Perspectives of laser driven particle acceleration in radiation oncology

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Complex tumor therapy

15 million cancer cases/year

Advanced diagnostics
imaging/histo/mol

Improved outcome

Targeted therapy
Immunotherapy
Radiotherapy
Chemotherapy
Surgery

15 million cancer cases/year
Historical view on radiotherapy

1896
- X-ray tube

1925
- Radioactive needles
- Orthovolt

1950
- Synchrocyclotron

1970
- Simulator
- Cobalt beam
- Afterloader

1998
3DCRT IMRT/VMAT SRS/ SABR

Selectivity, effectivity, accuracy

RT today

IGRT
Motion control

Hadron therapy
new gen. part. acc
Compact superconducting synchro-cyclotrons (IBA and Varian) provide a KHz proton source with nanoampere current with 34 to 250 MeV.


<2% of all RT
Future of RT

Novel approaches under clinical evaluation

- **Fractionation:** hypofr./Acceler, Individ fr.
- **Technique:** Dose painting, Hadron Th
- Mixed energy RT
- Combined treatment
- sensitisation/protection
- Chemo-, hormon, biol.m., hypoxic sens.
- BNCT
- Immuno-Radiotherapy

Novel approaches under preclinical evaluation

- **FLASH-RT** 500ms pulses of >40 Gy/s
- **VHEE - PHASER** patented US20130231516
- Nanoparticles for RT sensitisation
- Mixed particle therapy
- Microbeam radiotherapy
- Dose and LET painting
- BPCEPT

PERSONALISED RT
BASED ON RADIOMICS/GENOMIC

The implementation of precision medicine, such as genomics, radiomics, and mathematical modelling open the possibility to personalised RT adaptation and treatment.
Dose rate effectiveness factor DREF

FLASH irradiation: <500ms pulses of >40 Gy/s

A 17 Gy conventional irradiation induced pulmonary fibrosis in 100% of the animals 24-36 weeks post-treatment, whereas no animal developed complications below 23 Gy flash RT. 30 Gy flash irradiation was required to induce the same extent of fibrosis as 17 Gy conventional irradiation.


Large animal single dose FLASH-RT studies on SSC at a dose rate of 25-41Gy/s confirmed its advantage and shows promise as a new treatment option for the future.

Microbeam radiation therapy (MRT)

Synchrotron-based MRT composed of spatially fractionated, planar x-ray (50-600keV) 25-75 micron-wide beams, with a very sharp penumbra, separated by a distance several times of their beam width. These microbeams create unique dose profiles of alternating peaks and valleys with high peak-to-valley-dose-ratios (PVDR)

Highly brilliant Synchrotron sources:
- very small beam divergence
- extremely high dose rate >100Gy/s.

GRID therapy (field size of mm), monoplanar beam arrays, Compton sources, pencil beam, Carbon nanotube X-rays, Proton MBT

Donzelli et al.: Conformal image-guided MRT at the ESRF
With the implementation of conformal image-guided MRT, the treatment of deep-seated tumors in large animals will be possible for multiple port irradiations.

Physiologically gated microbeam radiation using a field emission x-ray source array
The CNT field emission x-ray source array can be synchronized to physiological signals for gated delivery of x-ray radiation to minimize motion-induced beam blurring. The technique allows for more precise MRT treatments and makes the CNT MRT device practical for extended treatment.

E. Brauer-Krisch a, J-F.s Adam et al. Medical physics aspects of the synchrotron radiation therapies: Microbeam radiation therapy (MRT) and synchrotron stereotactic radiotherapy (SSRT) Physica Medica 31 (2015) 568e583

Synchrotron-based MRT resulted in 10 fold prolonged survival of the treated animals with brain tumor xenograft, larger animal studies are ongoing

2013-17 COST action – common effort accelerated experimental research toward clinical application

Potential indication: GBM, DIPG, Osteo-, chondro sarcomas, soliter-, oligo-metastasis, epilepsy, radio-immunotherapy

Delivery: single-, oligo fraction (≤3), sequential-, integrated-boost, reirradiation
After the proton reacts with the boron (11B), the boron changes to carbon (12C).

It splits into alpha particle of 3.76 MeV and beryllium (8Be).

Subsequently, the beryllium is divided into the two alpha particles of 2.74 MeV.
Both chromosoma abberation analysis and colony forming assay confirmed the enhanced effectivity of BPF in cell cultures using natural (80% $^{11}$B containing) BSH at a 62 MeV proton source.
PBF Enhanced Proton Therapy
PBFEPT

In addition to selective proton therapy
High spatial resolution
High LET,
High RBE
Low OAR

Binary approach
Dose- and LET-painting with PBFEPT

Simultaneous dose and LET optimisation has a potential to achieve higher tumour control and/or reduced normal tissue control probability.

