and RBE in the brainstem for patients treated with pencil beam scanning (PBS) proton therapy at our institution.

Methods
A cohort of 15 patients was selected from 47 pediatric (younger than 18 years) brain tumor patients treated with PBS with selection criteria: Focal brain irradiation and maximum dose to the brainstem above 50Gy. All plans used at least 3 fields spaced by at least 30 degrees to mitigate high LET. The total dose prescription was 50.4Gy (n=6), 54Gy (n=7) or 59.4Gy (n=2) in 1.8Gy fractions. Dose-averaged LET (LETd) was calculated for all plans by Monte Carlo simulations in TOPAS v.3.5. Variable RBE was calculated using the McNamara model with an α/β of 2Gy. Brainstem D10% was calculated using both constant RBE 1.1 and the variable RBE.

Results
The mean (confidence interval, CI) brainstem D10% using the McNamara model in the cohort was 54.6Gy (53.0Gy;56.2Gy). The mean (CI) increase in brainstem D10% compared to constant RBE was 5.9% (4.5%;7.3%). McNamara D10% exceeded 58Gy for three patients: two ependymoma patients with a boost plan (59.4Gy prescription), and one ATRT patient (54Gy prescription). All three were younger than 4 years at treatment (compared to a median age in the cohort of 7.4 years).

Conclusion
Although RBE in the brainstem varies considerably between patients, brainstem D10% will increase significantly when evaluated with the McNamara model compared to a constant RBE, since the distal edge of treatment fields often end in the brainstem. RBE weighted dose may be particularly high for very young patients.

85. Villads Jacobsen, Aarhus, Denmark

Investigating Neutron Dose to Pregnant Patients Undergoing Proton Therapy: Validation of a MC Framework with H*(10) Measurements

Jacobsen VL, Bassler N, Søndergaard C, Jensen K, Lægdsmand P, Stolarczyk L

Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark

Radiotherapy is typically not a first choice when treating cancer in a pregnant patient due to radiation risk to the foetus. PBS proton radiotherapy may significantly reduce dose to the foetus when compared with photon radiotherapy, and potentially become a standard radiotherapy technique for pregnant patients. However, appropriate dosimetry protocols to measure and calculate foetal doses during radiotherapy are missing. This work aims to validate the MC framework dedicated for neutron H*(10) calculations during proton therapy for both the pregnant patient and foetus.

Neutron measurements were performed with a WENDI-II detector in various positions around a MP1 PTW water phantom. The phantom was irradiated from gantry 270 position with a 10x10x10 cm^3 SOBP. The isocenter was located at a depth of 10.25 cm.The detector was placed at three positions in the beam direction (50, 100 and 150 cm behind the phantom) and at three positions at a 90° angle (55, 75 cm from the phantom surface). The measurements were followed by Monte Carlo simulations, performed in TOPAS 3.9, in which both the experimental setup as well as the couch were simulated, to account for neutron scattering.

The Monte Carlo simulations were compared to neutron H*(10) measurements with a WENDI-II detector. For the 10 x 10 x 10 cm^3 SOBP plan for all investigated positions, the measured H*(10) range from 14 µSv/Gy (perpendicular to the beam direction, 75 cm from the phantom surface) to 0.19 mSv/Gy (50 cm behind the phantom in the beam direction) . The simulations were on average 30 % below the measured values. This may be attributed to the missing simulation of the room geometry and the energy response of the detector. The energy response of the detector is still under investigation. The work will be continued for the University of Florida (UF) anthropomorphic phantoms at different gestational stages and clinically realistic treatment plans (brain, breast, thyroid and craniospinal irradiations).

Poster discussion group 7: Proton therapy B

Chairs: Esben Worm, Eirik Malinen

86. Andreas Havsgård Handeland, Bergen, Norway

Robustness evaluation of linear energy transfer in proton therapy of paediatric posterior fossa tumours

Handeland AH (1, 2, 3), Lægdsmand PMT (3, 4), Toussaint LV (3, 4), Muren LP (3, 4), Lassen YA (3), Klitgaard R (3, 4), Henjum H (2), Ytre-Hauge KS (2), Tjelta J (1, 2), Lyngholm E (2), Stokkevåg CH (1, 2)

(1) Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway (2) Department of Physics and Technology, University of Bergen, Bergen, Norway (3) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark (4) Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

Introduction

The relative biological effectiveness (RBE) of protons varies with linear energy transfer (LET) motivating dedicated LET-optimised planning (LOP) in proton therapy. Robust optimisation planning (ROP) with range and setup uncertainties may benefit LOP since LET varies sharply around the dose fall-off. Hence, this work aimed to explore LOP and evaluate LET distribution robustness.

Materials and Methods

Three paediatric posterior fossa cases treated with proton therapy were re-planned in Raystation 11B (RaySearch Laboratories, Stockholm, Sweden), with prescription dose 54 Gy(RBE) over 30 fractions. We used three optimisation schemes: ROP, PTV-based LOP avoiding high brainstem (BS) dose-averaged LET (LETd) and dose; and PTV-based LOP with a 2 mm margin around the BS (denoted LOPM). For the ROP, a 2 mm universal spatial uncertainty and a 3.5% range uncertainty was used, and these were also used in the robust evaluation of all three plans. Dose to the CTV and BS, and the LETd to the BS with dose over 50 Gy(RBE), particularly the L1% (LETd to the 1% of voxels with the highest LETd), were assessed.

Results

The nominal L1% was 0.4 - 0.5 keV/µm lower with LOP than with ROP for all patients, and 0.1 - 0.8 keV/µm lower with LOPM than ROP. Minimum L1% values were within 2.6 - 4.3 keV/µm. Most LOP and LOPM scenarios had lower L1% than the ROP, with best and worst case differing by 0.6 - 1.2 keV/µm, 0.4 - 1.2 keV/µm and 0.4 - 0.8 keV/µm for the LOP, LOPM and ROP, respectively. Other LETd levels showed similar trends. Best and worst case scenario in CTV D98% and BS D1% differed at most by 1.0 Gy(RBE) for the ROP, while LOP and LOPM varied similarly and within 0.6 - 3.4 Gy(RBE). However, all scenarios had acceptable CTV-coverage (D98% ≥ 51.3 Gy(RBE)).

Conclusion

LOP reduced the BS LETd for the nominal case and most robustness scenarios. However, the lower LETd from LOP/LOPM reduced dose robustness. The use of a margin did not improve LETd robustness in the BS.

87. Anne Holm, Aarhus, Denmark

Does proton radiotherapy have an advantage in ipsilateral radiotherapy (RT) for neck metastases from unknown primary squamous cell carcinoma (CUP) in the primary and recurrent setting?

Holm AIS1, Elstrøm UV2, Nielsen SB3, Jensen K2

1: Department of Oncology, Aarhus University Hospital, Aarhus, Denmark, 2: Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, 3: Departments of Head and Neck Surgery & Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark

Background
CUP patients are often treated with RT of both sides of the neck and suspected primary site i.e. elective mucous membranes (EMM) of pharynx and larynx. The treatment is effective but toxic. New data suggest that treatment of the ipsilateral-neck-only without EMM is sufficient for many patients, but may include a risk of occurring primaries. The present study simulates the efficiency of photon versus proton therapy based on clinical primary cases and simulated recurrences. Results for ipsilateral targets are presented. Results for bilateral targets with EMM will be ready for the conference.

Materials and method
Twelve cases previously treated for CUP were selected. Ten had primary bilateral treatment and updated photon plans were generated. For each case, photon and proton plans were generated independently, targeting unilateral neck without EMM. Subsequently, reirradiation plans targeting a fictitious but possible tumour were generated. Arc therapy was used for photons, and 3-4 field IMPT for protons. Cumulated doses of the primary treatment plans and reirradiation plans for A) photon+photon, B) photon+proton and C) proton+proton, were compared on the volume (cm3) receiving 70Gy (V70) to 130Gy (10Gy increments) and V100Gy of the ipsilateral carotid artery.

