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CANCER CENTER

Dose rate effect in external radiotherapy: biology and clinic

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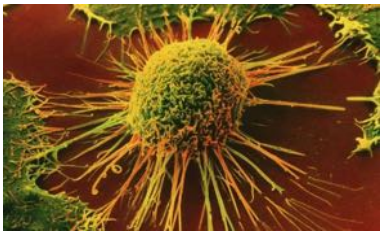
Brescia – October 8th/9th, 2015

Flattening Filter Free beam

1. Radiobiology



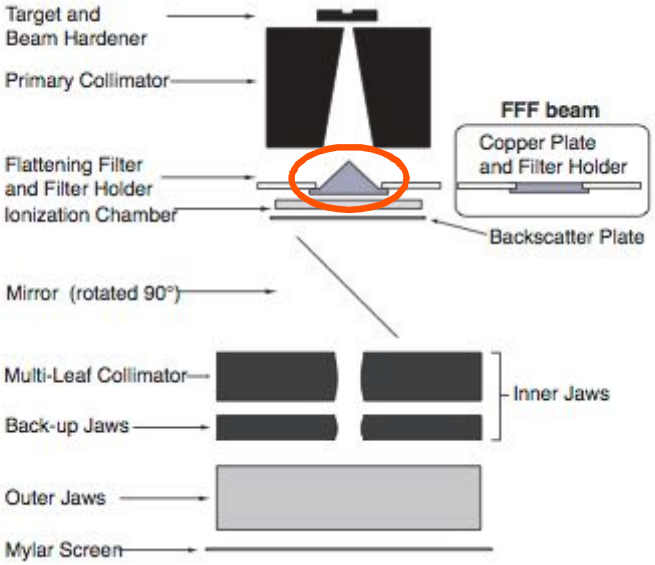
2. Clinical applications

Flattening Filter Free beam

Flattening filters (FFs) have been considered as an **integral part of the treatment head of a medical accelerator** for more than 50 years.

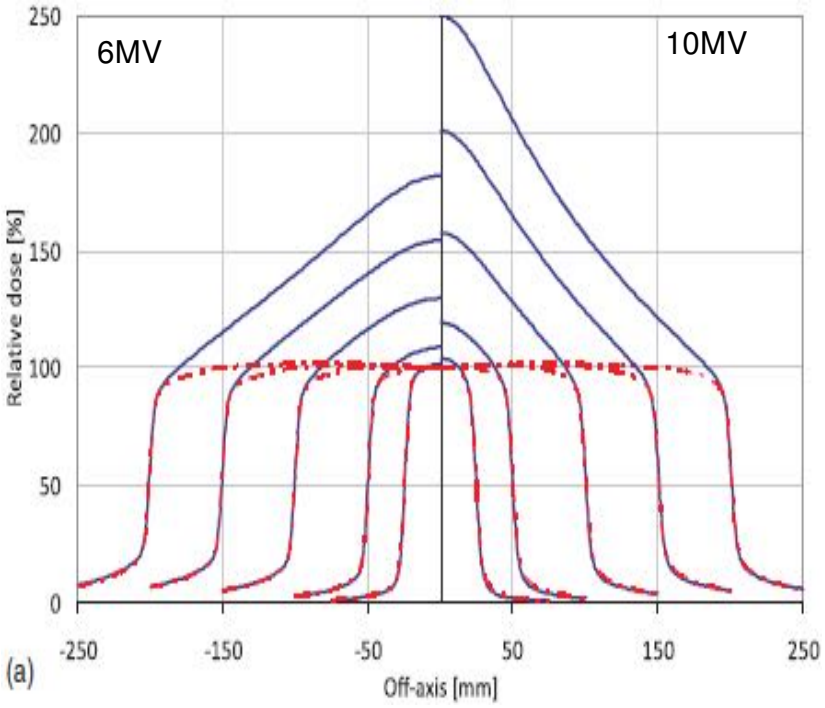
Advanced treatment techniques, such as **stereotactic radiotherapy or intensity modulated radiotherapy** have stimulated the **interest in operating linear accelerators in a flattening filter free FFF mode**.

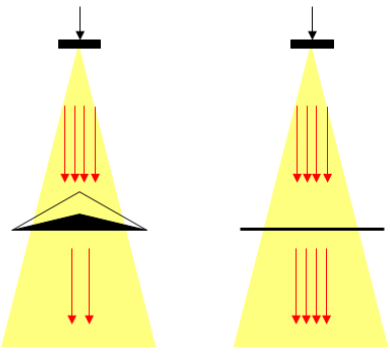
In the 1990s, several groups studied flattening filter free **(FFF) high-energy photon beams.**



Georg 2011

Flattening Filter Free beam





The removal of the flattening filter generates a higher output, leading to a completely different beam profile shape.

