SBRT2006 - 3rd Acta Oncologica symposium

# Stereotactic Body Radiotherapy

June 15-17, 2006 – Copenhagen

**Programme**
**&**
**Abstract book**

# Stereotactic Body Radiotherapy

June 15-17, 2006 – Copenhagen

## Welcome!

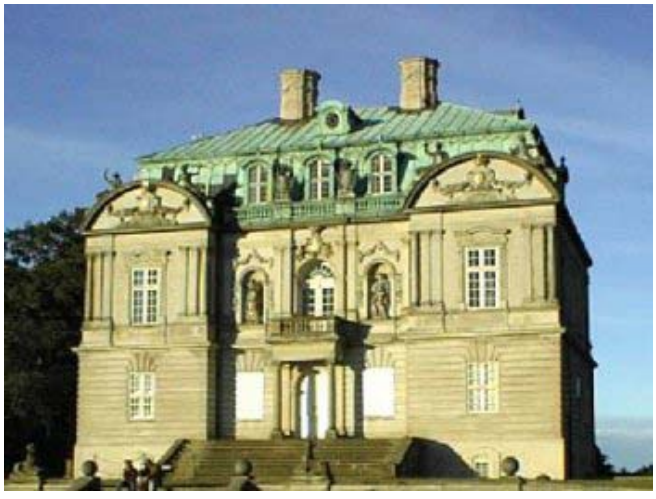
Welcome to the 3rd Acta Oncologica Symposium, held in Copenhagen 15-17 June 2006. This meeting will focus on the benefits and problems associated with stereotactic body radiotherapy (SBRT). The meeting has attracted a large group of physicians, physicists, radiobiologists and other scientists with active interest in SBRT. The format will include a mix of invited presentations, proffered papers and discussion rounds.

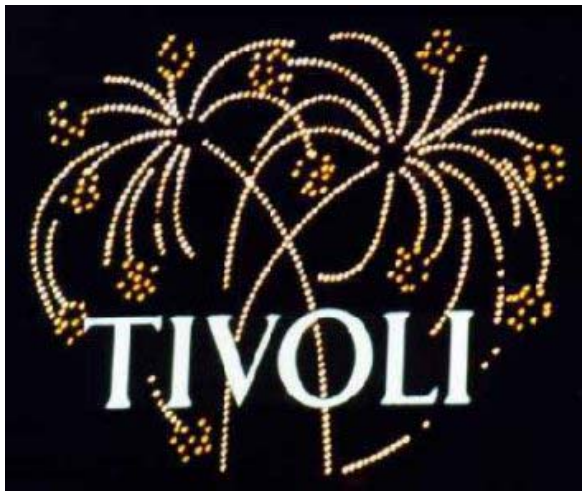
We are proud to present a comprehensive programme with contributions by leading scientists from Europe and North America. Key topics include overview of clinical trials with SBRT, methods for target localization and patient set-up, dose delivery and geometrical verification, image-guided SBRT, morbidity, and fractionation.

All participants and registered accompanying persons are invited to social programme. Thursday night, the dinner at Schaeffergaarden will be followed by a horse carriage tour of Dyrehaven, one of Denmark's prettiest natural areas, which also include the Erimetage Castle. Stags and deer graze freely within the 1000 hectare big fencing. Friday night, busses will take you to Tivoli, where there will be a conference dinner at Restaurant Paafuglen. After dinner, you are welcome to enjoy one of the world most famous amusement parks on your own. Founded in 1843 it is a beautiful, romantic park with lanterns in the trees that create a unique atmosphere. Old and young alike will find entertainment – from open air rock concerts to classical ballet and pantomime. On the rock stage this particular Friday night is Beth Hart.

We hope you will enjoy the meeting and your time in Denmark.

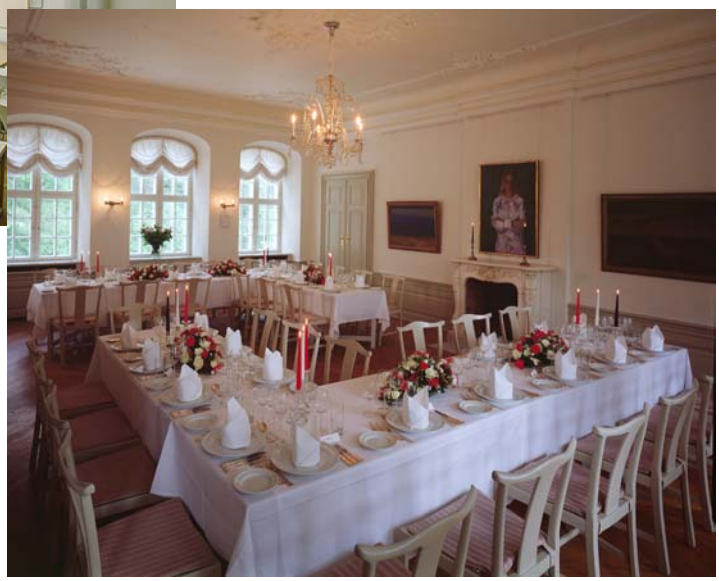
Jens Overgaard  Jacob Lindegaard  Morten Hoyer  Cai Grau





## Hotel Schaeffergaarden

The conference is held at Hotel Schaeffergaarden, which is owned by the Danish-Norwegian Collaboration Foundation. The Foundation works to promote increased understanding and close links between Denmark and Norway. Schaeffergaarden's history stretches all the way back to 1750's. Since the Foundation took over Schaeffergaarden, much of the emphasis has been placed on the décor and furnishing of the rooms with the very best of modern Danish craftsmanship. The most prominent Danish furniture designers in the period 1930 - 1960 are well represented - Ole Wanscher, Kaare Klint, Palle Suenson and Hugo Wegner, with textiles woven by Lis Ahlman, Gerda Henning, Vibeke Klint, Hanne Vedel and Kim Naver. The collection of the works of Sven Havsteen-Mikkelsen are displayed throughout the house. Havsteen-Mikkelsen (1912-1999) has been selected as official artist to Schaeffergaarden, since his motifs are often from the Nordic countries. There are also works by Egill Jacobsen, William Scharff, Gerhard Henning, Haagen Müller, Jeppe Vontillius and Lars Nørgaard. Hanging in the hotelrooms may be seen works by well-known Danish artists, on loan from the National Art Foundation.



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**Invited speakers**
Paul Okunieff, Rochester
Robert Timmerman, Dallas
Laura Dawson, Toronto
Brian Kavanagh, Denver
Martin Fuss, San Antonio
Wolfgang Tomé, Madison
Reinhard Wurm, Berlin
Ingmar Lax, Stockholm
Rolf Lewensohn, Stockholm
Håkan Nyström, Copenhagen
Ben Slotman, Amsterdam
Joost J. Nuyttens, Rotterdam
Peter Wersäll, Stockholm
Klaus Herfarth, Heidelberg
Jörn Wulf, Würzburg/Berne
Michael Molls, München
Morten Høyer, Aarhus
David Jaffray, Toronto
Anders Brahme, Stockholm

**Local organising committee**
Jens Overgaard, Aarhus
Jacob Chr. Lindegaard, Aarhus
Morten Høyer, Aarhus
Cai Grau, Aarhus

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# Programme

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| | **THURSDAY June 15, 2006** | | |
| 12.45 | Welcome + practical information | | |
| | **Session I: Clinical studies - lung cancer**<br>Chairmen: Morten Hoyer, Martin Fuss | | |
| 13.00 | Robert Timmerman | Dallas | Multicentre experience with SBRT for lung cancer |
| 13.25 | Michael Molls | München | The Munich results in stereotactic radiotherapy of T1/T2-non small cell lung cancer |
| 13.50 | Rolf Lewensohn | Stockholm | Treatment of early stage lung cancer using SBRT – studies within the Nordic Cooperative Group for SBRT |
| 14.15 | Jörn Wulf | Würzburg /Berne | Stereotactic irradiation of lung tumors: improved local control by dose escalation |
| 14.40 | Melissa Joyner | San Antonio | Stereotactic body radiation therapy for centrally located lung malignancies: Tumor control and toxicity |
| 14.55 | Coffee break | | |
| | **Session II: Dose – volume – fractionation**<br>Chairmen: Jacob Lindegaard, Brian Kavanagh | | |
| 15.25 | Michael Horsman | Aarhus | Preclinical studies on hypofractionation using a C3H mouse mammary carcinoma model |
| 15.40 | Niclas Pettersson | Gothenburg | DVH analysis of radiation-induced rib fractures after hypofractionated SBRT for NSCLC |
| 15.55 | Merete Paludan | Aarhus | Can acute pulmonary morbidity following stereotactic radiotherapy for NSCLC be predicted by DVH parameters? A prospective study of 28 patients |

# Programme

| THURSDAY June 15, 2006 | | |
|---|---|---|
| 16.10 - 17.30 | **Meet the Industry: Company presentations**<br>Chairmen: Jacob Lindegaard, Brian Kavanagh | |
| Accuray Inc. | Calvin Maurer | CyberKnife Intelligent Robotic Radiosurgery: A Combination of Image-Guidance Technology and Computer-Controlled Robotics Enabling Treatment of Lesions throughout the Body |
| Varian Medical Systems | Karyn A. Goodman | Four-Dimensional Metabolic and Anatomical Imaging in the Planning and Delivery of Radiotherapy for Gastrointestinal Malignancies |
| Elekta AB | Jürgen Meyer | Stereotactic body radiotherapy verification with 3D volume imaging |
| BrainLAB AG | David James | Advanced image guided targeting and dynamic target tracking |
| 18.00 | **Dinner at Schaeffergaarden, tour of Dyrehaven** | |