Results
Changing guidelines to ipsilateral-no EMM will lead to a significant mean decrease in dysphagia grade 2 of 15% and xerostomia grade 3 of 4.0%. For unilateral targets little is gained with protons instead of photons, due to the already low toxicity. The cumulated reirradiation plans in scenarios A, B and C: V70 [142, 70, 51], V80 [66, 41, 33], V90 [32, 25, 22], and V100 [17, 16, 8]. For V100Gy of the ipsilateral carotid artery no differences were observed.

Conclusion
Not treating the EMM and contralateral neck will significantly reduce the toxicity. The cumulated high dose volumes can be minimised using protons for re-irradiation. However, the use of protons for primary treatment provides little benefit.

88. Camilla Hanquist Stokkevåg, Bergen, Norway
Presented by Andreas Handeland, Bergen, Norway

First application of an LET-inclusive NTCP model for brainstem necrosis following paediatric proton therapy in an independent cohort

Handeland AH (1, 2, 3), Lægdsmand PMT (3, 4), Toussaint LV (3, 4), Stokkevåg CH (1, 2), Lassen YA (3), Klitgaard R (3, 4), Henjum H (2), Ytre-Hauge KS (2), Indelicato D (5), Tjelta J (1, 2), Lyngholm E (2), Muren LP (3, 4)

1. Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway, 2. Department of Physics and Technology, University of Bergen, Bergen, Norway, 3. Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, 4. Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, 5. Department of Radiation Oncology, University of Florida, Jacksonville, Florida, USA

Introduction
Normal tissue complication probability (NTCP) models specific to proton therapy accounting for linear energy transfer (LET) in addition to dose may improve NTCP estimates in proton patients. The aim of this study was to assess the generalisability of an LET-inclusive model describing the risk of symptomatic brainstem necrosis following paediatric posterior fossa tumours by applying it in an independent patient cohort.

Materials and Methods
The NTCP model was used on 47 paediatric brain tumour patients treated with proton therapy at the Danish Centre for Particle Therapy. The previously developed model is based on a case-control study cohort of 28 patients selected from 954 paediatric brain tumour patients treated with proton therapy at the University of Florida Health Proton Therapy institute and estimates risk of symptomatic brainstem necrosis based on the L10% (D > 54 Gy(RBE)), i.e. the dose-averaged LET (LETd) to the 10% of voxels with the highest LETd, of the total brainstem with dose over 54 Gy(RBE). Dose and LETd-distributions were recalculated in TOPAS v.3.5 and L10% (D > 54 Gy(RBE)) values were calculated. The model is based on focally irradiated patients so craniospinal patients were excluded from the validation cohort.

Results
Ten focally irradiated patients received dose ≥ 54 Gy(RBE) to parts of the brainstem. The estimated risk ranged from 6-10% [95% confidence interval: 3%, 20%] with L10% (D > 54 Gy(RBE)) in the brainstem between 2.6 and 4.1 keV/µm. The remaining focally irradiated patients received less than 54 Gy(RBE) to the brainstem which would give lower risk than the previous patients but this is outside the range of the model.

Conclusion
An LET-inclusive NTCP model was applied to an independent cohort and estimated low but non-negligible risks of symptomatic brainstem necrosis following proton therapy for patients with high brainstem dose, while patients with low brainstem dose were considered at low risk of brainstem necrosis.

89. Esben Worm, Aarhus, Denmark

Motion variability and setup accuracy in CBCT-guided exhale-gated spot scanning proton therapy of hepatocellular carcinoma

Worm ES (1), Nankali S (2), Thomsen JB (2), Stick L (2), Høyer M (2), Weber B (1,2), Mortensen H (2), Poulsen PR (2)

(1) Department of Oncology and (2) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark.

Introduction
This study investigates (1) the motion variability between planning 4DCT (p4DCT) and treatment and (2) the accuracy of CBCT match to implanted fiducial markers in exhale gated proton therapy of liver cancer.

Methods
Five patients received exhale gated proton therapy (April-Nov 2022) with doses of 58-67.5 GyRBE in 15 fractions. The study includes the p4DCT and CBCTs from the first 1-5 fractions of each patient (20 CBCTs). A target iCTV was defined on the exhale phase of the 10-phase p4DCT as the union of the CTVs in the 5 phases closest to exhale, corresponding to ~50% duty cycle respiratory gating. Daily setup was based on free-breathing CBCT with manual match to the motion-blurred exhale position of 2-3 implanted markers. Retrospectively, the markers were segmented in each 2D CBCT-projection (~700 images per CBCT) and the marker centroid 3D motion trajectory during CBCT was estimated by a probability-based method. Motion variability was investigated by comparing the full motion range and motion range within the 50th percentile around exhale (corresponding to the iCTV expansion and gating window) during CBCTs and p4DCT. Online match accuracy was investigated by comparing the 95th percentile position along the marker trajectory during CBCT in each direction (defined as true exhale position) with the manual online marker match.

Results
The mean (±SD) difference between the full motion range during p4DCT and CBCTs was 1.2±1.1mm (LR), 8.9±3.2mm (CC) and 5.0±2.9mm (AP). Within the 50th percentile gating window the difference was 0.4±0.4 mm (LR), 0.5±1.4mm (CC) and 0.5±0.8mm (AP). The mean online marker match error was -0.3±0.6mm (LR), 0.6±1.1mm (CC) and -0.1±0.4mm (AP).

Conclusions
Respiratory gating effectively limits motion and motion variability and improves consistency between internal target volumes in 4DCTs and actual motion during treatment. Manual CBCT match to motion-blurred markers is prone to uncertainty but acceptable errors were observed.

90. Ivanka Sojat Tarp, Aarhus, Denmark

Clinical benefit of range uncertainty reduction in robust optimization for proton therapy

Tarp IS (1), Taasti VT (2), Jensen MF (1), Vestergaard A (1), Jensen K (1)

(1) Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark (2) Department of Radiation Oncology (MAASTRO), GROW - School for Oncology, Maastricht University Medical Centre+, Maastricht, The Netherlands

Introduction
The range uncertainty in proton therapy can lead to under-dosage of the target or the over-dosage of the organs at risk (OARs). One of the main causes of range uncertainty for proton treatment is the CT-based estimation of the stopping power ratio (SPR) relative to water. Robust optimization is applied to ensure target coverage in all error scenarios and account for setup and range uncertainties (RU), resulting in an expansion of the irradiated volume. This study investigates the dosimetric effect of reduction in RU for a diverse patient population and the level of RU that leads to a clinically relevant reduction of dose to OARs.

Materials and Methods
The study included treatment planning CT scans of 40 adult patients with brain (N=30), head-and-neck (HN; N=5) and breast (N=5) cancer. Seven new plans with a RU of 3.5% (original plan), 3.0%, 2.5%, 2.0%, 1.5%, 1.0% and 0.0%, respectively, were robustly optimized for each patient applying the same field directions and optimization objectives as the original treatment plans. Each plan was optimized until a clinically acceptable plan was obtained (D95%>98% for the clinical target volume (CTV)) for fourteen setup and range scenarios according to our clinical protocol for each diagnosis. The dosimetric effect of reduced RU was evaluated for OARs surrounding the CTV. Comparisons were made by evaluating mean and max dose to the OARs.

Results
As an example, reducing the RU from 3.5 to 2% results in an average reduction of the volume receiving 80% of the prescribed dose by 6 cm3 for the brain, 8 cm3 for HN and 56.1 cm3 for breast cancer patients. The volume of brain tissue outside the CTV receiving 30 Gy shows an average reduction of 5.3 cm3 for the brain patient cohort.

Conclusion
Reducing the range uncertainty leads to a reduction in dose to OARs. Whether the achieved dose reduction is clinically relevant or not depends on the affected organs and the dose constraints applied in the optimization.