Radiobiology

Current status and future perspective of flattening filter free photon beams[a)]

Dietmar Georg,[b)] Tommy Knöös, and Brendan McClean
Department of Radiotherapy, Division of Medical Radiation Physics, Medical University of Vienna/AKH Vienna, A-1090 Vienna, Austria; Department of Physics, St. Luke's Hospital, Highfield Rd., Rathgar, Dublin 6, Ireland; and Radiation Physics, Lund University and Skåne University Hospital, S-221 85 Lund, Sweden

A number of dosimetric benefits have been determined for FFF beams:

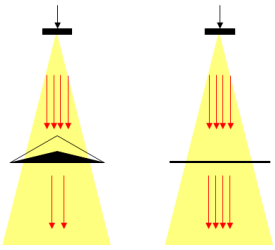
✓ significant decrease in treatment times by increasing the instantaneous dose-rate of the accelerator

✓ reduced head scatter

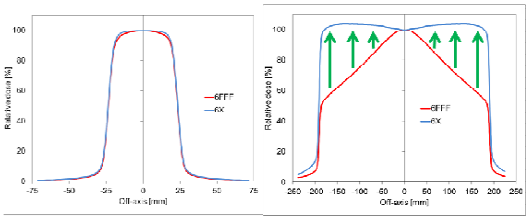
✓ reduction in the out-of-field dose

Flattening Filter Free beam

- High dose rate: *SHORT DELIVERY TIME*
  HIGH DOSE/FRACTION



- Field profile shape: *STEREOTACTIC TREATMENTS*
  INTENSITY MODULATION



- Lower out-of-field dose*: INTEGRAL DOSE REDUCTION*

- Reduced head scatter: *LOWER DOSE-BATH*

Radiobiology

Dose rate

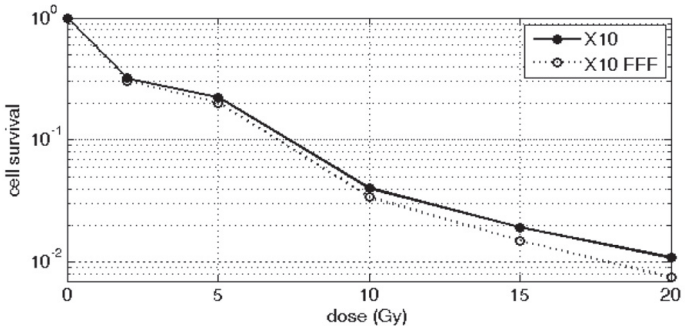
Effect of high dose per pulse flattening filter-free beams on cancer cell survival

Ines Lohse [a], Stephanie Lang [a], Jan Hrbacek [a], Stephan Scheidegger [c], Stephan Bodis [b], Nadia S. Macedo [a], Jianhua Feng [a], Urs M. Lütolf [a], Kathrin Zaugg [a,*]

[a] Department of Radiation Oncology, University Hospital Zürich, Switzerland; [b] Institute of Radiation Oncology, Kantonsspital Aarau, Switzerland; [c] Centre of Applied Mathematics and Physics, Zurich University of Applied Science, Switzerland

Materials and methods: To validate the radiobiological effect of the flattened and FFF beam**, two glioblastoma cell lines** were treated with either 5 or 10 Gy using different dose rates. Dose verification was performed and colony formation assays were carried out. To compare the predictability of our data, radiobiological models were included.

Results: The results presented here demonstrate **that irradiation of glioblastoma cell lines using the FFF beam is more efficient in reducing clonogenic cell survival** than the standard flattened beam, an effect which becomes **more significant the higher the single dose**.



Dose–response curve of U87-MG cells irradiated with either the X10 (full circles) or X10FFF (empty circles) beam. Clonogenic survival was accessed as a measure for irradiation efficiency. ** $p \leq 0.001$.

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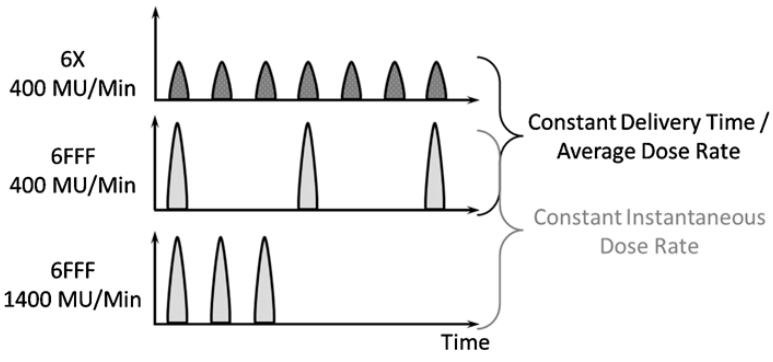
Radiobiology

An *in vitro* study of the radiobiological effects of flattening filter free radiotherapy treatments

R B King [1], W B Hyland [1], A J Cole [2,3], K T Butterworth [3], S J McMahon [3], K M Redmond [3], C Trainer [3], K M Prise [3], C K McGarry [1] and A R Hounsell [1,3]