# Programme

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| | **FRIDAY June 16, 2006** | | |
| | **Session III: Assessment of organ motion**<br>Chairmen: Reinhard Wurm, David Jaffray | | |
| 8.15 | Håkan Nyström | Copen-hagen | Challenges in applying margin reduction in lung treatments by IGRT |
| 8.40 | Anders Traberg Han-sen | Aarhus | Internal movement and set-up accuracy in SBRT using a stereotactic body frame |
| 8.55 | Olfred Hansen | Odense | Inter- and intrafractional movement of the tu-mour in extracranial stereotactic radiotherapy of NSCLC |
| 9.10 | Matthias Guck-enberger | Würz-burg | Benefit of cone-beam CT based image guidance for hypo-fractionated treatment of intrapulmon-ary targets |
| 9.25 | Ben Slotman | Amster-dam | 4-dimensional imaging for target definition in stereotactic RT for lung cancer |
| 9.50 | Coffee break | | |
| | **Session IV: Respiratory gating**<br>Chairmen: Håkan Nyström, Ben Slotman | | |
| 10.20 | Wolfgang Tomé | Madison | The use of 4-dimensional image guidance in SBRT |
| 10.45 | Reinhard Wurm | Berlin | Image guided real-time respiratory gated SBRT for liver and lung tumors |
| 11.10 | Jürgen Meyer | Würz-burg | Tracking of lung tumours without markers: cor-relation between tumour trajectory and breath-ing motion |
| 11.25 | F.Casamas-sima | Firenze | Use of a motion tracking system in radiosurgery and hypofractionated radiotherapy of the tho-racic and abdominal regions |
| 11.40 | Stine Korre-man | Copen-hagen | Comparison of respiratory surrogates for gated lung radiotherapy without internal fiducials |
| 11.55 | Lunch break | | |

# Programme

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| | **FRIDAY June 16, 2006** | | |
| | **Session V: Clinical studies - liver tumours**<br>Chairmen: Rolf Lewensohn, Michael Molls | | |
| 12.55 | Morten Hoyer | Aarhus | Phase II trial on stereotactic body radiotherapy of liver tumors |
| 13.20 | Laura Dawson | Toronto | Individualized, image guided, iso-NTCP based liver cancer SBRT |
| 13.45 | Klaus Herfarth | Heidel-berg | Radiosurgery of liver tumours - effects and side effects |
| 14.10 | Brian Kavanagh | Denver | Interim report of the University of Colorado prospective phase I/II trial of SBRT for liver metastases |
| 14.35 | Alejandro Romero | Rotter-dam | Stereotactic radiotherapy for primary and metastatic liver tumors: a single institution phase I-II study |
| 14.50 | Coffee break | | |
| | **Session VI: Clinical studies – miscellaneous**<br>Chairmen: Morten Hoyer, Robert Timmerman | | |
| 15.20 | A.L. Petersen | Roches-ter | Stereotactic Body Radiation Therapy (SBRT) for Lung Metastases |
| 15.35 | Jo-Aasmund Lund | Trond-heim | Implementation of stereotactic radiotherapy in a small hospital. |
| 15.50 | Karin Dieck-mann | Vienna | Stereotactic Body Radiation Therapy at the Medical University Vienna: 6 years clinical experience and future perspectives |
| 16.05 | Peter Wersäll | Stock-holm | Results of a prospective phase II trial of SBRT for primary and metastatic renal cell carcinoma |
| 16.30 | Paul Okunieff | Roches-ter | Cooperative group efforts in the incorporation of radiosurgery into national clinical studies |
| 16.55 | General discussion: Future clinical trials | | |
| 18.30 | Dinner at Restaurant "Paafuglen" Tivoli Copenhagen | | |

# Programme

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| | **SATURDAY June 17, 2006** | | |
| | **Session VII: Quality assurance and dose calculations**<br>Chairmen: Ingmar Lax, Wolfgang Tomé | | |
| 8.45 | Ingmar Lax | Stock-holm | Dose distributions in SBRT |
| 9.10 | E. Djärv | Gothen-burg | Dummy run for a phase II study of stereotactic radiotherapy of T1-T2 N0M0 inoperable non-small cell lung cancer |
| 9.25 | P. Rassiah | San An-tonio | Characterization of lung lesion doses in stereo-tactic body radiation therapy (SBRT) via Monte Carlo |
| 9.40 | Coffee break | | |
| | **Session VIII: Emerging techniques**<br>Chairmen: Cai Grau, Laura Dawson | | |
| 10.10 | Karyn A. Goodman | Stanford | Image-Guided Radiotherapy for Upper GI Malig-nancies |
| 10.25 | Martin Fuss | San An-tonio | Clinical experience with serial and helical tomo-therapeutic SBRT |
| 10.50 | Joost Nuyttens | Rotter-dam | The CyberKnife: clinical applications and early results |
| 11.15 | Anders Brahme | Stock-holm | Light ion therapy: the ultimate stereotactic treatment technique |
| 11.40 | David Jaffray | Toronto | Radiation therapy 2006 - images, guidance sys-tems, and robots |
| 12.05 | Closing remarks | | |
| 12.15 | **Box lunch** | | |

Robert Timmerman

## Multicentre experience with SBRT for lung cancer

*Robert Timmerman*

Department of Radiation Oncology, University of Texas Southwestern, Texas, USA

Starting in 2002, the Radiation Therapy Oncology Group in North America began the process of developing multicenter prospective trials in lung cancer using Stereotactic Body Radiation Therapy (SBRT). Much of the work was based on the prospective single institution trials from Indiana University that had been presented and published. In late 2004, RTOG 0236 using SBRT for medically inoperable patients with clinical stage I non-small cell lung cancer (NSCLC) was activated for accrual. This was the first cooperative group study of its kind. Prior to activation, representatives from the Lung Committee, Image-Guided Therapy Committee, Physics Committee, and Radiobiology Committee met on regular occasions to design the multicenter study and quality assurance measures. SBRT is not a black box, and the essence of the therapy had to be distilled via guidelines. Issues related to patient selection, method of dosimetry construction, equipment requirements, motion assessments and control, site accreditation, data exchange, and follow-up policies were worked out by compromise and consensus. RTOG 0236 has nearly completed its accrual. The Lung Committee has initiated the development of several other trials, each building on the last, to investigate the therapy in central tumors, in combinations with systemic therapy, and in operable patients. The guidelines developed for RTOG 0236 will be refined to take advantage of more modern innovations including heterogeneity corrections and intensity modulation when appropriate. The development of RTOG 0618 using SBRT in operable patients with early stage NSCLC is a testament to both the enthusiasm from already published works and the care of prospective clinical testing using SBRT techniques.

Michael Molls

## The Munich Results in Stereotactic Radiotherapy in T1/T2-Non-Small Cell Lung Cancer

*Frank B. Zimmermann, Hans Geinitz, Sabine Schill, Ulrich Schratzenstaller, Michael Molls*

Department of Radiation Oncology, Klinikum rechts der Isar, Technical University Munich, Germany

Introduction: For patients with early stage non-small cell lung cancer (NSCLC), unsuitable for resection (board inculuding surgeous), hypofractionated stereotactic radiotherapy has been introduced as treatment of choice in our department.

Material and methods: We report on 68 patients (median age 76 (59-92) years; follow-up 17 (3-44) months) with early stage NSCLC (cT 1-2 cN0 cM0; CT-scan of thorax, abdomen and brain (in Adenocarcinoma) and FDG-PET), treated between December 2000 and January 2006 by hypofractionated stereotactic radiotherapy (mean total dose 37.5 Gy (24-40 Gy; in surrounding 60 %-isodose) in 3-5 fractions.

Results: There have been 4 local recurrences (6 %), making an overall local control rate of 96 %, 88 % and 88 % at 1, 2 and 3 years.19 pat. died, with 8 (12 %) due to lung cancer but only 2 by local progression. Cancer specific survival is 96%, 82 % and 73 % at 1, 2 and 3 years, respectively. 11 pat. died from comorbidities (liver cirrhosis, cardial failure, secondary cancer, apoplexia a.o.), resulting in an overall survival of 51 % at 3 years. Acute and subacute side effects (43 %) were mild (fatigue grade 1-2 15 %; shivering 5.7 %; nausea 6.8 %; Dysphagia 1.1 %; dermatitis 3.4 %; pneumonitis grade I 19.2 %, grade II 12.8 %), with only one patient developing Grade III pneumonitis (3.2 %). Severe late sequelae was low (3.2 % grade III lung fibrosis, 3.7 % rib fracture; 3.7 % benign pleural effusion).

Conclusion: Hypofractionated stereotactic radiotherapy of early stage lung cancer is feasible with low rate of severe side effects, but high local control rates. Distant metastases is the main cancer-related cause of death, and systemic therapy should be taken into account in younger patients.

Rolf Lewensohn

## Treatment of early stage lung cancer using Stereotactic Body Radiation Therapy – studies within the Nordic Cooperative group for SBRT.

*Rolf Lewensohn MD Phd[1], Pia Baumann MD[1], Lars Ekberg MD Phd[2], Cai Grau MD Phd[5], Morten Höijer MD Phd[6], Suzanne Rehn-Eriksson MD Phd[3], , Karl-Axel Johannson Phd[4], Ingmar Lax Phd[1],Jo-Åsmund Lund MD Phd[6], Nina Levin Phd[6], Jan Nyman MD Phd[4], Elisabeth Morhed Phd[3], Merete Paludan MD[5], Signe Friesland MD Phd[1], Anders Traberg Phd[5], Lena Wittgren Phd[2],*

Radiumhemmet Karolinska University Hospital1, Malmö University Hospital[2], Uppsala University Hospital[3], Sahlgrenska University Hospital[4], Sweden, Aarhus University Hospital[5], Denmark, Trondheim University Hospital [6], Norway

We report treatment of inoperable stage I NSCLC at our institutions 1996-2003. Mean age was 74 years (range 56-90 y) with 69 men and 72 women. Cytological verification was obtained in 76% (107/141). Inoperability reasons were COPD or CVD. Treatment doses varied from 30-48 Gy (at the 65% isodose to the periphery of the PTV) in 2-4 fractions. Median equivalent dose (2 Gy fractions) was 93.8 Gy (50-100). Mean GTV was 39 cm³ (2-436) with a planning target volume 101 cm³ (11-719).
Overall response rate (CR, PR, SD) was 97% (134/138). During a mean follow up period of 33 months (0.7-107), 16 (11%) local recurrences were observed, 11 with additional metastatic disease. Fourteen patients experienced grade 3-4 toxicity according to RTOG. Central tumour location, tumour size and target definition were related to risk for relapse. Distant metastases occurred in 25% (35/141) of the patients. Three- and 5-year overall survival was 52 and 26%. The cause specific 3- and 5-year overall survival was 66 and 40% respectively.
In the period 2003-2005 we included 60 patients into a multicentre GCP controlled phase II study using a radiation dose of 15 Gy x 3 (EQD2 93.8 Gy) at the 65% isodose to the periphery of the PTV, in NSCLC stage I. Primary end point is local control at 3 years. Early lung toxicity will be reported.
Using an EQD2 of 50-100 Gy to stage I NSCLC in our hands results in acceptable toxicity and favourable local control non inferior reported with fractionated RT.