91. Simon Heebøll Vindbæk, Aarhus, Denmark

Investigating the dose degradation around gold markers in spot-scanning proton therapy using 3D dosimeters

Valdetaro LB, Vindbæk SH, Stolarsczyk L, Skyt PS, Petersen SE, Rønde HS, Balling P, Petersen JBB, Muren LP

Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark; Department of Radiotherapy, Odense University Hospital, Odense, Denmark; Department of Clinical Medicine, Aarhus University, Aarhus, Denmark; Department of Physics and Astronomy, Aarhus University, Aarhus, Denmark

Introduction
Fiducial markers are necessary to ensure safe and accurate delivery of radiotherapy including proton therapy (PT) for several tumour sites. However, the high metal content of the markers may lead to shadowing of the proton beam along all the different beam directions. In this study, three different gold markers in different configurations (straight or folded) were implanted into a 3D dosimeter, which was subsequently irradiated with a clinically relevant PT plan.

Material and methods
A four-field pencil beam scanning proton plan mimicking a clinically realistic scenario for a prostate cancer patient was made for the Gammex (CIRS) phantom. Two cylindrical radiochromic silicone-based 3D dosimeters (Ø 10 cm, diameter 10 cm) were prepared, one with gold markers and one without (control dosimeter). The dosimeters were subsequently inserted into the phantom and irradiated in the same geometry using a Varian ProBeam Machine. The dosimeters were read out using an optical CT scanner providing 3D distributions of the radiation-induced changes in optical attenuation coefficients ($\Delta\alpha$). A reconstruction of the control dosimeter with an artificial mask of the gold markers was also performed.

Results
Optical artefacts in the marker-containing dosimeter were visible 3-5 mm from the markers but did not affect the measurement quality in other regions. The artificial mask on the control dosimeter indicated that the low and high optical attenuation values around the markers originated from optical artefacts related to the image reconstruction algorithm. Overall, there was very good agreement between the marker and control dosimeters. Gamma pass-rates using a 2%-2mm criteria were 92% between the control and marker dosimeters, and 97% between the artificial mask control and the marker dosimeters.

Conclusion
Our results indicated that gold markers did not influence the overall dose distribution in a realistic scenario with a clinical beam arrangement.

92. Nina Ubbesen, Aarhus, Denmark

Dose to heart substructures between photon and proton therapy for esophageal cancer patients

Ubbesen NS, Nordsmark M, Milo MLH, Hoffmann L, Nyeng TB, Møller DS

Department of oncology, Aarhus University Hospital, Aarhus, Denmark and Department of Clinical Medicine, Faculty of Health Sciences, Aarhus University, Aarhus, Denmark.

Purpose/objective
The aim of this study is to compare the dose to the heart and 24 cardiac substructures between intensity-modulated radiotherapy (IMRT) and pencil beam scanning (PBS) proton therapy for patients with esophageal cancer (EC).

Material/methods
26 patients with EC were treated with chemo-radiotherapy using 5-8 IMRT fields covering the planning target volume (PTV). The PBS plans were created retrospectively using two posterior fields. All patients were delineated and treated based on a 4D CT scan with contrast and a FDG PET scan. The heart and 24 cardiac substructures were auto-segmented by using an atlas-based approach in MIM software and subsequently manually adjusted per Danish national guidelines. The mean dose and D0.1cm3 (near max) were calculated for all structures. Statistical calculations to compare the dose metrics between the two modalities were performed and the Wilcoxon signed-rank test was used to compare the mean dose and D0.1cm3 for IMRT and PBS with $p<0.05$ considered statistically significant.

Results
Compared with IMRT, PBS resulted in significantly lower mean radiation dose to the heart, aorta, right atrium, right and left ventricle. For the left atrium, there was no significant difference in mean dose. For the coronary arteries the mean dose was significantly lower for PBS to the LMCA, LAD (proximal, middle, distal) and RCA (proximal, middle, distal). There was no significant difference for the CX and RDP.
The D0.1cm3 doses were significantly lower for PBS to the LMCA, LAD (proximal, middle, distal) and RCA (proximal, middle).

Conclusion
PBS significantly reduced mean doses to the heart, aorta, right atrium, right and left atrium, and the LMCA, LAD and RCA compared to IMRT. The near max doses were significantly lower in the majority of the coronary artery structures.
Studies are needed to determine how this cardiac sparing effect impacts the development of coronary heart disease and other cardiac events in patients with EC.

93. Sarah Eckholdt, Aarhus, Denmark

Patient-Specific Quality Assurance Using Monte Carlo Dose Calculations in Patients with Early Breast Cancer Treated with Proton

Eckholdt S (1), Vindbæk SH (1,2), Offersen BV (1,3,4), Kronborg CJS (1), Stolarczyk L (1), Stick LB (1), Petersen SE (1), Muren L (1,2,3), Jensen MF (1)

a Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark. b Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark. c Department of Oncology, Aarhus University Hospital, Aarhus, Denmark. d Department of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark.

Introduction
Patient-specific quality assurance (PSQA) is essential in radiotherapy and required by law in many countries. In proton therapy, PSQA is typically performed by dose measurements in a flat solid water phantom, but clinical "gold standards" are moving towards calculations with Monte Carlo (MC) dose algorithms. This study compares proton therapy PSQA dose measurements for breast cancer with dose calculations using either a pencil beam (PB) or a local MC algorithm.

Materials and methods
Four loco-regional proton plans made for treatment of node-positive breast cancer were selected based on a low gamma pass rate between the PSQA measurements and the PB dose calculations. The clinical plans had two en face proton fields and were created using single-field optimization, a 5 cm range shifter, and robust optimization to account for uncertainties in range and setup. The PSQA measurements of the deposited dose were performed for at least at two depths per field within PSQA setup (ionization chamber and solid water slabs). Both calculated dose distributions were compared to the PSQA measurements within both the validation setup and the planning computed tomography (CT).

Results
The properties of the beam and dose profiles of the MC calculations and the PSQA measurements were similar for all patients. Conjoint for these two dose planes was the elevated behavior within the primary clinical target volume (CTV) before the distal edge of around 4% compared to the PB calculations. The 2D gamma index analyses between measured and the two calculated dose planes passed the tolerance criterion (> 90%) with a global criterion of 3%/2mm. The same tendencies were observed within the planning CT indicating a higher CTV mean dose.

Conclusion
The MC dose calculations showed a better agreement with the PSQA measurements than the PSQA measurements and the PB calculations did, validating the use of the local secondary MC dose algorithm for PSQA of patients with breast cancer.

Poster discussion group 8: Treatment planning, automation, artificial intelligence A

Chairs: Joseph Deasy, Ditte Sloth Møller

94. Anne Andresen, Aarhus, Denmark

Auto delineation of organ at risk in brain cancer patients using deep learning

Andresen, A. H,1,2, Lassen, Y.A 1, Lucakova, S3, Hansen, CR1,4,5, Kallehauge, J 1,2

1 Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark 2 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark 3 Department of Oncology, Aarhus University Hospital, Aarhus 4 Laboratory of Radiation Physics, Odense

Introduction

High precision and consistent delineations of normal tissues are essential to minimize damage and to provide high-quality radiotherapy (RT) for brain tumors. Consistency in delineations can be obtained using deep learning (DL) models for auto segmentation. Recently advances have been made in deep learning methods for semantic segmentation. Therefore, we compare nnUNet, with a DL transformer model to investigate if a transformer can provide segmentations with higher precision of OAR delineations.

Methods

Two DL models were trained with k-fold, for multi organ segmentation, nnUNet and nnFormer, a transformer model that gives patches as sequential inputs to a multi head attention mechanism in the network. Dataset consisted of forty-nine brain cancer patients. Models' performances were assessed for one-fold for determination of the predictive performance, with Dice (DSC) and Hausdorff distance 95(HD95).

Results

Average DSC scores for nnUNet for segmented organs was between 0.03 and 0.83, with median 0.054, and the estimated HD95 distances was 1.5-61.4 with 7.14 as median. Evaluation of nnFormer had DSC mean DSCs of 0.29 to 0.90, with a median at 0.64 and HD95 in the range of 1.15 -24.5 with 2.78 for the median, but with DSCs for one patient on smaller structures with a range of 0.65 to 0.85.