To determine the radiobiological impact of the increased dose-rates from FFF exposures a Varian Truebeam medical linear accelerator was used to **irradiate two human cancer cell lines in vitro,** DU-145 **prostate** and H460 **non-small cell lung, with both flattened and FFF 6 MV beams.**



Schematic illustrating the different dose-per-pulse and pulse repetition frequencies of the x-ray fields used in this study

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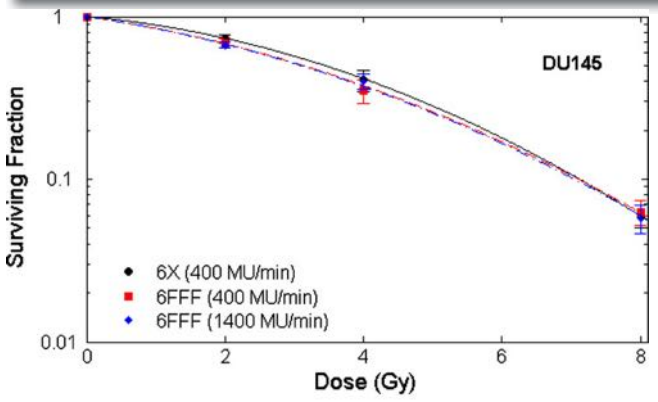
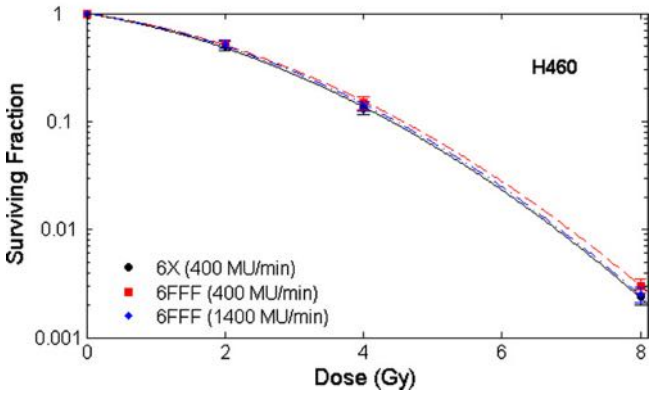
Radiobiology

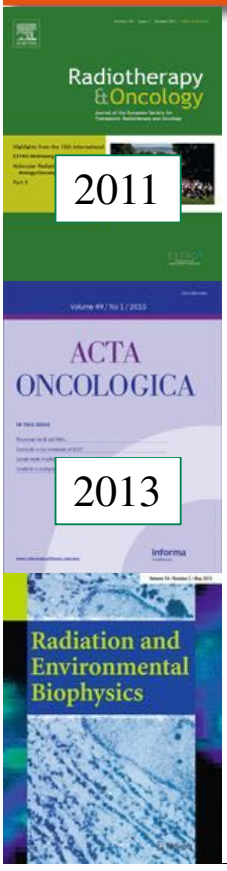




The results indicate that collective damage behaviour does not occur at the instantaneous dose-rates investigated here and that the use of either modality should result in the **same clinical outcome**, however this will require further validation *in vivo*.

Flattening filter-free treatments **offer many clinical advantages** over the traditional flattened treatments, including **significantly faster delivery of dose fractions**.

Radiobiology



Dose rate

Dependence of cell survival on instantaneous dose rate of a linear accelerator

Brita Singers Sørensen [a,*], Anne Vestergaard [b], Jens Overgaard [a], Lars Hjorth Præstegaard [b]

[a] Department of Experimental Clinical Oncology; and [b] Department of Medical Physics, Aarhus University Hospital, Denmark

Comparable cell survival between high dose rate flattening filter free and conventional dose rate irradiation

WILKO F. A. R. VERBAKEL[1,2], JAAP VAN DEN BERG[1], BEN J. SLOTMAN[1] & PETER SMINIA[1]

[1]Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands, and [2]Department of Physics and Medical Technology, VU University Medical Center, Amsterdam, The Netherlands

Effect of varying dose-per-pulse and average dose rate in X-ray beam irradiation on cultured cell survival

G. Lasio · M. Guerrero · W. Goetz · F. Lima · J. E. Baulch

Available Technology

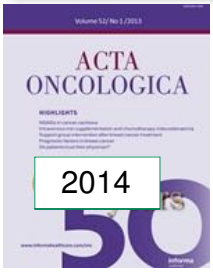
Tomotherapy
6MV 8Gy/min

CyberKnife
6MV up to 10Gy/min

Elekta HD Versa
6MV 16Gy/min
10MV 22Gy/min

VARIAN TrueBeam
6MV 14 Gy/min
10MV 24 Gy/min

Planning studies



A treatment planning and delivery comparison of volumetric modulated arc therapy with or without flattening filter for gliomas, brain metastases, prostate, head/neck and early stage lung cancer

DANIEL GASIC[1], LARS OHLHUES[1], N. PATRIK BRODIN[2], LOTTE S. FOG[1], TOBIAS POMMER[1,3], JENS P. BANGSGAARD[1] & PER MUNCK AF ROSENSCHÖLD[1,3]

A total of 120 patients treated for **H&N tumors**, **high-grade glioma**, **prostate cancer**, **early stage lung cancer** and **intra-cranial metastatic disease** were included in the study.