Jörn Wulf

## Stereotactic radiotherapy of lung tumors: improved local tumor control by dose escalation due to high precision treatment

*Joern Wulf* [1,2]

[1] Lindenhofspital, Dept. of Radiooncology, Bremgartenstrasse 117, CH-3001 Berne, Switzerland; wulf@lindenhof.netline.ch
[2] previously University of Wuerzburg, Dept. of Radiotherapy, Wuerzburg, Germany

Purpose: The results of radiotherapy for local treatment of medically inoperable non-small cell lung cancer (NSCLC) stage I and II or metastases are often inferior to surgical resection due to insufficient dose. Therefore dose escalation performed by shortening of treatment time (less tumor cell repopulation) and reduction of the irradiated volume (to decrease toxicity) as performed by stereotactic treatment might be an advantageous strategy. The results of this approach and an analysis of a dose-effect-relation based on the Wuerzburg experience are presened.
Method: From 11/97-12/04 hundred pulmonary targets (41 NSCLC, 59 metastases) were treated. Dose-fractionation was 3x10Gy (n=23), 3x12-12.5Gy (n=31), all of them normalized to the PTV-enclosing 65%-isodose. Forty patients received single dose irradiation with 1x26Gy/PTV-encl. 80%-isodose and 6 patient received different schedules (8x6Gy, 4x7Gy, 5x7Gy). To analyze the dose-effect relation of local tumor control the different dose-fractionation regimes were recalculated as BED [(BED = dose/fraction x fraction number (1 + fraction dose / α/ß) using an alpha/beta of 10Gy] and a logistic regression and a multivariate analysis were performed.
Results: Median f/u was 15 months (2-85 months), 11 local failures were observed. The actuarial local control rate after 2 years and later was 86% for NSCLC and 85% for metastases (n.s.). Nevertheless local control was dose dependent: tumors treated with higher dose (3x12-12.5Gy or 1x26Gy) achieved 93% actuarial local control while tumors treated with 3x10Gy or other regimes reached 71% (p=0.034 log-rank test). The rate of serious side effects was very low with less than 3%. The TCD 50 was 50Gy at the PTV-margin and 94Gy at the isocenter, the TCD 90 was 74Gy at the PTV and 124Gy at the isocenter. In multivariate analysis of dose, tumor volume and histology only the dose at the PTV-margin was significantly predictive for local control.
Conclusion: Dose escalation by stereotactic irradiation of lung tumors leads to very high local control rates of >90% if adequate dose is delivered (>100Gy isocenter, >74Gy/PTV). These results can be achieved with very low risk for side effects if volume restriction to high precision therapy is performed. Prospective studies for ESRT of NSCLC stage I/II are open in Japan (JCOG-0403, 4x12Gy/isocenter) and the USA (RTOG-0236, 3x20Gy/PTV-encl. 80%-isodose) to confirm these results.

Melissa Joyner

## Stereotactic body radiation therapy for centrally located lung malignancies: Tumor control and toxicity

*Melissa Joyner, Niko Papanikolaou, Martin Fuss*

University of Texas Health Science Center, Department of Radiation Oncology; San Antonio Cancer Institute

Hypofractionated or single dose stereotactic body radiation therapy (SBRT) for lung metastases and primary lung tumors has been documented to be feasible and to yield excellent local tumor control. However, there is concern regarding treating centrally located tumors due to a perceived risk of increased toxicity. The aim of this analysis was to determine outcomes and toxicity of SBRT delivered to centrally located lesions, and to compare this data with a population of patients treated for peripheral targets.
Of 108 patients treated for malignant lung lesions between 8/01 and 12/05, 9 patients were treated by SBRT for lesions in close proximity to the hilum or hilar lesions. Sequential and helical tomotherapeutic intensity-modulated radiation techniques were used to deliver 3 fractions of 12 or 20 Gy (total dose 36 or 60 Gy). Doses were prescribed as the minimum dose to the planning target volume (PTV) which initially included safety margins of 5 mm axially and 10 mm cranio-caudally to the gross tumor volume (GTV). Since implementation of 4D CT data for SBRT planning, 5 mm PTV margins were used. We analyzed tumor response, survival and treatment associated toxicity in this population.
Results: For all 9 patients, at least 1 (median 3, maximally 8) follow-up imaging study (CT or CT and PET) were available. Clinical follow-up ranges from 6 weeks to 35 months. Tumor response, typically no evidence of disease were confirmed in imaging as early as 6 weeks post SBRT. Fibrotic changes in normal lung tissue were observed as early as 12 weeks post SBRT. No lung collapse or atelectasis was observed. However, in a subset of patients, the walls of major airways appeared thickened without clinical correlate. Clinically, no patient complained of decreased lung function. At analysis, 5 patients are alive.
Conclusions: SBRT in patients with centrally located tumors appears safe based on the outcomes in the observed population. Tumor location was not associated with an increase in clinical or imaging toxicity. Changes such a major airway wall thickening have been followed for up to 2.5 years, without the occurrence of long-term clinical symptoms.

Michael Horsman

## Preclinical studies on hypofractionation using a C3H mouse mammary carcinoma model.

*Horsman, M.R., Nielsen, T., Østergaard, L. and Overgaard, J.*

Dept. Experimental Clinical Oncology and Neuroradiological Research Unit, Aarhus University Hospital, Aarhus, Denmark.

Purpose: Radiation given in a hypofractionated schedule has a greater anti-tumour effect than the same total radiation dose given in a conventional fractionated schedule. The aim of this study was to demonstrate this difference in a C3H mammary carcinoma and to investigate the postulated role of the tumour vasculature as a target for this effect.
Materials and Methods: A C3H mammary carcinoma grown in the right rear foot of female CDF1 mice was used in all experiments. Treatments were performed on retrained non-anaesthetised mice when tumours had reached 200 $mm^3$ in size. Radiation (240 kV x-rays) was given locally to the tumour bearing foot either as a single large dose (1 x 20 Gy) or in a fractionated schedule (10 x 2 Gy) given as 2 fractions/day (separated by a 6-hour interval) for 5 consecutive days. Tumour response to irradiation was assessed by calculating the tumour growth time (TGT; time taken for tumours to grow to 3 times their treatment volume). Vascular effects were monitored using magnetic resonance imaging (MRI). This involved injecting mice with gadolinium (Gd)-DTPA and then performing dynamic contrast enhanced (DCE)-MRI using a 3-Tesla magnet. The MRI protocol included a T1 map and dynamic T1-weighted imaging, with the initial area under the concentration curve (IAUC) for 90-seconds following Gd-DTPA being calculated pixel-wise for regions of interest containing whole individual tumours. Results were analysed using either a Student's t-test (TGT) or 1-way ANOVA (MRI), with the significance level being $p<0.05$ for both tests.
Results: The mean ($\pm$ 1 S.E.) TGT for untreated control mice was 4.0 days ($\pm$ 0.2). Irradiating tumours with 10 x 2 Gy significantly increased this TGT to 12.9 days ($\pm$ 0.6). However, when this same total dose of radiation (20 Gy) was given as a single fraction the TGT was further significantly increased to 19.8 days ($\pm$ 0.7). Preliminary DCE-MRI measurements showed a time-dependent decrease following treatment with 1 x 20 Gy. The mean ($\pm$ 1 S.E.) of the median IAUC values measured in non-irradiated tumours was 0.261 ($\pm$ 0.022). At 3, 6 and 24 hours after irradiating these values were 0.258 ($\pm$ 0.019), 0.251 ($\pm$ 0.010) and 0.215 ($\pm$ 0.011), respectively. However, the difference between the controls and 24-hour samples was not statistically significant ($p=0.08$), which may reflect the low number of animals in each group (n= 4-6). Additional measurements are being made to determine the optimal time for the maximum drop in IAUC after 1 x 20 Gy, and how these effects compare to those seen following 10 x 2 Gy.
Conclusions: Our results confirm that radiation given in a large single dose is relatively superior to the same dose given in a more conventional fractionated schedule. The exact role of the tumour vasculature in explaining this difference is still under investigation.
*Supported by a grant from the Danish Cancer Society.*

Niclas Pettersson

## DVH analysis of radiation-induced rib fractures after hypofractionated SBRT for NSCLC

*Niclas Pettersson, Jan Nyman, Karl-Axel Johansson*

Sahlgrenska University Hospital

Following the renewed interest in hypofractioned radiation therapy there is not only a need for evaluation of late effects, but also to test the validity of current NTCP-models, under these conditions.
During 1998-2004, 65 patients with inoperable stage1 NSCLC were treated with SBRT at Sahlgrenska University Hospital. The dose prescription was 45Gy/3fr. at the periphery of the PTV. Follow-up CTs (every sixth month post treatment) were checked for evidence of radiation-induced rib fractures. Patients with adequate follow-up time and the tumour situated reasonably close to the rib cage were identified. The corresponding ribs were separately contoured and the DVHs were exported. The DVHs were evaluated using cut-off models and two widely used NTCP-models. The LKB- and the relative seriality models were tested with published parameters using LQ-transformation of the DVHs.
Twenty-one patients with a total of 64 ribs were identified and four ribs in two patients were radiographically diagnosed as fractured. The mean follow-up time were 33.7 months (range: 11.4-62.8) with fractures diagnosed after 11 and 15 months.
Correlations between fractures and DVH parameters were found. Using V35 Gy, the absolute volume receiving 35 Gy or more (EQD2, $\alpha/\beta$=3 Gy =103 Gy), as a cut-off it was found that 0/57 ribs were fractured if V35Gy < 6cm3 compared to 4/7 fractures for V35Gy > 6cm3.
Both NTCP models, however, greatly overestimated the NTCP with mean NTCPs for all 64 ribs exceeding 40%, compared to the clinically observed rate of 6%.

Merete Paludan

## Can acute pulmonary morbidity following stereotactic body radiotherapy for non-small cell lung cancer be predicted by dose-volume histogram parameters? A prospective study of 28 patients.

*Merete Paludan[1], Anders Traberg Hansen[2], Jørgen Petersen[2], Cai Grau[1], Morten Høyer[1].*

Department of Oncology[1] and Department of Medical Physics[2], Aarhus University Hospital, Denmark.