Conclusion

Predictions for nnFormer indicates that transformers can be used for delineation of OARs in the brain, with the potential to obtain higher DSCs for smaller structures, such as optic nerve-and tracts. It did not significantly improve the average DSC for delineations of larger structures within the first fold. Therefore, additional training and validation is needed. However, a combination of convolutional models, such as nnUNet and a transformer, might increase accuracy for all structures independent of size.

95. Helena Vivancos Bargalló, Barcelona, Spain

Laterality and lumpectomy/mastectomy classification for AI contouring of breast targets

Vivancos H (1,2), Stick LB (1), Korreman SS (1,3), Kronborg CJS (1), Nielsen MM (1), Borgen AC (1), Nørrevang O (1), Kallehauge J (1,3)

(1) Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark. (2) Medical Physics department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. (3) Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.

Introduction
When using a patient group with mixed left/right and mastectomy/lumpectomy to train a single nnUnet for auto segmentation of lymph node volumes in breast cancer patients for radiotherapy (RT), it results in a high percentage of target-volumes delineated in the contralateral side, bilaterally or missing a significant volume. Therefore, we wish to use 4 networks, one per class: left/right and mastectomy/lumpectomy. To auto select the correct network we propose a method to classify patients in the four groups.

Materials and Methods
112 breast cancer patients treated at DCPT (unilateral and without previous breast surgery/RT) were stratified and used to train (90%) and validate (10%) the two classifiers. A separate set of 16 patients was used to test the whole classification model.
Laterality: An automated spinal cord segmentation was used to divide the image. HU-histograms for each half were obtained and the left was subtracted from the right. The result for each patient was used to train a Support Vector Machine classifier (α=0,001).
Mastectomy/lumpectomy: Targets were contoured, using the appropriate side mastectomy and lumpectomy segmentation networks. This resulted in two structure sets for all 112 patients. The following features were used to train a Support Vector Machine classifier (α=0,001):
-number of clips inside CTVp(Mastectomy)
-(CTVp(Mastectomy) volume) / (contralateral breast volume(Mastectomy))
-(CTVp(Mastectomy) volume) / (CTVp(Lumpectomy) volume)

Results
Laterality: The mean accuracy of the classifier was 99% (STD 2%). In the test set 15 out of 16 patients were classified correctly.
Mastectomy/lumpectomy: The mean accuracy of the classifier was 97% (STD 5%). In the test set 14 out of 15 (patient misclassified for laterality excluded) patients were classified correctly. The misclassified patient in the test set had breast implants.

Conclusion
This classifying method results in 87,5% of the targets in the test set classified correctly.

96. Jintao Ren, Aarhus, Denmark

Highly uncertain regions reveal potential errors: uncertainty analysis for improving deep learning segmentation of head and neck cancer tumor

Jintao R, Jasper N, Mathis ER, Jesper GE, Stine SK

Dept. of Clinical Medicine, Aarhus University, Aarhus, Denmark; Dept. of Oncology, Aarhus University, Aarhus, Denmark; Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark; Dept. of Experimental Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark.

Accurate segmentation of Gross Tumor Volume of primary (GTV-T) and nodal metastases (GTV-N) is paramount for Head and Neck Cancer (HNC) treatment planning. Despite the potential of deep learning (DL) to automate segmentation, its reliability and generalization remain a concern. This study aimed to assess if DL uncertainty estimation can be used to identify false positive (FP) and negative (FN) regions in HNC GTV segmentation.

We employed the 3D nnUNet framework with the deep ensemble and trained it on a diverse multimodal (CT, PET, T1w, and T2w) dataset of 567 HNC patients (470 for training and validation, 97 for testing) with various sites. Uncertainty maps were generated using the entropy of ensembling probability maps from 10 randomly initialized trained networks using random split data. We identified regions with high uncertainty (entropy>0.7) and determined whether they were FP or FN regions by assessing their overlap with the DL contour.

Using the uncertainty maps, we successfully identified all the FP regions (40 for GTV-T and 50 for GTV-N), and 4 out of 13 FN regions for GTV-T and 20 out of 42 for GTV-N. Our efforts to correct these regions led to improvements in segmentation accuracy, with the median Dice Similarity Coefficient increasing from 0.76/0.80 to 0.77/0.84 for T/N, decreased in the 95% Hausdorff Distance from 6.1/5.1 to 5.4/3.1 mm, and decreased in the Mean Surface Distance from 1.3/1.0 to 1.2/0.7 mm. These results were statistically significant with p-values<0.01/<0.0001 for T/N, as determined by a Wilcoxon signed-rank test.

Our study demonstrates that uncertainty estimation can effectively identify erroneous targets, especially false positives. Correcting these targets significantly improves accuracy. These findings suggest that uncertainty estimation can be a valuable tool for improving the reliability of DL segmentation in HNC treatment planning.

97. Kristoffer Moos, Aarhus, Denmark

Deep learning-based segmentation of organ-at-risk in the thorax region using a high-quality curated dataset

[1,2]Moos K., [1,2]Ren J., [3]Aagaard T., [3]Nyeng T.B., [3]Knap M.M, [3]Mortensen H.R., [3] Hoffman, L. [3]Møller D.S., [3]Jellesmark L.B.T., [1,2]Korreman S.

[1]Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, [2] Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [3] Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Introduction
Delineation of organ at risk (OAR) is an essential procedure in radiotherapy treatment planning and is presently a manual procedure making it highly time-consuming and prone to inter-observer variability.
In this study, we investigated the potential of automated delineation of OAR in the Thorax region based on a 'from-scratch' institutionally developed deep learning algorithm.

Materials & Methods
The dataset consisted of 96 patients with the following OAR delineated on CT images: Aorta, Heart, Lungs (left & right), Trachea, Esophagus, Bronchi, Spinal Cord, and Spinal Canal. All OAR were delineated with the intention of training a deep learning model. The OAR were delineated in accordance with consensus guidelines and were approved by an independent observer.
We trained a 3D UNet developed from scratch for 500 epochs with dice loss as cost function and ADAM algorithm for optimization. The dataset was split into 75 patients for training, 14 for validation, and 7 for testing. We used Dice Similarity Coefficient (DSC) and 95 percentile Hausdorff distance (HD95) averaged across the 7 test patients as evaluation metrics.

Results
The average DSC and HD95 were ranging between 0.69-0.96 and 1.58-14.15mm, respectively. The highest DSC was observed in both lungs (0.96 & 0.96, respectively) and the lowest for Esophagus (0.69). The smallest HD95 was observed for the spinal canal (1.58mm) and the greatest for spinal cord (14.15mm). The 3D UNet was able to achieve following DSC and HD95 for each of the OAR, respectively; Aorta = 0.87, 9.03mm, Heart = 0.94, 6.03mm, Right Lung = 0.96,4.55mm, Left Lung = 0.96,5.02mm, Trachea = 0.91,3.54, Esophagus = 0.69,7.26mm, Bronchi = 0.86, 5.04mm, Spinal Cord = 0.80, 14.15mm, and Spinal Canal = 0.92, 1.58mm.

Conclusion
We demonstrated that a 3D UNet trained on a high-quality curated dataset for OAR in the Thorax region, can achieve accurate segmentations, aiming for implementation in a clinical workflow.

98. Liheng Tian, Dortmund, Germany
Presented by Armin Lühr

CT or stopping power ratio prediction by deep learning for MR-only proton dose calculation?

Tian L, Lühr A
Department of Physics, TU Dortmund University, Dortmund, Germany

Introduction
Magnetic resonance (MR)-only proton dose calculation requires an MR to stopping power ratio (SPR) data conversion. Taking MR images (MRI) as input, deep learning (DL) models can predict synthetic computed tomography (sCT). The subsequent conversion from CT Hounsfield units (HU) to SPR is, however, non-linear. Therefore, it remains unclear if direct SPR prediction from MRI can improve proton range uncertainty. This work investigates whether choosing HU or SPR as output impacts the performance of a conditional generative adversarial network (cGAN) model [Isola et al., 2017] using an open source dataset [Nyholm et al., 2018].