The plans were generated **using Standard- and FFF-VMAT for both 6 MV and 10 MV**, and were compared with respect to plan quality, monitor units and delivery time using Wilcoxon signed rank tests.

Conclusion: It was generally possible to produce FFF-VMAT plans with the **same target dose coverage and doses to organs at risk** as Standard-VMAT plans. **Target dose homogeneity tended to be somewhat inferior for FFF-VMAT for the larger targets investigated**.

For stereotactic radiotherapy, FFF-VMAT resulted in a considerable time gain while maintaining similar plan quality compared to STD beams.

Planning studies

Volumetric modulated arc planning for lung stereotactic body radiotherapy using conventional and unflattened photon beams: a dosimetric comparison with 3D technique

Geoffrey G Zhang[1*], Lichung Ku[2], Thomas J Dilling[1], Craig W Stevens[1], Ray R Zhang[3], Weiqi Li[1] and Vladimir Feygelman[1]

The Use of Photon Beams of a Flattening Filter-free Linear Accelerator for Hypofractionated Volumetric Modulated Arc Therapy in Localized Prostate Cancer

Daniel R. Zwahlen, M.D., Stephanie Lang, M.Sc., Jan Hrbacek, M.Sc., Christoph Glanzmann, M.D., Stephan Kloeck, Ph.D., Yousef Najafi, M.D., Tino Streller, Ph.D., Gabriela Studer, M.D., Kathrin Zaugg, M.D., Ph.D., and Urs M. Luetolf, M.D.

Chest wall radiotherapy with volumetric modulated arcs and the potential role of flattening filter free photon beams

S. Subramaniam[1] · S. Thirumalaiswamy[1] · C. Srinivas[1] · G.A. Gandhi[1] · M. Kathirvel[1] · K.K. Kumar[1] · S. Mallik[1] · M. Babaiah[1] · Y. Pawar[1] · A. Clivio[2] · A. Fogliata[2] · P. Mancosu[3] · G. Nicolini[2] · E. Vanetti[2] · L. Cozzi[2]

Clinical Applications

- Lung
- Liver
- Prostate

Clinical Applications

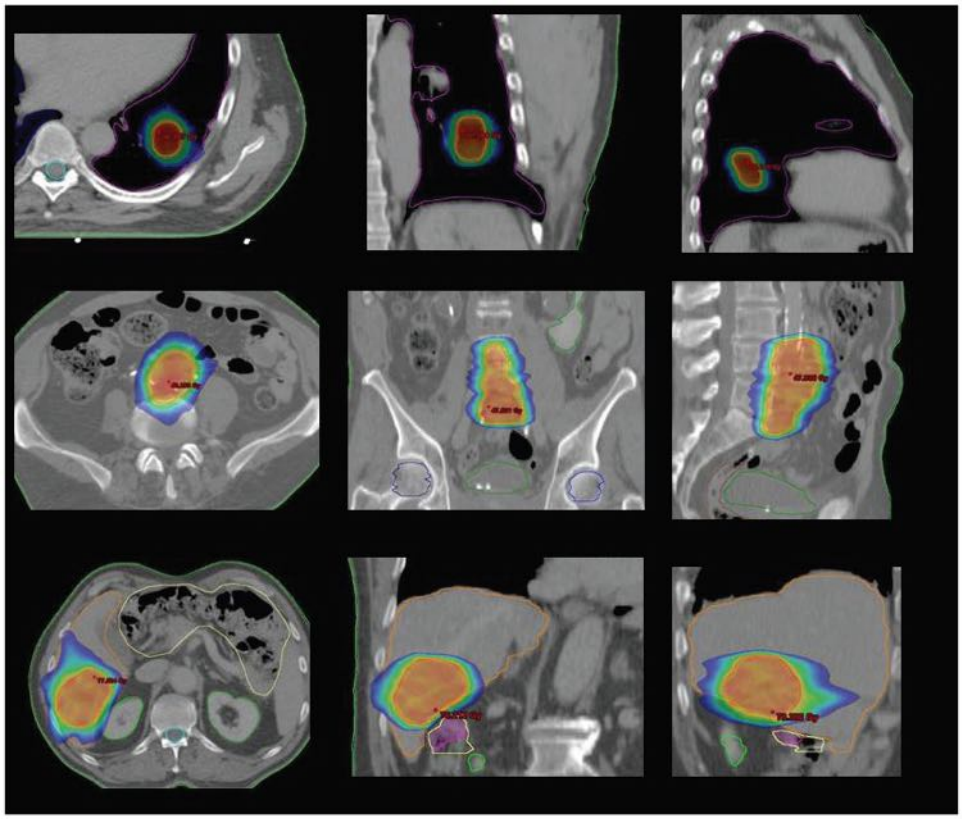
Feasibility and early clinical assessment of flattening filter free (FFF) based stereotactic body radiotherapy (SBRT) treatments