Purpose and background; Stereotactic body radiotherapy (SBRT) is acknowledged as an effective treatment for patients with medically inoperable NSCLC. It involves the delivery of radiation doses of high biological potency to patients with frequent pre-irradiatory compromise of pulmonary function. Care must be taken for pulmonary toxicity not to outbalance the benefits of tumor control. If they predict the risk of pulmonary toxicity, DVH parameters may serve as tools for optimised dose planning and patient selection.
Material and methods: The study population consisted of 28 patients with medically inoperable stage I NSCLC. Between 2000 and 2003, the patients received SBRT at our department with a central dose of 45 Gy delivered in 3 fractions in 5-8 days. Using the WHO scale for dyspnea, acute pulmonary morbidity was prospectively recorded at follow-up visits within the first 6 months after completed SBRT. DVH parameters for pulmonary tissue were retrieved from the three-dimensional dose distributions.
Results: Radiation exposure of the tumor-bearing lung mounted to a median physical MLD of 5.4 Gy (range 2.6-14.7 Gy). Acute pulmonary morbidity was registered in 11 patients during follow-up. Four patients experienced aggravation of dyspnea corresponding to an increase of ≥1 grade above baseline. The dyspnea in seven patients increased by ≥2 grades above baseline. The time-course showed pronounced intra- and inter-individual variability. No clear relation to the onset of radiation exposure was observed. We found no association between DVH parameters and acute pulmonary morbidity. When accounting for potential confounders, we identified COPD as the factor showing the closest association with acute pulmonary morbidity after SBRT.
Conclusion: The observed aggravation of dyspnea during a 6-month-follow-up after SBRT reflects habitual exacerbations of COPD rather than treatment-related toxicity. The study supports our notion of SBRT as being not only an effective, but also very safe treatment for NSCLC. Concern about acute pulmonary toxicity should not be prohibitive for future studies targeting current limitations to radiation dose, irradiated volume, and tumor localization in SBRT for NSCLC.

Håkan Nyström

## Challenges in applying margin reduction in lung treatments by IGRT

*Stine Korreman, Trine Nøttrup, Marika Björk and Håkan Nyström*

Image Guided Radiation Therapy can be used to reduce the systematic set-up uncertainties and, if applied at each fraction, also the random variations in target positioning. For IGRT of the prostate the margin between CTV and PTV can be reduced from the conventional margin of 10 – 15 mm to less than 5 mm therefore allowing for dose escalation and/or a reduction in rectal toxicity. Whereas the motion of the prostate is more or less random, the motion of a lung tumour may be dominated by the breathing motions. Such a motion may be observed by external substitutes such as the motion of the chest wall. By gating the irradiation to a pre-specified fraction of the breathing cycle, could open up the possibilities of margin reduction also for lung treatments. However, for margin reduction to be feasible, first of all the correlation of the tumour motion and the breathing signal must be firm. Secondly, the motion as monitored during the planning phase of the treatment must remain the same during all the fractions. For many patients these requirements cannot be met well enough over a full course of treatment to make gated treatments with margin reduction possible, without the use of internal markers. In the case of hypofractionated treatments, more efforts can be spent on every single fraction to verify the breathing signal and it's correlation with target motion. Non-moving targets can be assigned smaller than standard margins and for moving targets, the standard margins can be verified or maybe slightly adjusted. For a sub-population of patients with targets with very large motions, where the standard margins are not wide enough, gated treatments could be considered.

Anders Traberg Hansen

## Internal Movement, Set-up accuracy and Margins for Stereotactic Body Radiotherapy using a Stereotactic Body Frame.

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Purpose
Stereotactic body radiotherapy is used in the treatment of primary and secondary tumors of the lung and liver. The treatment technique differs from traditional radiotherapy by the use of complex field arrangements to deliver a hypo fractionated treatment to a small tumor volume within tight margins. High accuracy in target localisation is therefore of major importance. The aim of this study is to investigate the set-up accuracy and the inter-fractional movement of the tumor by use of the Elekta body frame (SBF) and based on these to estimate suitable margins.

Materials and methods
This study is based on the treatments of 30 patients of whom 8 had liver metastases and 22 with primary lungs cancer. All patients are immobilized by the Elekta SBF. From a total of 69 CT-studies and by use of the Helax-doseplanning system, it is possible to measure the tumor displacement as well as the displacement of bony structures from one CT-study to the next. These measurements made a calculation of the standard deviations of the movements possible.

Results and conclusions
It is concluded that the fixation within the SBF of the bony structures of the patient is accurate, and that the dominant source of tumor displacement is the internal organ movement. Margins based on the standard deviations are derived and it is found that the used margins are reasonable in there relative size.

Olfred Hansen

## Inter- and intrafractional movement of the tumour in extracranial stereotactic radiotherapy of NSCLC.

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Background: Respiration may be a limiting factor in the accuracy of extracranial stereotactic radiotherapy of NSCLC.
Methods: We have treated 8 patients with NSCLC with a dose of 45Gy/3F. Fixation was in SBF (Lax-Blomgreen). At the time of simulation and before each treatment 6 consecutive CT-scans were performed. The aim of this project was to quantify the inter- and intrafractional changes in location of the tumour due to respiration and setup errors. The setup error was examined by registration of the CT-scans for each day. The registration was performed for the SBF as well as the anatomy of the patient by the image fusion application SyntegraTM in the PinnacleTM planning system. The variation was divided into 1) patient position in the SBF, 2) interfractional changes (=changes in daily mean position of the tumour), and 3) intrafractional changes (=changes in tumour position during respiration).
Results: In total, 187 scans were obtained. Preliminary calculations showed the uncertainty (2xSD) to be (x= medio-lateral, y=A-P, z=cranio-caudal): 1) Patient position: x=2.4mm, y=1.4mm, z=3.1mm, 2) Interfractional: x=3.3mm, y=3.2mm, and z=4.5mm and 3) Respiration: x=1.9mm, y=2.6mm, z=4.5mm. The total uncertainty was: x=4.6mm, y=4.2mm, z=8.3mm.
Conclusion: Syntegra provides a systematic and accurate way to register uncertainty in treatment positioning. Since the inter- and intrafractional errors are in the same magnitude, cone beam CT verification of the treatment position and gating of the treatment delivery would provide equal improvement in the precision of dose delivery to these NSCLC patients.

Matthias Guckenberger

## Benefit of cone-beam CT based image guidance for hypo-fractionated treatment of intrapulmonary targets

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The benefit of image-guidance with cone-beam CT volume imaging and online correction of set-up errors was evaluated for hypo-fractionated treatment of intrapulmonary targets.
In treatment of 17 patients a stereotactic Bodyframe (SBF) was used for positioning and immobilization. Prior to every fraction a cone-beam CT (CB-CT) was acquired and set-up errors of the actual tumor position were corrected online. After treatment a second CB-CT study was acquired.
Patient positioning in the SBF was reproducible and in accordance to the literature. Set-up errors of the actual tumor relative to the SBF coordinates were 2.9mm±1.8mm (longitudinal), 4.8mm±1.3mm (AP) and 2.0mm±1.9mm (left-right). Errors exceeding 3mm, 5mm and 8mm were observed in 42%, 22% and 6%, respectively. Correlation between position of the bony anatomy and the soft-tissue tumor itself was poor (r=0.52): errors larger than 3mm, 5mm and 8mm were seen in 29%, 12% and 3%, respectively, if the bony anatomy was used as a surrogate for the tumor position. Intra-observer variability for evaluation of the tumor position in the CB-CT was 0.9mm±0.7mm (maximum 3.4mm). The grey-value match (XVI software) of planning CT and CB-CT showed highly reproducible results but introduced a systematic error in the direction of the tumor motion compared with the set-up errors measured manually. Displacements of the tumor position after treatment were small but maximum errors of 4mm were recorded.
Reproducibility of the tumor position relative to the SBF and relative to the bony anatomy was poor. Volume imaging using CB-CT significantly reduced set-up errors and allows a reduction of safety margins.

Ben Slotman

## 4-Dimensional imaging for target definition in stereotactic radiotherapy for lung cancer

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Local control after conventional radiotherapy for non-small cell lung cancer is disappointing. Even high dose (70Gy) conformal radiotherapy leads to a local failure rate above 50%. A number of studies have shown that after hypofractionated stereotactic radiotherapy (SRT), local control rates above 90% can be obtained with acceptable toxicity. In SRT, equivalent doses of 120 Gy and above are delivered. This can only be done with a very accurate target definition and maximal sparing of normal tissues.One of the main challenges in SRT is movement of the tumor and intrathoracic organs. Since 2004, we have started 4D radiotherapy for the (stereotactic) treatment of lung tumors. 4D radiotherapy is defined as the explicit inclusion of temporal information during imaging, planning and treatment. In this presentation, the various aspects of implementation of 4D radiotherapy for stereotactic treatment of lung cancer, including 4D scanning, contouring, generation ofr internal target volumes, evaluation of motion and breathing pattern, benefits of breathing control and respiratory gating, treatment delivery and verification, will be discussed.

Wolfgang Tomé

## On the use of 4-dimensional image guidance for SBRT

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The technical and treatment planning aspects of 4D image guided Stereotactic body radiotherapy (SBRT) for peripheral lung tumors are presented. Patients are immobilized using a vacuum based immobilization system. A vacuum of 80mbar together with an abdominal pressure pillow is used to reduce tumor motion. For treatment planning a regular thin slice CT is acquired for localization and 4D-CT is acquired to define the motion envelope of the target. The CTV is defined by adding 6 to 8mm margin to the motion envelope depending on histology. Treatment plans are generated using inverse planning and a dose fractionation schedule of 5 fractions of 12 Gy is employed. In order to keep the incidence of clinically significant radiation pneumonitis below 20% the mean NTD to the total lung – PTV is kept below 18Gy3. Prior to the delivery of each treatment fraction, patients are placed in their custom made double vacuum whole body mold and immobilized. In order to confirm the correct internal target position a pretreatment MVCT scan of the patient in the treatment position is obtained and fused to the treatment planning CT. Any modification to patient position based upon the cross correlation of these two image stets are made prior to treatment. All treatments are delivered within 10 calendar days of initiation. We have treated a total of 10 patients using this approach and have not observed any clinical toxicities and up to this point in time all patients have achieved local control of their disease.