Methods
The cGAN takes MRI as input. Two derivations of SPR maps (SPRM) were compared: (1) generate synthetic SPR (sSPR) as output, (2) generate sCT as output and derive sSPR. A CT-SPR look-up table was used. Paired pelvic CT and MRI data of 17 male patients were used for modeling. For each model, 50 SPRM were generated for each input MRI using Monte Carlo dropout to obtain mean and standard deviation (SD) maps. Models were compared in terms of precision and accuracy as well as resulting range differences for 150 and 200 MeV proton beams.

Results
Both models were comparable: differences between predicted fake and ground truth real SPR were not biased from 0 (-0.01±0.11) and the mean absolute error was 0.039±0.07 . High SD of modeled SPRM were primarily observed at the object edges: ~0.3 in a 2-voxel band at the outer body contour and ~0.04 within the body. For 150 (200) MeV proton beams, relative range differences were 0.7%±1.2% (0.5%±1.2%) and 0.4%±1.0% (0.2%±1.2%) for SPR and sCT models, respectively.

Conclusion
For DL-based MR-only proton dose calculation, model precision and accuracy were observed to be worse near the edge of objects, which may be caused by (ground truth) image mismatch. Models choosing either sCT or sSPR as output perform comparably. Resulting errors, e.g. proton range and SPRM, were unbiased.

99. Rasmus Klitgaard, Aarhus, Denmark
Presented by Ludvig Muren

The impact of range and treatment uncertainties on normal tissue complication probability models based on the rectum volume vs. wall during proton therapy of high risk prostate cancer

(1) Klitgaard R, (1) Tilbæk S, (1) Vestergaard A, (1) Stolarczyk L, (1) Petersen SE, (2) Pilskog SMC, (1) Muren LP

(1): Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark; (2): Department of Physics and Technology, University of Bergen, Bergen, Norway

Introduction
Normal tissue complication probability (NTCP) models are often used to compare treatment plans in radiotherapy, including between different modalities. NTCP models are usually based on dose volume metrics, while variations from patient positioning, anatomical changes, and range uncertainties are usually not considered in the model development. In this study we aimed to examine the impact of range and treatment uncertainties on NTCP model predictions following proton therapy (PT) of high risk prostate cancer, and to compare the robustness of rectal volume vs wall based models developed from the same cohort.

Materials and methods
For eight retrospective test patients, planned in preparation of an ongoing clinical trial evaluating PT of high risk prostate cancer, we calculated NTCP for all robustness scenarios (5 mm set-up and 3.5% range uncertainties) of all CT scans (plan-CT=14 scenarios, re-CT=3 scenarios). The prescribed dose was 78 Gy to the prostate and 56 Gy to the pelvic lymph nodes, delivered in 39 fractions using two lateral-posterior oblique and two posterior oblique fields. We used two NTCP models, one based on dose to the rectum volume and one on the rectum wall, derived from the same PT cohort of 1151 prostate cancer patients with a rectal grade 2 incidence rate of 14%. We compared the NTCP predictions between the two models by the interquartile range (IQR; between the 75th and 25th percentile) across all scans and uncertainty scenarios, and by the difference between the median and nominal values (MNV) for each patient.

Results
For the rectal wall based NTCPs, the IQRs were between 9-45%, compared to 2-9% for the rectal volume. Similarly, the MNVs ranged between -10% and 25% for the wall, compared to -1% to 3% for the rectal volume.

Conclusion
Treatment uncertainties in PT of high risk prostate cancer introduces variations in NTCP predictions of rectal morbidity - the variations were considerably reduced when using the rectum volume based model.

100. Sofie Tilbæk, Aarhus, Denmark

Evaluation of plan robustness in proton therapy for high-risk prostate cancer patients included in a national clinical trial

Tilbæk S (1,2), Petersen SE (1), Stolarczyk L (1), Vestergaard A (1), Søndergaard J (3), Høyer M (1), Bentzen L (4), Muren LP (1,2)

(1) Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark. (2) Department of Clinical Medicine, Aarhus University, Aarhus, Denmark. (3) Department of Oncology, Aalborg University Hospital, Aalborg, Denmark. (4) Department of Oncology, Vejle Hospital, University of Southern Denmark, Vejle, Denmark.

Introduction
Inter-fractional anatomical changes challenge robust delivery of proton therapy for high-risk prostate cancer. Isocenter shifts and range uncertainties are taken into account in pre-treatment robust evaluation (PRE) of treatment plans. The aim of this study was to evaluate the robustness of clinical proton treatment plans by comparing an off-line during-treatment robust evaluation (DRE) based on weekly control CT scans (cCTs) to the PRE.

Materials and methods
Treatment plans and cCTs form five pilot patients included in the PROstate PROTON Trial 1 (NCT05350475) were analyzed. Treatment planning followed protocol guidelines with 78 Gy to the primary target (CTVp; prostate and involved seminal vesicles) and 56 Gy to the elective target (CTVe; pelvic lymph nodes) in 39 fractions. Margins were added to CTVp to form an internal target volume (iCTV) to account for anatomical deformations and displacements. Recalculations of the treatment plans were performed for the total of 34 cCTs from the five patients, and dose/volume measures corresponding to clinical constraints were evaluated for this DRE against the predicted range from the PRE. CTVp dose/volume measures from the DRE were compared to the iCTV PRE. The DRE was labelled as outside the PRE range for a structure if that was the case for a worst case measure corresponding to any of the up to six constraints for a structure.

Results
Of the 34 cCTs, 32 showed CTVp measures within the robustness range from the PRE; this was also the case for 23 of the cCTs for the CTVe measures. However, CTVe coverage was still within constraints for 28 of the 34 cCTs. All worst case DRE measures for the rectum, bladder and bowel were inside the PRE range in 34, 23, and 10 cCTs, respectively.

Conclusion
All treatment plans and most of the DREs showed acceptable target coverage and doses to organs at risk. Treatment robustness will continue to be assessed for the remaining pilot patients in the trial.

Poster discussion group 9: Treatment planning, automation, artificial intelligence B

Chairs: Thomas Ravkilde, Ebbe Lorenzen

101. Karolina Klucznik, Aarhus, Denmark

Accuracy of motion-including prostate dose reconstruction based on pre- and post-treatment cone-beam CT scans

Karolina Klucznik1, Thomas Ravkilde2, Simon Skouboe1, Ditte Møller2, Steffen Hokland2, Paul Keall3, Simon Buus2, Lise Bentzen2, Per Poulsen1,2

1Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark; 2Department of Oncology, Aarhus University Hospital, Aarhus, Denmark; 3ACRF Image X Institute, University of Sydney, Sydney, Australia

Purpose

Prostate motion during radiotherapy can induce dose distortions. This study uses intra-treatment imaging to determine the prostate dose deficit caused by dynamic translations and rotations and investigates the accuracy of using pre- and post-treatment cone-beam CT (CBCT) for dose deficit estimations.

Materials and Methods

Six prostate cancer patients were treated in 39 fractions with 78Gy using 3-arc VMAT. A CBCT matched on three implanted prostate markers was used for setup. At ten fractions per patient, the prostate motion during treatment was determined by kilovoltage intrafraction monitoring (KIM) using triggered kV images acquired every 3s during treatment delivery. A post-treatment CBCT was also acquired at these fractions. Afterward, the intra-treatment prostate motion was estimated based on the CBCTs using three different assumptions: 1) static position as in the pre-CBCT; 2) static position as in the post-CBCT; 3) linear drift from pre-CBCT to post-CBCT position.
In-house developed software (DoseTracker) was used for rotation- and translation-including prostate dose reconstructions with the KIM and CBCT estimated motion. The motion-induced percent point difference in minimum dose to 95% of the CTV (ΔD95%) was calculated for all motions. The accuracy of the CBCT-based ΔD95% estimations were determined using the KIM-based ΔD95% as ground truth.