Marta Scorsetti[1], Filippo Alongi[1*], Simona Castiglioni[1], Alessandro Clivio[2], Antonella Fogliata[2], Francesca Lobefalo[1], Pietro Mancosu[1], Pierina Navarria[1], Valentina Palumbo[1], Chiara Pellegrini[1], Sara Pentimalli[1], Giacomo Reggiori[1], Anna M Ascolese[1], Antonella Roggio[1], Stefano Arcangeli[1], Angelo Tozzi[1], Eugenio Vanetti[2] and Luca Cozzi[2]

Purpose: To test feasibility and safety of clinical usage of Flattening Filter Free (FFF) beams for delivering SBRT doses to various tumor sites, by means of Varian TrueBeam™ (Varian Medical Systems).

Methods and Materials: **70 patients were treated with SBRT and FFF**: 51 lesions were in the **thorax** (48 patients), 10 in the **liver**, 9 in isolated **abdominal lymph node**, **adrenal gland** or **pancreas**.
Lung lesions were treated with cumulative doses of 32 or 48 Gy, delivered in 4 consecutive fractions. The liver patients were treated in 3 fractions with total dose of 75 Gy. The isolated lymph nodes, adrenal glands and pancreas were irradiated in 6 fractions with doses of 45 Gy.

Clinical Applications



Examples of dose distributions for the 3groups of patients.

Colour wash scale is from 20 to 50 Gy for the lung and the abdominal cases and from 35 to 80 Gy for the liver case.

Results: The minimum follow-up was 3 months.

Six cases of acute toxicities were recorded (2 G2 and 2 G3 in lung and 2 G2 in abdomen).

No patient experienced acute toxicity greater than G3.

Clinical Applications

Flattening filter-free linac improves treatment delivery efficiency in stereotactic body radiation therapy

Brendan M. Prendergast,[1] John B. Fiveash,[1a] Richard A. Popple,[1] Grant M. Clark,[1] Evan M. Thomas,[1] Douglas J. Minnich,[2] Rojymon Jacob,[1] Sharon A. Spencer,[1] James A. Bonner,[1] Michael C. Dobelbower[1]

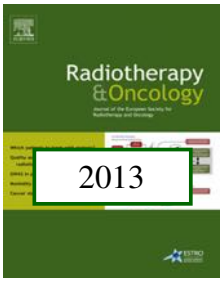
A total of 111 **lung** and **liver** SBRT cases treated from July 2008 to July 2011 were reviewed and 99 cases with complete data were identified.

Treatment delivery time for cases treated with a **FFF linac versus a conventional dose rate linac were compared.** The frequency and type of intrafraction image guidance was also collected and compared between groups.

In the FFF cohort, the mean treatment time and patient's immobilization was 11.44 (± 6.3) and 21.08 (± 6.8) minutes compared to 32.94 (± 14.8) and 47.05 (± 17.6) minutes for the conventional cohort ($p < 0.01$ for all values).

For lung and liver SBRT, a FFF linac reduces treatment and immobilization time by more than 50% compared to a conventional linac.

Clinical Applications: NSCLC



SBRT of lung cancer

Volumetric modulated arc therapy with flattening filter free (FFF) beams for stereotactic body radiation therapy (SBRT) in patients with medically inoperable early stage non small cell lung cancer (NSCLC)

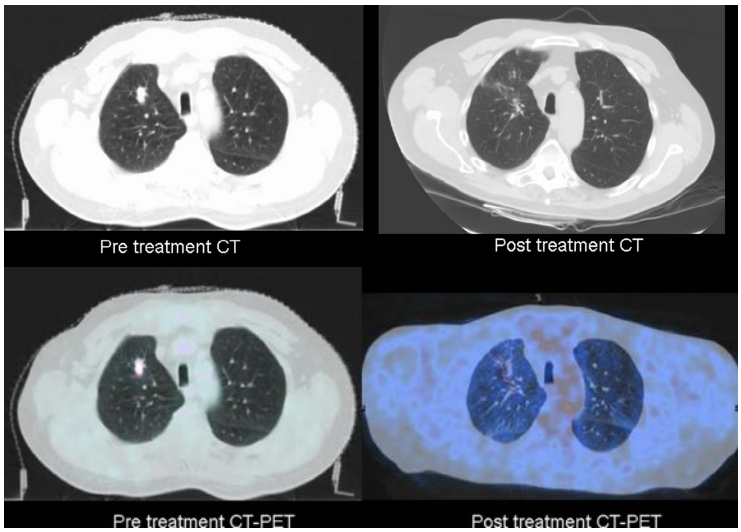
Pierina Navarria [a,*], Anna Maria Ascolese [a], Pietro Mancosu [a], Filippo Alongi [a], Elena Clerici [a], Angelo Tozzi [a], Cristina Iftode [a], Giacomo Reggiori [a], Stefano Tomatis [a], Maurizio Infante [b], Marco Alloisio [b], Alberto Testori [b], Antonella Fogliata [c], Luca Cozzi [c], Emanuela Morenghi [a], Marta Scorsetti [a]