Reinhard Wurm

## Image guided real-time respiratory gated SBRT for liver and lung tumors: Initial experience

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Purpose: To evaluate our initial experience of real-time respiratory gated SBRT for liver and lung tumors.
Methods: The system combines stereoscopic X-ray cameras (ExacTrac X-Ray 6D) with a dedicated CSRS/T linear accelerator (Novalis) and an automatic six-degree-freedom treatment couch (ExacTrac Robotics) for real-time dynamic adaptive treatment targeting (BrainLAB, Heimstetten, Germany, Varian Palo Alto, USA). Moving targets are located and tracked relative to fiducial markers (Visicoil™, USA) using real-time image guided gating. Digital reconstructed radiographs from reference CT scans are compared with verification stereoscopic images using fully-automated matching software for real-time quantification and correction of axial and rotational deviations between reference and stereoscopic images. We present our acceptance testing and initial experience in patients with liver and lung tumors. For treatment planning FDG-PET and CT scans taken at free breathing and expiration breath hold with internal and external fiducials present were used. The target volume based on the FDG-PET plus a 5mm safety margin and the internal fiducials were both manually delineated. Patients were treated were treated with 8-11 consecutive fractions to a dose of 78 Gy.
RESULTS: Tests demonstrated alignment of the treatment dose with moving targets within + 1mm. Inter- and intrafractional axial set-up displacements were also largest in the cranio-caudal direction and rotational errors in the sagittal plane. The total 3D displacement was 1.9 mm (mean), 0.7 mm (SD) with a range of 0.3-4.9 mm.
Conclusion: This initial evaluation shows the accuracy of the system and the feasibility of image guided real-time respiratory gated SBRT for liver and lung tumors.

Jürgen Meyer

## Tracking of Lung Tumours without Markers: Correlation between Tumour Trajectory and Breathing Motion

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For irradiation of lung tumours with stereotactic body radiotherapy (SBRT) the treatment margins depend on the mobility of the tumour, i.e. in maximum inspiration and expiration. These margins could be considerably reduced by tracking the tumour and correcting for movement in real-time. In this preliminary work tumour mobility during treatment was assessed by means of fast image acquisition of the treatment fields (movie) on an electronic-portal imaging device (EPID) and retrospective automatic tracking of the tumour trajectory. Detection and tracking of the tumour was accomplished by applying a similarity measure to compare each frame of the EPID movie with a reference image. Simultaneously, the breathing patterns of the patients were recorded by placing a passive sensor tool on the abdomen of the patient that was also tracked with an infra-red stereo camera. Both tracking curves, i.e. the tumour trajectory as well as the abdominal movement due to breathing, where then resampled to a uniform step size and the correlation between the tumour trajectory and the breathing signal determined. A least-square parameter estimation approach using System Identification methods was applied to establish a model to correlate the two data sets. Excellent correlation between the two data sets was obtained in all three dimensions. The next step is to investigate whether the model can be applied to consecutive treatment fractions to predict tumour motion and drive the treatment table to compensate for tumour motion.

F.Casamassima

## Use of a motion tracking system in radiosurgery and hypofractionated radiotherapy of the thoracic and abdominal regions: evaluation of uncertainty in off-target dose distribution and optimization strategies

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Purpose: . Spatial accuracy in extracranial radiosurgery is affected by organ motion. The Synchrony system is able to avoid PTV enlargement while preserving reasonably short treatment times compared to gated techniques. However, by using Synchrony one shall be very careful in situations where the set of fiducial markers used to identify the target could move towards organs at risk (OAR)
Material and method: 6 patients treated by means of the Synchrony system were taken into account (2 lung, 2 pancreas, 2 liver treatments). For each patient 2 CT scans were available, one describing the end-exhale and the other one describing the end-inhale condition. A treatment plan was generated for Synchrony using the end-exhale CT, obtaining a dose distribution that encompassed the planning target volume (PTV). Dose volume histograms (DVH) and Equivalent Uniform Dose (EUD) were calculated for the organs at risk. The dose distribution was then recalculated on the end-inhale CT by aiming at the target using a shift corresponding to the displacement of the center of mass of the internal fiducial markers compared to the end-exhale condition. DVH and EUD were recalculated for the organs at risk. Finally, a dose distribution was calculated by weighted average using 1/3 and 2/3 weighting factors for end-inhale and end-exhale, respectively.
Results: In the cases for which the target moved closer to the OAR (3 cases out of 6), a small but significant increase was detected in the DVH and EUD of the OAR. In other 3 cases no significant variation or a significant decrease was detected
Conclusions: Significant uncertainty may arise from the use of a motion tracking device in the dose distribution to organs at risk. The uncertainty is due to the relative motion between PTV and OAR, which is not taken into account during tracking. However, with a double CT scanning representing end-inhale and end-exhale conditions it is possible to limit this uncertainty or The breathing condition in which the OAR is closer to the PTV should be selected for planning. This strategy, however, implies that a linear model is assumed for the displacement. A full understanding of the dose distribution would only be possible by means of a complete 4D-CT representation.

Stine Korreman

## Comparison of respiratory surrogates for gated lung radiotherapy without internal fiducials

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Purpose: This study aims to evaluate the efficacy of external and internal respiratory surrogates to minimize the residual breathing motion during gated lung radiotherapy.
Materials and methods:
Seven lung cancer patients referred for radiosurgery using a CyberKnife robotic linear accelerator (Accuray), underwent placement of gold fiducial markers directly into the tumor under CT-guidance. The RPM system (Varian Medical Systems) was used to record several consecutive fluoroscopic movies during audio coached breathing, synchronously with the movement of an external optical marker. The positions of the internal fiducial markers were used as the standard ("truth") of tumor motion.
Two surrogates for respiratory motion were compared; an external optical marker, and an image correlation trace excluding the internal fiducials. Receiver-operator characteristics (ROC), and residual gated motion analysis was performed.
Results:
The image correlation performed better than the external marker, with respect to both discriminating power in the ROC analysis, and residual motion extent. The discriminating power was >0.8 (area under ROC curve) for 6 out of 7 patients, with the highest magnitude for the image correlation trace for 6 patients.
The reduction of internal movement by gating was mimicked well by both respiratory surrogates. Deviations between external and internal motion reductions were smaller than 25 percent points. Gating based on the image correlation trace gave comparable or smaller residual internal motion than gating based on the external marker in the majority of cases.
Conclusion:
Respiratory gated radiotherapy for lung cancer based on either external marker monitoring or image correlation, provides consistent reduction of internal (intra-session) lung tumor breathing motion. Fluoroscopic gating based on correlation of native image features in most cases perform better than gating based on an external marker.

Morten Hoyer

## Phase II trial on stereotactic body radiotherapy for colo-rectal metastases

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Surgical resection and radiofrequency ablation (RFA) are widely used in the treatment of colo-rectal metastases (CRM). Retrospective studies of large series of patients with CRM in the liver have shown that resection results in long term survival of 25-30% of the patients. Studies of patients with CRM in the lungs show similar results. Unfortunately, more than 80% of patients with CRM of the liver and even more patients with extra-hepatic CRM are considered inoperable. In the present Danish phase II trial, the effect and toxicity of SBRT was tested in the treatment of patients with CRM who were not amendable for resection or RFA. Sixty-five patients with a median of 2 (range 1-6) and a total number 142 CRM in liver, lung or suprarenal gland were included into the trial. Sixty-one patients had metastases in one organ and 4 patients in 2 organs. All patients were considered inoperable by a multi-disciplinary hepato-biliary team or a thoracic surgeon. The patients were immobilized by the Elekta stereotactic body frame (SBF) or a custom made body frame. SBRT was given on linear accelerator with standard multi-leaf collimator. Central dose was 15 Gy x 3 and overall treatment time 5-8 days. Local control 2 years after SBRT was 79% in an individual tumour based analysis. Since most patients had multiple metastases, the patient based local control rate was 64%. However, due to development of new metastases, only 19% were without progression after 2 years. Overall survival was 38, 23 and 13% at 2, 3 and 5 years after SBRT, respectively. Size of largest metastasis was the only prognostic factor related with survival. Patients with a metastasis smaller or larger than 3.0 cm had median survival of 2,07 and 1,23 years, respectively ($p<0.05$). Hepatic CRM and adjuvant chemotherapy were related with short progression free survival. However, neither of these factors correlated with overall survival. One patient died 7 weeks after SBRT due to hepatic failure, 1 patient had a colonic and 2 patients duodenal ulceration caused by the treatment. Grade> 2 toxicity was observed in 47% of the patients within 6 months after SBRT. Most frequent side effects were nausea, diarrhoea, pain and skin reaction.
In conclusion, SBRT in patients with CRM results in high probability of local control and acceptable survival rate. The toxicity after SBRT of CRM is moderate.

Laura Dawson

## Individualized Image Guided Iso-NTCP based Liver Cancer SBRT

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Background/ Purpose: Stereotactic body radiotherapy (SBRT) has been used safely in patients with small liver tumors (< 6 cm) requiring a low volume of liver to be irradiated (i.e. < 25%). However, the majority of patients have larger tumors often requiring more volume of liver to be irradiated. Here, a highly individualized SBRT treatment strategy that allows a wide spectrum of patients with liver cancer will be reported on.
Methods: The SBRT protocol encompasses individualization of immobilization, radiation planning, PTV margin determination, image guidance strategy and prescription dose. Active breathing control is used to immobilize the liver when breath hold is reproducible. Image guidance strategies include orthogonal MV images and orthogonal kV fluoroscopy using the diaphragm for a surrogate for the liver, and kV cone beam CT using the liver or tumo for guidance. The prescription dose is individualized to maintain the same estimated risk of radiation-induced liver disease (RILD) at 3 levels (I – 5% risk, II – 10% risk, III – 20%, max. dose 60 Gy in 6 fractions). The risk of RILD is estimated with the Lyman-Kutcher-Burman NTCP model, with 'n' and 'm' parameters obtained from University of Michigan clinical experience (1). A linear-quadratic correction was used to normalize the TD50 NTCP parameter and the liver DVH to the prescription dose per fraction, used for NTCP estimation. Eligible patients have unresectable primary or metastatic liver cancer, liver enzymes < 6 x higher than normal, platelet count > 80, 000 bil/L, Child-Pugh liver score A, > 800 cc of uninvolved liver, and KPS performance status ≥ 60. Patients are stratified based on diagnosis (primary versus metastases) and effective liver volume irradiated (low <20%, mid 20-50%, high 50-80%).
Results: Since August 2003, 79 patients with hepatocellular carcinoma (33), intrahepatic cholangiocarcinoma (12) and liver metastases (34) were treated with highly individualized SBRT. The median age was 64 years (38-92 years). The median tumor volume was 293 cc (2.9-3088 cc). 17 patients with HCC (52%) had portal vein thrombosis. The median prescribed PTV dose was 36.6 Gy (24 Gy-60 Gy). The median effective liver volume irradiated was 45% (9-80%). The median mean liver dose was 16.8 Gy (1.5-25.2 Gy). The median potential follow-up was 9.6 months. No dose-limiting grade 4/5 toxicity or classic RILD was observed. A late tumor-duodenal fistula occurred 15 months following 36 Gy in 6 fractions. The median survival for patients with liver metastases, cholangiocarcinoma, and hepatocellular carcinoma was 14.6 months (6.7, -), 17.7 months (7.3, 25.3) and 8.8 months (3.9, 14.7) respectively.
Conclusion: Individualized Image Guided Iso- NTCP based Liver Cancer SBRT is a safe, promising treatment for unresectable liver cancer.