Results

The largest intra-treatment prostate translational and rotational errors were 4.3mm (AP direction) and 16.1° (LR rotation). The range of CTV ΔD95% across all fractions was [-6.5; +0.4]%. The CBCT-based estimation of ΔD95% had a mean (maximum) absolute error of 1.64% (5.2%) using pre-CBCT, 0.58% (2.6%) using post-CBCT, and 0.57% (2.8%) using both CBCTs.

Conclusion

Assuming a static prostate position as in the post-CBCT or linear drift motion between pre- and post-CBCT resulted in CTV ΔD95% estimates close to the ground truth.

102. Katrin Håkansson, Copenhagen, Denmark

Online adaptive radiotherapy for head and neck cancer – first experience analysis of plan difference and synthetic CT uncertainty

Håkansson K(1), Giannoulis E(2), Lindegaard A(1), Friborg J(1), Vogelius I(1)

(1) Department of Oncology, Centre of Cancer and Organ Diseases, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark. (2) Department of Health Technology, Technical University of Denmark, Copenhagen, Denmark

Introduction
Clinical experience with online adaptive radiotherapy (oART) for head-and-neck (H&N) cancer is still limited, and improved understanding of the process, risks and benefits is needed to move forward. Here, a dosimetric analysis of the first three patients treated with oART for H&N cancer at our institution is presented.

Materials and methods
Three palliative H&N cancer patients were treated with daily CBCT-based oART (4Gy x13), using standard PTV margins. The scheduled and adapted plans were compared as calculated on the synthetic CTs (sCT) of the vendor. The delivered plans were additionally re-calculated on corrected versions of the sCTs (sCT_corr), where areas of soft tissue, air and bone were identified on the CBCTs and manually modified in the sCTs if not represented correctly. Dose metrics were reported for each treatment fraction and compared by Wilcoxon signed rank test.

Results
The adapted plan was chosen 11/13 times for patient 1, 0/13 times for patient 2 and 6/13 times for patient 3. The adapted plans had higher CTV D99.9% than the scheduled for patient 1 (median 50.4Gy vs 49.5Gy, $p<0.001$), lower for patient 2 (50.3Gy vs 51.1Gy, $p<0.001$) and no significant difference for patient 3. The mean doses to oral cavity and salivary glands were a mix of higher and lower in the adapted plans for all three patients. The interquartile range of difference in mean dose calculated on the sCT_corr vs the sCT was within 1% for the relevant OARs. The corresponding difference in CTV D99.9% was up to 10%, but in a secondary analysis where parts of CTV unintentionally contoured in air on the CBCT were excluded, the difference was reduced to <0.5%.

Conclusions
The dosimetric effect of uncertainty in sCT generation was small in the three patients of the study. Dose metrics were a mix of higher and lower in the adapted plans when compared to the scheduled. This suggests that the possible clinical gain of oART in H&N cancer might require a margin reduction.

103. Kirsten Legård Jakobsen, Næstved, Denmark
Presented by Laura Kaplan, Næstved

An automated planning method to spare the rectal wall in treatment of prostate cancer

Jakobsen, K L1, Marseguerra, R C1,2, Bebek, M1, Hofland, K F1, Samsøe, E1

1: Department of Clinical Oncology, Zealand University Hospital, Radiotherapy, Denmark 2: Department of Oncology, Rigshospitalet, Denmark.

Introduction
An automated method and user friendly recipe for generation of rectal wall (RW) sparring dose plans (DPs) for patients with prostate cancer was evaluated. DPs for 10 patients were evaluated against standard method

Materials and Methods
Patients were planned with standard and new methods and doctors chose preferred DP (blinded). Prescribed dose was 78Gy/39fx to prostate and seminal vesicles (CTV-T) and 56Gy/39fx to elective lymph nodes (CTV-E).

Overlap-structure between rectum and PTV-T was defined and optimized using lower (76Gy) and upper (76.2Gy) objectives. Organs at risk (OARs) were cropped 5mm from PTV (oOARs). During optimization, Dmean to oOARs were minimized. After 1st optimization, planner delineated rectal volume receiving ≥ 50Gy. In 2nd optimization Dmax and Dmean to oOAR were decreased by ≈5 Gy and ≈3 Gy, respectively. The procedure was repeated iteratively. Guidelines direct 1/3 of rectal circumference ≤50Gy i.e. importance RW > importance rectal lumen. This subjective criteria is challenging to evaluate and re-optimization with PTV compromise is often preferred. To replicate V98% ≥ 95 for PTV, a new structure “RW Post” was introduced: RW (3mm inner rectum margin) cropped 5mm from PTV. The purpose was sparring of posterior rectum circumference without compromising PTV coverage. Optimization criteria for oOAR was not changed and similar constraints were used for RW Post. The method was formulated as a recipe by planner1 and applied by planner2 who produced DPs to same standard. Results

The standard method leads to V99%≥95% for PTVs in all plans. Doctors preferred plans obtained from new method in 7 out of 10 cases. The 50 Gy isodose and Dmean to rectum was reduced by 1,4% [-7,2% - 6,6%] and 3.0% [-8.0% - 3.1%], respectively. Negative values originate from same plan.

Conclusion
A method to reduce dose to the rectal circumference was developed and described as a recipe. It has optimized the plan approval process and lead to lower dose to RW.

104. Lars Hjorth Praestegaard, Aarhus, Denmark

Comprehensive automated structure QA in radiotherapy

Praestegaard, LH
Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Introduction
Despite the emerging use of artificial intelligence, the delineation of target and organs at risk (OAR) in radiotherapy remains a partly manual process heavily dependent on human intervention. Thus, there is a considerable risk of user-errors during both structure delineation (e.g. stray voxels and empty slices) and any subsequent structure manipulation (e.g. margin, Boolean operations, and postprocessing). This may result in treatment errors including target underdosage and OAR overdosage.

Materials and Methods
Structure Tool is an in-house-developed Eclipse scripting API application. Based on commands in an XML file specific to each treatment technique, the application performs 1) a comprehensive automatic QA of all target and OAR structures and 2) automatic creation of all optimization structures for dose planning. The application has 5 default structure QA checks that are always performed. Any error found by these checks are highlighted on the associated CT slice in a graphical user interface. In addition, the application supports 6 structure QA XML commands. For example, the CompareContours command can detect an incorrect GTV-CTV margin even if a substantial part of the CTV subsequently is cropped to anatomical structures. At present, Structure Tool is used for 46 treatment techniques including more than 90 % of all curative patients in our clinic.

Results
Structure Tool has detected numerous structure errors, thereby preventing serious treatment errors like missing boluses, incorrect GTV-CTV margins, target structures not fully included in elective volumes, match structures with an incorrect margin, and too large PTVs due to stray voxels. For example, in the period ultimo November 2022 to primo March 2023, 30 structure errors were detected by XML commands of which most were real errors.

Conclusions
Structure Tool provides comprehensive fully-automated structure QA of target and OAR structures, thereby improving treatment quality.

105. Maja Sand, Aarhus, Denmark
Presented by Line Ring, Aarhus, Denmark

Evaluation of manual and DirectOrgans algorithm for the delineation of organ at risk in thorax and pelvic radiation therapy

Ring LØ, Sand MV, Hansen J, Qvistgaard PA

Dept. of Oncology, Aarhus University Hospital, Aarhus, Denmark

Purpose
Delineation of target and organ at Risk (OAR) is one of the most important, time consuming and operator-dependent tasks in radiation therapy. There are different systems for automatic OAR contouring. One of them is Siemens DirectOrgans algorithm.
This study aims to: Evaluate manual and DirectOrgans algorithm for delineation of OARs in thorax and pelvic. b) Form the basis for future work to implement automatic DirectOrgan contouring in our clinic.