[a] Radiotherapy and Radiosurgery Department; [b] Department of Thoracic Surgery, Humanitas Cancer Center, Istituto Clinico Humanitas, Milan, Italy; [c] Oncology Institute of Southern Switzerland, IOSI, Bellinzona, Switzerland

Methods and materials: From July 2006 to December 2011 **132 patients** underwent SBRT, 86 by 3DCRT with flattened beams (FF), while the last 46 with VMAT RapidArc and unflattened beams (FFF). All patients were treated with **48 Gy in four fractions of 12 Gy** each.

Results: Both techniques achieved adequate dose conformity to the target but with a statistically significant reduction of ipsilateral lung doses in RapidArc plans and also of Beam-on-Time (BOT) with FFF mode. The median follow up was 16 months (range 2–24 months). **At 1 year, local control rate was 100% with FFF beams compared with 92.5% with FF beams ($p = 0.03$).**

Clinical Applications: NSCLC



CT and CT–PET scan performed before (left) and after (right) treatment.
A complete remission can be seen.

Conclusions: SBRT with FFF beams permitted us **a safe delivery** of high dose per fraction in a **short treatment time** and resulted in an **earlier radiological response compared with FF beams.**

Clinical Applications: Lung mets

Stereotactic body radiation therapy for lung metastases from soft tissue sarcoma

Pierina Navarria [a], Anna Maria Ascolese [a], Luca Cozzi [a,*], Stefano Tomatis [a], Giuseppe Roberto D'Agostino [a], Fiorenza De Rose [a], Rita De Sanctis [b], Andrea Marrari [b], Armando Santoro [b], Antonella Fogliata [a], Umberto Cariboni [c], Marco Alloisio [c], Vittorio Quagliuolo [d], Marta Scorsetti [a]

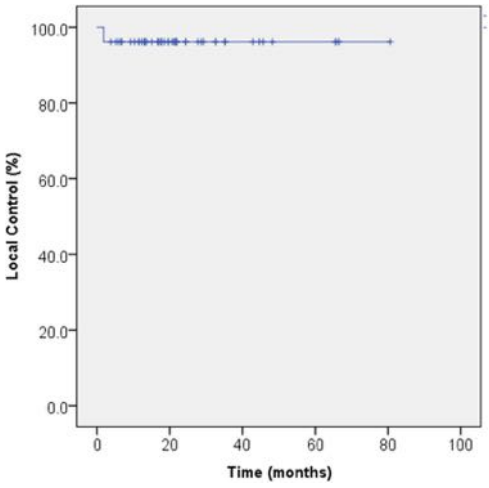
Materials and methods: Twenty-eight patients (**51 lesions**) were analysed.

In a risk adaptive scheme, the dose prescription was: **30 Gy/1 fr, 60 Gy/3 fr, 60 Gy/8 fr and 48 Gy/4fr**. Treatments were performed with Volumetric Modulated Arc Therapy - FFF beams.

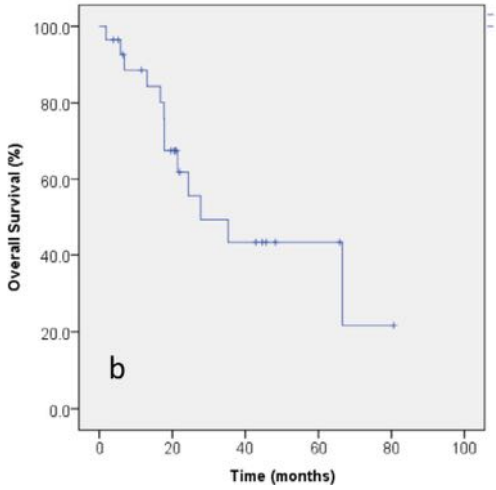
Clinical outcome was evaluated by thoracic and abdominal computed tomography (CT) scan before SBRT and than every 3 months. Toxicity was evaluated with Common Terminology Criteria for Adverse Events (CTCAE) scale version 4.0.