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Klaus Herfarth

## Radiosurgery of liver tumors – effects and side effects

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Malignancies in the liver are the second most target for extracranial stereotactic radiotherapy. Two regimen of therapy (hypofractionated and single-dose) have been established side by side. The university of Heidelberg conducted a phase I/II trial evaluating radiosurgery in liver tumors in 1997. Our group continued radiosurgery after this initial trial and a German Multi center trial comparing hypofractionation and single dose therapy was initiated in 2003. The updated results of the Heidelberg experience and the multi center trial will be presented.
Only minor side effects have been reported so far. However, every patient shows a focal radiation reaction in the liver. A threshold dose of the reaction after radiosurgery had been evaluated. In addition, animal experiments had been conducted looking for the histopathological counterpart of this focal tissue reaction.

Brian Kavanagh

## Interim analysis of the University of Colorado prospective phase I/II trial of SBRT for liver metastases

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Background: Stereotactic Body Radiation Therapy (SBRT) is a potent means of systemic cytoreductive therapy for selected patients with metastatic cancer. We here report a planned interim analysis of a prospective Phase I/II study of SBRT for liver malignancies (1), with special attention to tumor control and late toxicity.
Methods: The protocol was approved by the IRB of all participating institutions. Eligible patients with liver metastases met the following criteria: (a) maximum aggregate tumor diameter < 6 cm; (b) ≤3 discrete lesions; (c) treatment planning confirms ≥ 700 cc of normal liver receives ≤15Gy. The gross tumor volume (GTV) was expanded 5-10 mm to yield the planning target volume, which received 60 Gy in 3 fractions of SBRT over 3-14 days. Local control was scored after ≥6 mos follow-up to avoid uncertainty associated with early transient radiographic changes in the surrounding liver parenchyma. According to the statistical analysis plan, if ≥9/13 in the Phase II group maintains control at 6 mos, then up to 22 additional patients will be accrued.
Results: As of May, 2006, 36 patients have been enrolled: 18 in Phase I, 18 in Phase II (5 pts who died with < 6 mos post-SBRT follow-up imaging have censored and replaced in Phase II). The median age was 58 years (range 27-91); the M:F ratio was 20:16. The most common primary sites were lung (n=10), colorectal (n=9), and breast (n=4). Among 18 pts with ≥6 mos post-SBRT follow-up (median 19 mos, range 6-29), no SBRT-related grade 3 toxicity has occurred. For 25 discrete lesions treated (median GTV 14cc, range 1-98) the 1- and 2-yr actuarial local control estimate are 95% and 83%, respectively. The patients who had in-field failure received a prescription dose of 54 Gy and 60 Gy.
Conclusions: Durable in-field tumor control can be safely achieved with SBRT to 1-3 liver lesions as administered in this protocol. The results to date support continuation of the trial into the second stage of the Phase II component, though additional follow-up of enrolled patients is necessary. The fact that in-field failures are still observed even after doses of 54-60 Gy implies that the doses applied are not unnecessarily high.

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Alejandra Mèndez Romero

## Stereotactic radiotherapy for primary and metastatic liver tumors: a single institution phase I-II study

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Purpose: To investigate feasibility, toxicity and tumor response of stereotactic radiotherapy (SRT) for treatment of primary and metastastic liver tumors.
Materials and Methods: From October 2002 until February 2006, 23 patients not suitable for other local treatment were entered in the study. In total 42 lesions were treated, 31 metastases and 11 hepatocellular carcinoma (HCC). Median follow-up was 10.1 months (range 1-31). Median size was 3.2 cm (range 0.5-7.2). Patients with metastases, HCC without cirrhosis, and HCC<4 cm with cirrhosis were mostly treated with 3x12.5 Gy. Patients with HCC ≥4 cm and cirrhosis received 5x5 Gy or 3x10 Gy. The prescription isodose was 65%. Acute toxicity was scored following the Common Toxicity Criteria and late toxicity with the SOMA/LENT classification.
Results: All patients completed the treatment as planned. Acute toxicity grade≥3 was seen in 3 patients; one HCC patient developed a liver failure together with an infection and died (grade 5), one metastases patient presented elevation of gamma glutamyl transferase, and another asthenia (both grade 3). Late toxicity was observed in one metastases patient who developed a portal hypertension syndrome with melena (grade 3). Local failures were observed in 2 HCC and 2 metastases. Local control rates at 1 and 2 years for the whole group were 94% and 82%.
Conclusions: SRT was feasible, with an acceptable toxicity and encouraging local control. More studies are necessary to verify these results and to find the optimal dose-fractionation schemes for HCC with cirrhosis. New technical developments to improve/intensify the treatment will be discussed.

A.L. Petersen

## Stereotactic Body Radiation Therapy (SBRT) for Lung Metastases

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Background: The curative treatment of oligometastases with radiotherapy remains an area of active investigation. Whereas true oligometastases will be rare there is a real potential for new systemic therapies for down-stage patients to an oligometastatic state. We have studied the role that hypofractionated stereotactic radiation might play for lung metastases. We will discuss the outcomes with respect to prologation of life and to cure.
Purpose/Objective(s): To determine local control and toxicity after respiratory-gated stereotactic hypofractionated radiation as an adjunct to standard therapy for pulmonary metastasis.
Materials/Methods: 50 patients with one or more metastases to the lung were treated on protocol between February 2001 and December 2005. Individuals with 5 or fewer total lesions were treated with curative intent. Individuals with >5 metastases were treated to sites judged to impact respiratory function. One patient was lost to follow-up. 31 were treated curatively (30 evaluable) and 19 palliatively. 62% of patients (31/50) received 5 Gy per fraction for a total of 50 Gy in a median time of 2 weeks. Patient ages ranged from 37 to 86 years old (median 60) and the number of targets treated per patient ranged from 1 to 5 (mean 2.6). Tumor sizes ranged from 0.3–7.7 cm in maximal diameter (0.1–125 ml; medians 2.1 cm, 4.7 ml). Histograms were used to calculate the percentage of total lung volume (excluding the GTV) receiving ☐ 10 Gy (V10) and ☐ 20 Gy (V20). Mean follow-up was 18.7 months (range 3.7–60.9 months).
Results: The diameter of tumors that recurred ranged from 1.5 to 3.0 cm in diameter. The local control (LC) of treated lesions was obtained in 42 of 49 evaluable patients (82%). Of the 125 total lesions treated, 8 progressed after treatment (94% LC). Failures in other anatomic locations within the lung occurred in 12/30 (40%), and failures elsewhere in the body occurred in 10 of the 30 patients (33%) treated with curative intent. 7 of these 30 (23%) are disease free (median 33 months). Many patients had subsequent hypofractionated treatments for control of new lesions. Median survival from time of treatment completion was 14.9 months. Median time from diagnosis of metastatic disease to completion of radiation was 14.8 months (range 1–89 months). Results with breast cancer, wherein effective chemotherapy options are often available, were excellent. Actuarial disease free survival of women with breast cancer was 40% at 40 months (n=10).
Toxicity commonly included radiographic but clinically asymptomatic pulmonary changes (17/49), 3 (6.1%) had grade 2 complaints, and one had grade 3 toxicity. The grade 3 toxicity was a non-malignant pleural effusion successfully managed with pleurocentesis and sclerosis. Toxicity was not clearly associated with V20. Most grade 2 toxicity was cough which was self limited. The mean V20 of the entire cohort of patients was 13%, with a range of 1-34%.
Conclusion: Excellent local tumor control rate with low toxicity are seen with SBRT. Median survival time and disease free survival both appear better than that achieved with standard care alone. Long-term disease-free survival can be seen in a subset of patients when all tumors are targeted.

Keywords: hypofractionated radiation, radiosurgery, oligometastasis, tolerance

Jo-Aasmund Lund

## Implementation of stereotactic radiotherapy in a small hospital.

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Background: St Olavs University Hospital is a small hospital in a European perspective. The hospital's department of radiotherapy has 4 linacs, a single simulator and a single CT for doseplanning. The implementation of new techniques is always a challenge for the staff. The present study supports that stereotactic radiotherapy (SRT) using the stereotactic body frame (SBF) can be implemented in the daily routine in a safe manner in clinics of this size.
Methods and material: St Olavs University Hospital started training for SRT during the spring of 2002. After numerous dummy runs, the first patient was treated in December 2002. All patients treated by SRT have been followed prospectively. The present study reports on side effects and tumour control for the first 21 patients.
Results: Ten women and 11 men were treated by SRT during the period December 2002 – June 2005. Median age was 62 (46-82) years. Median follow up was 17 (0-30) months. Eight patients were treated for liver tumours, 13 patients for lung tumours. The planning target volumes varied from 9 to 120 cm3. All patients were given 15 Gy x 3 in one week. One patient treated for liver metastases was hospitalised due to possible treatment related side effects, 2 patients were medicated for side effects while 12 patients had no side effects from SRT. At 3 months, at least partial remission was achieved for all lung tumours, while 2 liver tumours had progressed.
Conclusion: SRT can be implemented in small oncology departments, achieving good remission rates and low number of side effects.