Methods
Manual and DirectOrgans-segmentation of OARs in the thorax and pelvic region of 100 patients simulated on Siemens Go Open Pro CT were made. Difference between manually delineated volume and automatic volume (ΔV, %), dice similarity coefficient (DSC), sensitivity (Se) and specificity (Incl) were calculated to compare the accuracy of these two methods. The contours were also compared visually slice by slice.

Results
The bladder, esophagus, femoral heads, heart, kidneys, liver, lungs, rectum and spinal cord volume were delineated manually and with DirectOrgans. DSC coefficient on more than 0.9 were found for femoral heads, heart, liver, lungs, between 0.9 and 0.8 for kidneys and under 0.8 for bladder, esophagus, rectum and spinal cord.
For bladder, femoral heads, heart, kidneys, liver and lungs we found Se over 0.9, for rectum between 0.8 and 0.9 and for esophagus and spinal cord under 0.8. Regarding the Incl the biggest score on above 0.9 were for femoral heads, liver and lung, between 0.8 and 0.9 for heart and kidneys, and the lowest of under 0.8 were for bladder, esophagus, rectum and spinal cord.

Conclusion
The best correlation between manual and DirectOrgans contouring were found for femoral heads, liver and lungs.
The greatest difference between volumes contoured using the two methods is seen in those patients who had an advanced disease in these organs of interest.
This is a pilot study and future work with more patient data is needed before implementing in clinical use.

106. Morten Nielsen, Odense, Denmark

A systematic approach to estimation of residual tolerances of organs being re-irradiated

Nielsen M (1), Schytte T (2,3), Hansen O (2,3)

1: Laboratory of Radiation Physics, Dept. of Oncology, Odense University Hospital 2: Institute of Clinical Research, University of Southern Denmark 3: Dept. of Oncology, Odense University Hospital

Introduction
The number of re-irradiations of organs/regions in patients to curative doses is increasing. In order to have an operational procedure for and in order to facilitate learning from these treatments, it is necessary to have a systematic approach to estimate residual tolerances of the organs being re-irradiated.

Materials and methods
The number of retreatments and doses delivered were extracted from the Record & Verify system of the department.
All OAR tolerance dose are considered in 2 Gy per fraction equivalents. Similarly, all previously delivered doses are considered in 2 Gy per fraction equivalents, as estimated by the linear quadratic model. Simple subtraction yields a residual tolerance for the OAR, which can be used as the organ tolerance in the retreatment.

Results and examples
In 2017, 564 out of 2608 treatment courses were re-irradiations. 155 were re-irradiations of the same or a neighboring organ, and 25 of these involved high doses, either as curative treatment or as stereotactic treatment. In 2022, 611 out of 2603 treatment courses were re-irradiations. 232 re-irradiations of the same or neighboring organ, and 103 of these involved high doses.
The calculation of residual tolerances have been used to estimate residual tolerances for the thoracic wall and the brachial plexus in thoracic re-irradiation, and to estimate residual tolerances of optic nerves, chiasm, inner ear and brainstem for sequences of intracranial stereotactic treatments and for whole brain radiotherapy following stereotactic treatment.
This method allows more cases of re-irradiation, which might not seem obviously possible. So far, we have not observed an excess of serious complications using this method.

Conclusions
Systematic use of the linear quadratic model to calculate residual organ tolerance doses for re-irradiations are a feasible approach.

107. Saber Nankali, Aarhus, Denmark

Spot scanning proton therapy of hepatocellular carcinoma: Intrafraction tumor motion monitoring and dose reconstruction

Nankali S(1,2), Worm ES(3), Thomsen JB(1), Stick L(1), H›yer M(1), Weber B(1,3), Mortensen H(1), Poulsen PR(1,2,3)

(1)Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark (2)Department of Clinical Medicine, Aarhus University, Aarhus, Denmark (3)Department of Oncology, Aarhus University Hospital, Aarhus, Denmark

Introduction
This study develops intra-treatment tumor motion monitoring during pencil beam scanning proton therapy (PBSPT) and performs motion-including dose reconstruction for individual hepatocellular carcinoma (HCC) treatment fractions.

Methods
Seven HCC-patients were planned to receive 58 GyRBE (n=6) or 67.5 GyRBE (n=1) of gated PBSPT in 15 fractions. Treatment planning was performed on the exhale phase of a 4DCT scan. Daily setup was based on a free-breathing CBCT with manual match of the exhale position of 2-3 implanted markers. An external marker block (RPM) on the patient's abdomen was used for exhale gating in free breathing with ~50% duty cycle. This study was based on 1-8 fractions per patient having a post-treatment control CBCT. The 2D marker positions in the post-treatment CBCT projections provided the estimated 3D tumor motion trajectory during the CBCT by a probability-based method. An external-internal correlation model (ECM) that estimated this motion from the RPM motion was built using the RPM signal recorded during the CBCT. The tumor position at the time of each spot delivery was then estimated by the ECM. Finally, the motion-including CTV dose was estimated by emulating tumor motion in beam's eye view as lateral spot shifts and in-depth motion as changes in the proton beam energy. The CTV homogeneity index (HI) was calculated as (D2% - D98%)/(D50%) ×100%.

Results
The tumor position during spot delivery had a root-mean-square error of 1.3 mm (LR), 2.9 mm (CC) and 1.5 mm (AP) compared to the planned position. The mean absolute difference between delivered and planned CTV HI was 3.3%-points (range: 1.0-6.6%-points) for individual fractions and 0.7%-points (range: 0.3-1.3%-points) for the averaged dose of 5-8 fractions.

Conclusion
Estimation of internal tumor motion and reconstruction of the motion-including doses for PBSPT of HCC was demonstrated successfully in the clinic. It showed a gradual smearing of interplay effects after 5-8 fractions.

108. Thomas Ravkilde, Aarhus, Denmark

An easily extendible framework for advanced automated plan checks

Thomas Ravkilde, Ditte Møller, Lars Nyvang, Stine Valentin Nielsen, Rune Hansen

Medical Physics, Dept. of Oncology, Aarhus University Hospital, Denmark

Purpose
Pre-treatment checks of dose plans are a ubiquitous and manual part of quality assurance (QA) in radiotherapy (RT). They typically involve many repetitive tasks that lend themselves to automation while being very specific to diagnosis, technique, institution, etc. We wanted to automate checks to increase quality and consistency and aimed to implement a software (SW) framework that was both easy and quick to use by end users as well as easy to extend by developers with limited programming experience, while at the same time being robust and safe.

Material and Methods
The SW utilizes ESAPI (Varian) for TPS operations. Additional data mining was obtained through Aria Access, Reports, and simple SQL lookups in the AURA database. Properties of images, structure sets, plans, beams, appointment/task scheduling, and more were checked. The framework was designed to encapsulate the checking of each property, providing a clear bound and centralized handling of errors and exceptions. Risk analysis was performed for each individual property check by multiple scoring (n=4) of severity and probability before adjusting the manual standard operating procedures in production.

Results
The SW has been an integrated part of the clinical workflow since April 2020. 57 manual checks were removed, 43 are only performed as spot checks, and 276 automatic checks that were too cumbersome to perform manually were introduced. 109 checks are still performed manually due to the risk of a faulty automatic check. Risk analysis of each check was instrumental in safely switching to automated checks. However, the lack of dedicated manpower severely challenged a regular CI/CD process. Reducing false positives is key to keeping end users vigilant during their QA tasks.

Conclusion
We implemented an automatic plan-checking SW that has become an integrated part of our daily clinic. It is a reliable way of catching errors that humans tend to overlook despite having checklists.