Clinical Applications: Lung mets

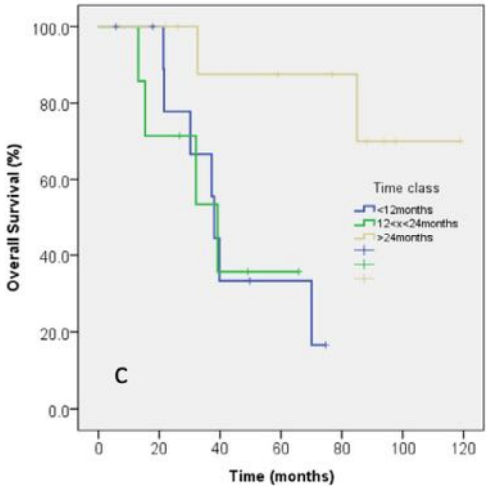
The median follow-up time from **initial diagnosis was 65 months** (5–139) and from **SBRT was 21 months** (2–80).



Actuarial local control from stereotactic body radiation therapy (SBRT) treatment.



Actuarial overall survival from stereotactic body radiation therapy (SBRT) treatment.



Actuarial overall survival from diagnosis stratified for the time-to-metastasis free interval.

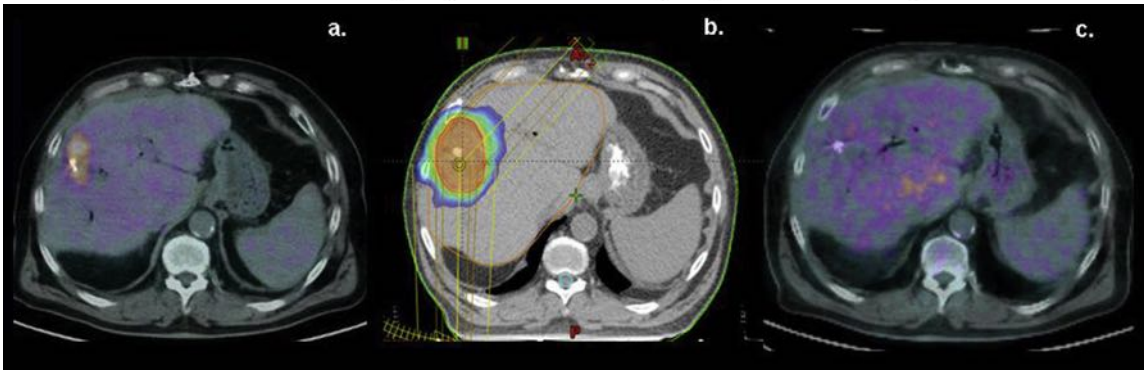
Conclusions: SBRT provides **excellent local control** of pulmonary metastasis from soft tissue sarcoma and may improve survival in selected patients.

No severe toxicity (G3-G4) was recorded and no patients required hospitalisation.

Clinical Applications: Liver

Is Stereotactic Body Radiation Therapy an Attractive Option for Unresectable Liver Metastases? A Preliminary Report From a Phase 2 Trial

Marta Scorsetti, MD,* Stefano Arcangeli, MD,* Angelo Tozzi, MD,* Tiziana Comito, MD,* Filippo Alongi, MD,* Pierina Navarria, MD,* Pietro Mancosu, MSc,* Giacomo Reggiori, MSc,* Antonella Fogliata, MSc,† Guido Torzilli, MD,† Stefano Tomatis, MSc,* and Luca Cozzi, PhD†



Patient treated with stereotactic body radiation therapy for recurrence of liver metastasis after surgery.
75 Gy \3 fr
BOT: 3 minutes

Conclusions: SBRT-FFF (25 Gy x 3 fractions) for unresectable liver metastases can be considered an **effective, safe, and noninvasive therapeutic option**, with **excellent rates of local control** and **a low treatment-related toxicity**