Karin Dieckmann

## Stereotactic Body Radiation Therapy at the Medical University Vienna: 6 years clinical experience and future perspectives

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Purpose: To present clinical results of stereotactic body radiotherapy (SBRT) for patients suffering from lung metastases or small lung tumours treated at the Medical University Vienna (MUW). The application of respiration-controlled delivery in stereotactic body radiotherapy (SBRT) remains still a challenge and the treatment technique for the optimal therapeutic benefit is still under evaluation. One option is deep inspiration breath hold (DIBH), and research results obtained with an in-house developed system for DIBH monitoring will be presented.
Material and Methods: Since 2001, 89 patients, median age 65y (range 40-88y), with small lung tumours (n=20), relapsed lung tumours (n=4), and lung metastasis (n=64) have been treated in a stereotactic body frame. Dose prescription was either 3x12.5Gy or 5x7Gy prescribed to the 65% isodose. Prior each fraction CT verification was performed and the isocenter was localized by stereotactic coordinates. Local control was defined as complete or partial remission and stable disease, measured after 4 weeks and in 3 months intervals. Treatment toxicity was evaluated according to WHO score. An infrared (IR) reflecting marker system and an in-house developed interface were applied to 35 patients to acquire online information about respiration movements of the thorax. Additionally, a patient feedback system was developed to visualize the respiration cycle to the patient and thus to utilize his/her ability for cooperation. In a multislice CT study, the underlying hypothesis that targets can be immobilized with a high accuracy with a DIBH maneuver was verified. In a subsequent treatment planning study, various respiration conditions and standard versus reduced margins were analyzed for SBRT. The shallow breathing (SB) plan with standard margins was used as a reference.
Results: The median PTV was 65 cm3 (range 6-278cm3). Median follow-up was 10,9 months (range 0,3-54 mo). After 20 months local control was 80 %. Grade 3 pneumonitis was observed in one patient, FEV1 was stable within nine month after treatment. Pneumonitis and fibrosis changes in CT are mostly correlated with the > 6Gy volume and therefore predictable. For DIBH monitoring the relative reproducibility of DIBH maneuvers was improved with the feedback device (74.5 % ± 17.1 % without versus 93.0 % ± 4.4 % with feedback). The correlation between tumor and marker was good (Pearson correlation coefficient 0.83 ± 0.17). The intra-breath hold stability was within 0.4 mm for all individuals. The treatment planning analysis showed that with DIBH it is possible to reduce lung dose parameters (Vol-Lung≥12Gy, Dmean, NTCP) by about 20%. Applying reduced margins in DIBH, this reduction was even increased to about 40%. The standard technique (SB+abdominal compression) with individual margins showed similar results as DIBH with standard margins.
Conclusion: Stereotactic radiosurgery is a good alternative for inoperable patients with small lung cancer and lung metastasis. Local complications are predictable. In order to limit dose to healthy lung tissue, DIBH and applying reduced margins is promising and found to be clinically feasible. For the realization of this technique a breathing control system is required. DIBH monitoring can be realized through external marker tracking in a non-invasive manner. However, for a successful application of such a DIBH technique the identification of suitable patients and training sessions are necessary.

**Peter Wersäll**

## A prospective Phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma

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ABSTRACT Background: There are few therapeutic options in metastatic renal cell carcinoma. A retrospective study have indicated that stereotactic radiotherapy (SRT) has a value in treating both primary tumours and singular metastatic lesions that cause local symptoms. We here present the results of a prospective study evaluating the safety and local efficacy of SRT in metastatic or inoperable renal cancer.Patients and Methods: 30 patients with metastatic RCC or inoperable primary RCC received high-dose fraction SRT. In total, 82 lesions were treated. Dose/fractionation schedules varied depending on target location and size. The most frequently used fractionations were 8 Gy x 4, 10 Gy x 4, 15 Gy x 2 or 15 Gy x 3, given over the course of one week. Results: Local control, defined as radiologiocally stable disease (SD) or partial/complete response (PR/CR) was obtained in 98% of treated lesions but 19% of lesions were in patients with a follow up time of less than 6 months. Including all patients but regarding those with a follow up of less than 6 months as possible treatment failures, CR was observed in 21% of the patients and 58% of the patients had a partial volume reduction or local stable disease after a median follow up of 25 months (SD 18, range 2,5-65). Local progression was seen in two lesions. Side effects were generally mild but one patient with a large lesion in the lung died within weeks after treatment and it cannot be excluded that it may have been treatment related. Conclusion: SRT for patients with primary and metastatic RCC resulted in high local control rate with generally low toxicity. The method can thus be considered an alternative therapeutic option to surgery in patients with a limited number of metastases, as local treatment in renal cell carcinoma with an indolent presentation or as a method of reducing tumour burden prior to medical treatment. Great consideration needs to be taken however, when treating large lesions in proximity to high risk organs or structures.

Paul Okunieff

## Cooperative group efforts for the incorporation of radiosurgery into national clinical studies

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The creation of studies featuring extracranial radiosurgery, that can be performed by multiple institutions using different technologies, has been an almost paralyzing challenge and has slowed progress in this exciting field. A first challenge is identifying the role of extracranial radiosurgery in the arsenal against metastatic disease. Without such a definition, the objectives of studies aimed at treatment are unclear. For example, do RECIST criteria apply? They are the usual endpoint for evaluation of regimen for metastases. Is a complete or partial response the goal or is the more usual radiation oncology definition of response the more important goal (local control)? Are the usually endpoints for evaluating local treatment for metastases the main response endpoint (vis pain or symptom control)? All of these impact on the tumor primary types that might be recruited, the number of patients required for statistical significance, allowable concurrent therapies, and the impact that a successful protocol has on the future of cancer care.

In this presentation I will focus on the role that extracranial radiosurgery could play in testing the hypothesis of oligometastasis. Notably, in the treatment of true oligometastasis, and in the supplimentation of chemotherapy-induced down-staging to create and oligometastasis state. Suggestions for appropriate protocol design, definition of primary aims, and relevant endpoint for evaluation of success will be made. Approaches used by the RTOG and SWOG along with QARC for designing studies that are technology independent and which allow for various methods of respiratory gating, dose calculation and immobilization, and which can easily accommodate emerging technologies like Tomotherapy and Cyberknife. The process likely to be required to progress cooperative group clinical studies from the feasibility stage to full phase III testing will also be discussed.

Protocol designs chosen for initial testing of extracranial radiosurgery by SWOG for breast cancer and sarcoma, and by the RTOG for colorectal cancer will be discussed. Future short and long-term plans will be addressed, and time will be left for a general discussion.

Ingmar Lax

## On dose distributions in SBRT

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In SBRT of lung- and liver-tumors there is a geometry aspect/problem related to breathing motions and set-up reproducibility, as well as a dose aspect/problem, to obtain a large therapeutic window. The main variables that deals with these aspect are; margin CTV-PTV, relative dose distribution, and fractionation (time and absolute dose). This work deals with absolute dose distributions (given a margin), calculated for spherical lung tumors located in lung tissue, and with simulated breathing motions.
Absolute dose distributions were calculated for clinically relevant treatment techniques, for simulated lung tumors of 2 and 5 cm (diameter), with a pencil-beam (PB) algorithm. The same beams were used in the PENELOPE, Monte–Carlo (MC) program to calculated the corresponding absolute dose distributions. The effect on the dose distributions from breathing motions were evaluated by convolutions of different breathing motion patterns with the static dose distribution. The relevance of using convolution, i.e. the degree of invariance of the dose distribution with the position of the tumor was verified from MC simulation.
The results confirms previous data that the PB algorithm, significantly overestimates the dose to the lung tissue in the volume between the CTV and PTV, and underestimates the dose outside the PTV. The PB-calculated dose to the CTV is in close agreement to the MC-calculated dose. These results are valid both for the static MC-calculated dose and the one with simulated breathing motion included. Advantages with a very heterogeneous dose distribution in the PTV will be discussed as well as aspects of relevant dose specification methods in SBRT.

E. Djärv

## Dummy run for a phase II study of stereotactic radiotherapy of T1-T2 N0M0 inoperable non-small cell lung cancer

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A dummy run was performed to evaluate the compliance of volumes and doses with the study protocol for a phase II study of stereotactic radiotherapy of T1-T2 N0M0 inoperable non-small cell lung cancer. All six Scandinavian centres participated in the dummy run.
Two patients with lung cancer stage T2N0M0 were selected. Each centre recieved CT-scans covering the whole lung volumes. They were asked to follow the study protocol when outlining tumour and target volumes and creating dose plans. The CT slices with structures, plans and doses were exported.
Eleven plans were evaluated. Margins between CTV and PTV were according to protocol. For the two patients the median GTV volume was 29 cm3, range 24-39 cm3, and 32 cm3, range 26-38 cm3, respectively. Median PTV volume was 106 cm3, range 90-114 cm3, and 129 cm3 , range 112-155 cm3, respectively. The joint GTV was 23 cm3 and 19 cm3, respectively, and the joint PTV was for the two patients 90 cm3 and 106 cm3, respectively.
The prescribed dose was for all centres 45 Gy/3 fractions (isocentre 66 Gy) according to the protocol. The mean GTV doses ranged from 63 to 67 Gy, median 64 Gy, for patient 1 and from 63 to 68 Gy, median 64 Gy, for patient 2. For the two patients the minimum doses for GTV were between 50-64 Gy, median 59 Gy, and between 55-65 Gy, median 61 Gy, respectively.
All parameters for the participating centres were in good compliance with the study protocol.

P. Rassiah

## Characterization of Lung Lesion Doses in Stereotactic Body Radiation Therapy (SBRT) via Monte Carlo

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Determining the optimal dose and fractionation scheme in SBRT of the lung, requires an understanding of the true delivered radiation dose. This study attempts to characterize the doses received by static targets located in the lung, and to critical structures ( lung, major airways, spinal cord and esophagus) for the serial tomotherapeutic IMRT delivery method used for SBRT in our clinic.
At least 77 NSCLC patients have been treated with SBRT between 2001–2004 with prescription dose for lung metastases of 36 Gys in 3 fractions and primary lung neoplasms (stage 1 NSCLC) between 3 times 16 Gy to 3 times 20 Gy. Dose distributions previously planned on a conventional planning system were recalculated using Monte Carlo which is accurate to better than 3% in an anthropomorphic phantom.
The mean CTV volume of the 90 lesions presented here is 35.6 cm3 (range: 0.3-370.2 cm3). The minimum dose to both CTV and PTV were overestimated by the conventional planning algorithm by an average of 17.3 ± 7.8% and 20.6 ± 10.8% of prescribed dose respectively. The magnitude of deviation depends on target location and dimensions. The minimum dose, mean dose and NTD for the lungs were in good agreement with MC. Larger, localized discrepancies exist for maximum dose. Other critical structures doses were generally in good agreement with those predicted by MC. MC may prove valuable in accurately assessing the delivered dose in SBRT and thus, contribute to a more informed decision on the optimal dose and fractionation scheme.