PARTICIPANTS

First name	Last name	City	Country
Alice	Clarke	Aarhus	DK
Amit Ben Antony	Bennan	Heidelberg	DE
Ana	Ureba	Stockholm	SE
Anders Tobias	Frederiksen	Aarhus	DK
Anders W. Mølby	Nielsen	Aarhus	DK
Andreas Havsgård	Handeland	Bergen	NO
Anna	Mann Nielsen	Herlev	DK
Anna	Kirby	Sutton	UK
Anne	Holm	Aarhus	DK
Anne	Vestergaard	Aarhus	DK
Anne	Andresen	Aarhus	DK
Anne	Bisgaard	Odense	DK
Anne	Lindegaard	Copenhagen	DK
Anne	Cobussen	Maastricht	NL
Anouk	Trip	Aarhus	DK
Armin	Lühr	Dortmund	DE
Azadeh	Abravan	Manchester	UK
Birgitte	Offersen	Aarhus	DK
Bob	Smulders	Aarhus	DK
Brita Singers	Sørensen	Aarhus	DK
Cai	Grau	Aarhus	DK
Camilla	Kronborg	Aarhus	DK
Camilla	Skinnerup Byskov	Aarhus	DK
Camilla Panduro	Nielsen	Odense	DK
Casper Dueholm	Vestergaard	Aarhus	DK
Christian Rønn	Hansen	Odense	DK
Christina	Truelsen	Aarhus	DK
Daniel	Zips	Berlin	DE
Daniella Elisabet	Østergaard	Copenhagen	DK
Demet	Özcan	Aarhus	DK
Ditte Sloth	Møller	Aarhus	DK
Ebbe	Lorenzen	Odense	DK
Einar	Dale	Oslo	NO
Eirik	Malinen	Oslo	NO
Eleni	Kanouta	Aarhus	DK
Emma	Riis Skarsø	Aarhus	DK
Erlend	Lyngholm	Bergen	NO
Esben	Worm	Aarhus	DK
Esther	Troost	Dresden	DE
Evangelia	Choulilitsa	Villigen	CH
Fardous	Reaz	Aarhus	DK
Filippa	Sundbye	Herlev	DK
Folefac Charlemagne	Asonganyi	Aarhus	DK

Fredrik	Kalholm	Stockholm	SE
Gabriel	Adrian	Lund	SE
Gerben	Borst	Manchester	UK
Guillermo	Garrido Hernandez	Trondheim	NO
Hanna	Mortensen	Aarhus	DK
Helena	Vivancos Bargalló	Barcelona	ES
Hendrik	Hansen	Maastricht	NL
Hjørdis Hjalting	Schmidt	Aarhus	DK
Ida Maria Henriksen	Borgen	Oslo	NO
Inga	Juvkam	Oslo	NO
Ingerid Skjei	Knudtsen	Trondheim	NO
Ingunn	Hanson	Oslo	NO
Ivanka Sojat	Tarp	Aarhus	DK
Jacob	Johansen	Aarhus	DK
Jacob	Lilja-Fischer	Aarhus	DK
Jacob Christian	Lindegaard	Aarhus	DK
Jan	Unkelbach	Zürich	CH
Jan	Alsner	Aarhus	DK
Jasper	Nijkamp	Aarhus	DK
Jens	Overgaard	Aarhus	DK
Jesper	Kallehauge	Aarhus	DK
Jesper Grau	Eriksen	Aarhus	DK
Jintao	Ren	Aarhus	DK
Johannes	Tjelta	Bergen	NO
Joseph	Deasy	New York	US
Julie	Frikke Depner	Copenhagen	DK
Julie	Kjems	Copenhagen	DK
Jørgen	Johansen	Odense	DK
Karen	Wind	Aarhus	DK
Kari	Tanderup	Aarhus	DK
Karin	Haustermans	Leuven	BE
Karolina	Klucznik	Aarhus	DK
Kathrine Røe	Redalen	Trondheim	NO
Katia	Parodi	Munich	DE
Katrin	Håkansson	Copenhagen	DK
Klara	Lanng	Aarhus	DK
Kristoffer	Petersson	Oxford	UK
Kristoffer	Moos	Aarhus	DK
Lars Hjorth	Praestegaard	Aarhus	DK
Laura	Toussaint	Aarhus	DK
Laura Patricia	Kaplan	Næstved	DK
Lene	Haldbo-Classen	Aarhus	DK
Line	Kristensen	Aarhus	DK
Line	Ring	Aarhus	DK
Lise	Thorsen	Aarhus	DK
Liv Cathrine	Heggebø	Oslo	NO
Lone	Hoffmann	Aarhus	DK
Ludvig	Muren	Aarhus	DK

Maja	Bruvo	Næstved	DK
Maja Halgren	Olsen	Copenhagen	DK
Maksym	Fritsak	Villigen	CH
Marianne	Guren	Oslo	NO
Marianne	Knap	Aarhus	DK
Marianne	Nordsmark	Aarhus	DK
Marie	Tvilum	Aarhus	DK
Marjolein	Heidotting	Aarhus	DK
Marta	Pelizzola	Aarhus	DK
Marte Kåstad	Høiskar	Trondheim	NO
Matthias	Guckenberger	Zürich	CH
Maximilian	Konrad	Odense	DK
Mayuri	Charnalia	Aarhus	DK
Mette	Felter	Herlev	DK
Mette	Lange	Aarhus	DK
Michael	Horsman	Aarhus	DK
Michael Ruben Teindl	Laursen	Herlev-Gentofte	DK
Mikko	Tenhunen	Helsinki	FI
Minea	Jokivuolle	Odense	DK
Moritz	Rabe	Munich	DE
Morten	Hoyer	Aarhus	DK
Morten	Busk	Aarhus	DK
Morten	Nielsen	Odense	DK
Morten Bjørn	Jensen	Aarhus	DK
Morten Egeberg	Evensen	Drammen	NO
Morten Horsholt	Kristensen	Aarhus	DK
Nadine	Vatterodt	Aarhus	DK
Navrit	Bal	Aarhus	DK
Nico	van Den Berg	Utrecht	NL
Niels	Bassler	Aarhus	DK
Niels	Ulsø	Aarhus	DK
Nina	Levin	Trondheim	NO
Nina	Ubbesen	Aarhus	DK
Ole	Nørrevang	Aarhus	DK
Olga	Zlygosteva	Oslo	NO
Per	Poulsen	Aarhus	DK
Peter	Qvistgaard	Aarhus	DK
Peter	Georgi	Aarhus	DK
Peter	Lægdsmand	Aarhus	DK
Petra	Witt Nyström	Bergen	NO
Pieter	Populaire	Leuven	BE
Priyanshu	Sinha	Aarhus	DK
Remi	Nout	Rotterdam	NL
Saber	Nankali	Aarhus	DK
Sakina	Khan	Aarhus	DK
Sandy	Mohamed	Aarhus	DK
Sara	Linde	Aarhus	DK
Sarah	Gulliford	London	UK

Sarah Eckholdt	Jensen	Aarhus	DK
Signe	Danielsen	Trondheim	NO
Signe Winther	Hasler	Odense	DK
Simon	Heebøll Vindbæk	Aarhus	DK
Simon	Skouboe	Aarhus	DK
Simon	Buus	Aarhus	DK
Simon Nyberg	Thomsen	Aarhus	DK
Simone	Bertelsen	Aarhus	DK
Sky	Rohrer	Aarhus	DK
Slavka	Lukacova	Aarhus	DK
Sofia	Spampinato	Aarhus	DK
Sofie	Tilbæk	Aarhus	DK
Stine Elleberg	Petersen	Aarhus	DK
Stine Sofia	Korreman	Aarhus	DK
Thomas	Ravkilde	Aarhus	DK
Tine Bisballe	Nyeng	Aarhus	DK
Tiril	Hillestad	Oslo	NO
Toke	Hansen	Aarhus	DK
Toralf	Husevåg	Oslo	NO
Torben	Aagaard	Aarhus	DK
Tord	Hompland	Oslo	NO
Trine	Tramm	Aarhus	DK
Ulrik Vindelev	Elstroem	Aarhus	DK
Veera	Ahtiainen	Helsinki	FI
Villads Lundsteen	Jacobsen	Aarhus	DK
Vincenzo	Valentini	Rome	IT
Yolanda	Prezado	Paris	FR
Yuqing	Xiong	Munich	DE