Clinical Applications: Lung and Liver

Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach

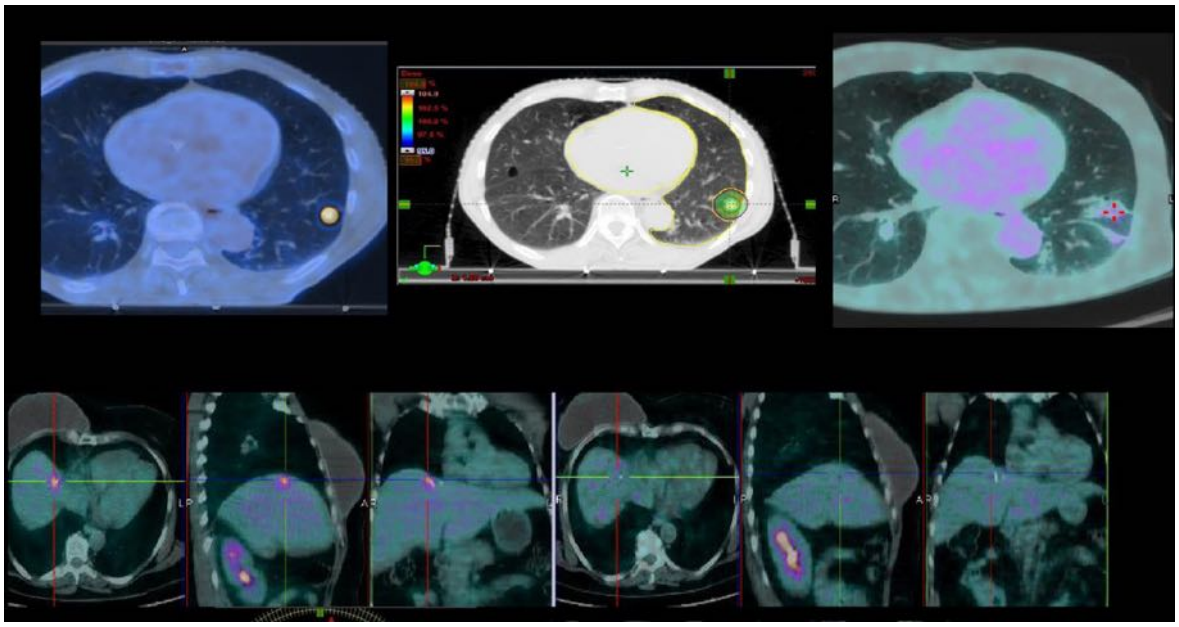
Tiziana Comito[1*], Luca Cozzi[2], Elena Clerici[1], Maria Concetta Campisi[1], Rocco Luca Emanuele Liardo[1], Pierina Navarria[1], AnnaMaria Ascolese[1], Angelo Tozzi[1], Cristina Iftode[1], Fiorenza De Rose[1], Elisa Villa[1], Nicola Personeni[3], Lorenza Rimassa[3], Armando Santoro[3], Antonella Fogliata[2], Pietro Mancosu[1], Stefano Tomatis[1] and Marta Scorsetti[1]

Materials and methods: **82 patients** with 1–3 inoperable metastases confined to one organ (liver or lung), were treated with
SABR for a total of **112 lesions** in an observational study. Prescription dose ranged between 48 and 75Gy in 3 or 4 consecutive fractions.

Results: Median follow-up was 24 months (range 3–47). **One, two and three years LC rate was 90%,80% and 75%.**

No patients experienced radiation-induced liver disease (RILD) or grade >3 toxicity.

Clinical Applications: Lung and Liver



Examples of complete response in two patients with liver and lung metastases.

Conclusions: SABR is a safe and feasible alternative treatment of oligometastatic colorectal liver and lung metastases in patients not amenable to surgery or other ablative treatments.

Clinical Applications: Prostate

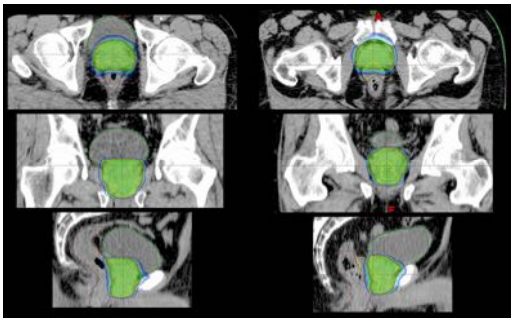
Linac based SBRT for prostate cancer in 5 fractions with VMAT and flattening filter free beams: preliminary report of a phase II study

Filippo Alongi[1,4*], Luca Cozzi[2], Stefano Arcangeli[1], Cristina Iftode[1], Tiziana Comito[1], Elisa Villa[1], Francesca Lobefalo[1], Pierina Navarria[1], Giacomo Reggiori[1], Pietro Mancosu[1], Elena Clerici[1], Antonella Fogliata[2], Stefano Tomatis[1], Gianluigi Taverna[3], Pierpaolo Graziotti[3] and Marta Scorsetti[1]

Prospective phase I-II study, started on February 2012.

The schedule was **35 Gy in 5 alternative days**.

Median follow-up was 11 months (range: 5–16); 40 patients were recruited in the protocol and treated.



Conclusions: Early findings suggest that SBRT with RapidArc and FFF beams for prostate cancer in 5 fractions **is feasible and tolerated in acute setting**.
Longer follow-up is needed for assessment of late toxicity and outcome.

Conclusions

1. Planning studies demonstrate **shorter delivery time** and **potential benefit for dose distributions**
2. Early clinical data focused on **LC** and **acute toxicity** demonstrate **good impact** on several primary indications
3. **Late results on OS and toxicity are maturing** but so far no unexpected findings
4. **Motion management**: faster delivery directly impacts on better control of organ motion and patient compliance
5. **Non conventional fractionation, retreatments, SABR, radiosurgery** in more areas are practically feasible with FFF opening to more clinical applications
6. **Cost effectiveness**: capital cost slighlty higher, running costs equivalent, throughput increased

Thanks

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