Karyn A. Goodman

## Image-Guided Radiotherapy for Upper GI Malignancies

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Objectives: Malignancies of the upper gastrointestinal tract, including carcinomas of the esophagus, stomach, pancreas, and primary and metastatic tumors of the liver, remain an oncologic challenge. Long-term survival and local control rates for these cancers are poor, even with aggressive therapy. Radiation therapy has been limited by the tolerance doses of these organs as well as their surrounding normal structures. More conformal techniques are hampered by the significant degree of organ motion in the thorax and abdomen. Novel imaging and radiotherapy delivery techniques are allowing for more targeted therapy of these tumors and are allowing for new attempts to dose escalate radiotherapy. We are incorporating 4 dimensional CT, PET, and cone beam CT (CBCT) into the treatment of upper GI tumors to enhance targeting and delivery of higher radiotherapy doses using hypofractionation with the goal of improving local control.

Methods: Patients with malignancies of the thoracic esophagus, pancreas, and liver, will be enrolled onto protocols of either a hypofractionated boost after conventional chemoradiotherapy or a single fraction of high dose radiosurgery using IMRT-based stereotactic planning with the Trilogy system. We are developing the methods of incorporating 4D CT into our treatment planning process and using respiratory gating during the delivery of the boost or single fraction. Software to perform 4D PET has been developed in our department to more precisely delineate target volumes with higher metabolic activity. CBCT is being used to verify positioning of the tumor and/or fiducials during the course of treatment and will be used prior to the stereotactic boost or single fraction treatment to confirm the location of the GTV as defined by the fiducials. Efforts to improve the precision of the pre-treatment CBCT include the development of 4D CBCT.

Results: Two protocols using Trilogy-based stereotactic radiosurgery have been IRB approved at Stanford University. The first is a phase I dose escalation study of a hypofractionated stereotactic boost after conventional chemoradiation for esophageal cancer. The second is a single fraction of 25 Gy to the pancreas for locally advanced pancreatic cancer. To date, we have not enrolled any patients due to on-going work on verifying the treatment planning for delivering the stereotactic treatments using either IMRT non-coplanar plans or arcs. We have been gaining experience with 4D CT, 4D PET and 4D CBCT in anticipation of using these modalities as part of the planning process for these protocols.

Conclusions: Advances in imaging modalities such as high resolution CT, MRI, and functional imaging allow for more precise delineation of GTV + CTV. Tumor localization using 4D CT/4D PET/4D MRI and treatment delivery using real-time image guidance allow for more conformal treatment fields. Increasing the precision of treatment and reducing uncertainties allow for decreased normal tissue toxicity and ability for dose escalation as well as delivery of a single fraction of high dose radiation.

Martin Fuss

## Clinical experience with serial and helical tomotherapeutic SBRT

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Since 8/2001 more than 180 patients have been treated by tomotherapeutic SBRT at UTHSCSA/CTRC. Treatment delivery was initially based on serial tomotherapy, since 12/2006 a helical tomotherapy unit is used. The principles of tomotherapeutic SBRT planning, associated image-guidance, and delivery will be presented. Based on 13 patients treated on the helical tomotherapy unit for inoperable stage 1 non small-cell lung cancer (n=5), lung metastases (n=1), liver metastases (n=3), adrenal gland metastasis (n=1), and vertebral body/paraspinal metastases (n=3), a comparison between the two tomotherapy modalities will be presented. The comparison will focus on strategies for inverse IMRT planning specific to SBRT delivery, resulting plan quality, time to deliver the respective treatment fractions, as well as the quality and clinical feasibility of megavoltage CT based image-guidance inherent to the helical tomotherapy unit.

Joost Nuyttens

## Stereotactic radiotherapy with the CyberKnife: clinical applications and early results for tumors in the abdominopelvic region and lung.

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Introduction: The CyberKnife is a frameless image-guided radiotherapy system involving a 6 MV linear accelerator mounted on a robotic arm possessing six degrees of freedom. The imaging system uses 2 diagnostic X-ray sources mounted to the ceiling paired with amorphous silicon detectors to acquire live digital radiographic images of the patient. The CyberKnife is able to follow a moving tumor (in the lung) due the Synchrony system. However, it requires the insertion of markers in or near the (lung) tumor which are used to define the position of the tumor. The CyberKnife at the Erasmus MC –Daniel den Hoed Cancer Center is used to treat tumors in the brain, head and neck region, thorax, abdomen and pelvis. We evaluated the early results of the stereotactic radiotherapy treatments of the CyberKnife in the abdominopelvic region and lung.
Methods and materials: in the abdominopelvic region, 9 patients were treated with curative intention: 5 patients were treated for para-aortic tumors and received a total dose ranging from 5*6 Gy to 3*12 Gy, 4 patients were treated for a tumor in the pelvis and received a dose ranging from 3*8 Gy to 6*7 Gy. Six patients were treated palliatively after previous radiotherapy with doses ranging from 2*8 Gy to 6*6 Gy.
For the tumors in the lung, 78 markers (37 intrathoracal, 25 intravascular and 16 extrathoracal) were placed in or around 22 tumors in 20 patients: 13 patients were treated with curative intention (T1-2N0M0 lung cancers), and 7 with palliative intention (2 with recurrent lung cancer, and 5 with metastasis). A median dose of 45 Gy (range: 30-60 Gy, in 3 fractions) was prescribed to the 70-85% isodose line.
The median follow up for all groups was 4-5 months (range 2-12).
Results: In the abdominopelvic region, a local control rate of 100 % was seen for the patients treated for curative intention. A moderate to good palliative effect was noted in the palliative group. The local control of the tumors in the lung was 100%: 3 tumors in 3 patients had a complete response, 16 tumors in 15 patients had a partial response and 3 tumors in 2 patients with metastatic disease had stable disease. No severe toxicity due to the marker placement was seen.
Conclusion: Stereotactic radiotherapy with the CyberKnife is feasible and results in excellent tumor response. Longer follow up is needed to validate the local control. No severe toxicity due to the marker placement was seen.

Anders Brahme

## Development of light ion therapy: the ultimate stereotactic treatment technique

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Background. The fast development of stereotactic radiotherapy as well as energy, intensity and radiation quality modulated radiation therapy (IMRT and QMRT) during the last two decades using photon and electron beams has resulted in a considerable improvement of radiation therapy, particularly when combined with radiobiologically based treatment optimization techniques. This development and the recent development of advanced tumor diagnostics based on PET-CT imaging of the tumor clonogen density opens the field for new powerful radiobiologically based treatment optimization methods.
Purpose. The main purpose of this presentation is, to discuss the principal areas of development of therapy optimization considering the whole therapy chain from tumor diagnostics and patient fixation through therapy planning and treatment optimization to the repeated treatment setups and dose delivery on a patient that hopefully has a shrinking tumor and often may loose weight. Finally, it is the integral dose delivery and the biological effect distribution that matters so the shaping of the optimal incident beams is a truly complex inverse problem, which is hard to solve by such a simplistic concept as a planning target volume.
Methods. The above introduction indicates that Biologically Optimized Adaptive Radiation Therapy (BIOART) is really the ultimate way to perform high precision radiation therapy using checkpoints of the integral dose delivery and the tumor response, and based on this information, performing compensating corrections of the dose delivery. By using biologically optimized scanned high energy photon or ion beams it is possible to measure in vivo the 3-dimensional (3D) dose delivery using the same PET-CT camera that was used for diagnosing the tumor spread. This method thus opens up the door for truly 3D biologically optimized adaptive radiation therapy where the measured dose delivery to the true target tissues can be used to fine adjust the incoming beams so that possible errors in the integral therapy process are eliminated towards the end of the treatment. Interestingly enough practically all major error sources can be corrected for in this way such as organ motions, treatment planning errors, patient setup errors, and dose delivery problems due to gantry, multileaf or scanning beam errors.
Results. Several examples of radiobiologically optimized dose delivery are presented and examples of the above mentioned new treatment techniques are illustrated for a number of clinically relevant targets. The unique properties of light ion therapy in this context are also presented in more detail.
Conclusions. Using the recently available biologically based treatment optimization algorithms it is possible to improve the treatment outcome for advanced tumors by as much 10 – 40%. The adaptive radiotherapy process based both on 3D tumor cell survival and dose delivery monitoring has the potential of percent accuracy in tumor response and dose delivery, not least with 3D geometric Bragg peak scanning and intensity modulated ion beam dose delivery. There is no doubt that the future of radiation therapy is very promising and gradually more and more patients may not even need advanced surgery but instead could be cured by photon and electron IMRT and ultimately biologically optimized light ion therapy, where the high LET-RBE Bragg peak is solely placed in the gross tumor volume.

David Jaffray

## Radiation Therapy 2006: Images, Guidance Systems, and Robots

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The field of radiation therapy is undergoing a time of unprecedented change. Current standards of delivery have been developed over nearly a century of maturing clinical practice intertwined with technical capacity. Prescribed dose, fraction size, and geometric safety margins have evolved together with the bounds on our ability to target and tailor the dose distribution within the body. The past ten years have seen the departure from technique-based approaches, the testing of the 3D hypothesis, and the adoption of volumetric treatment planning. This transition is a major turning point for radiation therapy practice and opens the possibility of a rich and diverse practice of radiation prescription that will offer the possibility of improved therapy as well as the risks associated with non-standardized practice. The struggle to free radiation therapy from the technical constraints of delivery has been hard fought. Ironically, we may find ourselves paralyzed with the myriad of choices we are faced with when deciding how to employ these novel tools for the benefit of our patients. Images, guidance systems, and robots, to name a few, are the new tools of radiation therapy. The current situation speaks volumes on our need to develop a better understanding of the nature of the radiation therapy target and how this powerful agent can be better exploited. The impact these new tools are having on current clinical practice will be presented and efforts to improve our capacity to apply them knowingly will be highlighted.