LET-painting increases tumour control probability in hypoxic tumours

N. BASSLER  J.TOFTEGAARD et al.
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Figure 3. Dose and dose-averaged LET profiles shown in left and right column, respectively. First row is a carbon-12 ion plan using four conventional fields with homogeneous dose. The highest LET is then found at the rim of the SOBP’s as seen in the upper right figure. LET-painting, as shown in the middle row, allows for redistributing LET to cover the assumed hypoxic structure, depicted as the black entity, with increased LET. The energy fluence budget for the amount of particles used is the same for both plans in the upper two rows. The last row shows LET-painting again, but now with oxygen-16 ions, resulting in a pronounced increase of LET in the HTV. HTV, hypoxic target volume; LET, linear energy transfer; SOBP, spread out Bragg peak.
Boron Neutron Capture Therapy (BNCT)

Thermal neutrons captured by high probability by $^{10}$B desintegrates into two particles.

The two particles $\alpha$ and $^7$Li absorption ranges in tissue (~9 mm and ~5 mm respectively). All the energy is released inside the tumor cell.
### Neutron beam requirements for BNCT

- **epithermal neutron flux**: $\approx 10^9$ neutrons/cm$^2$ s (at the therapy position)
- **neutron energy**: $\sim 1$ eV to $\sim 10.0$ keV
- **gamma dose rate**: $\leq 1.0$ Gy/hr
- **fast neutron dose rate**: $\leq 0.5$ Gy/hr
- **current:flux ($J/\Phi$) ratio**: $> 0.8$

- the parameter $J/\Phi$ reflects the forward directionality (degree of collimation) of the beam of neutrons, which equals 0.5 for a completely isotropic beam and 1.0 for a purely parallel beam.
Dose components

- $D_{\text{Boron}}$
- $D_{\text{Nitrogen}}$
- $D_{\text{Photon}}$
- $D_{\text{neutron}}$

Dose Depth curve centre line of beam 110

- Total Dose
- $B_{10}$ Dose
- Photon Dose
- $N_{14}$ Dose
- Recoil Dose

Neutron capture reactions

BNC: High LET radiation: range: 10-15 $\mu$m, energy: 2.3 MeV

HNC: 2.2 MeV photons

NNC: back scattered protons
Clinical application of BNCT

N>200

Malignant melanoma

$^{10}$B carrier: BPA+BSH

Extracorporeal liver BNCT

BPA

Recurrent H&N tumors

$^{10}$B carrier: BPA

Boro-phenylalanine

HFR Research reactor

GBM $^{10}$B carrier BSH

Na$_2$B$_{12}$H$_{11}$SH

10M after BNCT

24M Disease free survival
Neutron sources for BNCT

Nuclear reactors
Charged particle accelerators
Compact neutron generators
LINAC based neutron source

High power laser facilities may provide via \((p, n)\) reaction intense epithermal neutron beam
Boronated agents for BNCT and BPCEPT

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\[ ^{11}\text{Boron delivery agents for Boron Proton Capture Enhanced Proton Therapy (BPCEPT)} \] – Anticancer Research submitted

BNCT Selective, cell-targetted energy deposition

- High LET, High RBE
- Binary approach

The highest cross-section occurs with protons around 600-700 keV corresponding to the Bragg peak

Starting experiments
Laser driven particle beams

- X-UV, X-ray photons
- Very high energy electron
- Protons Carbon ions

Integrated facilities with particle selection

Ultra short pulses
Ultra high dose rate ($<1\text{Gy/s}^{-10}$)
High repetition rate

Ultra high time and spatial resolution
Emerging approaches

General radiotherapy

- VHEE
- FLASH MBT
- BPFEPT

DOSIMETRY, DOSE CALCULATION

Radiobiology

Effects on normal tissue / tumor response

RBE of pulsed, ultraintense beams

BNCT, BPCEPT $^{10}$B/$^{11}$B carriers

MRT Flash

Classic *In vitro* and *in vivo* biological systems

Novel vertebrate model
Advantages

- Easy to handle, good reproduction captivity
- Body transparency (embryo and larva)
- External fertilization
- Rapid embryonic development
- Genomic similarity to the human genome
- Availability of several transgenic lines
- High resilience
Establishment of zebrafish embryo system for radiobiology studies

Definition of the embryo related factors (type, age, handling)

Validation of dose dependent biological endpoints (cell cultures/small animals)
  - survival, morphological deterioration
  - histopathological changes
  - Molecular damages (gammaH2AX, caspase3)
  - molecular pathway activation (RT-PCR)

Irradiation parameters: setup, dose delivery, dose escalation, fractionation,

Observation (period, frequency, assessment, documentation/photo/

Qualitative measurements

Automatisation
Irradiation of zebrafish embryos

**Age:** 24 hpf

In: plates/tubes/plastic bags

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**6 MV foton** - 0 Gy, 5 Gy, 10 Gy, 15 Gy, 20 Gy

**<En=1 MeV> hasadási neutron**

0 Gy, 1,25 Gy, 1,875 Gy, 2 Gy, 2,5 Gy

**p(18 MeV)+Be,** **<En>=3.5 MeV**

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**ATOMKI cyclotron neutron**

2 Gy, 4 Gy, 6,8 Gy, 8,12 Gy, 10,28 Gy
End points of zebrafish embryo experiments
detection of malformation and survival
RBE of fission neutron and $p(18\text{ MeV})+\text{Be}$ fast neutron

fission neutron LD50: 2Gy / photon LD50: 20Gy \hspace{1cm} \text{RBE} = 10

$p(18\text{ MeV})+\text{Be}$ fast neutron LD50: 8Gy / photon LD50: 20Gy \hspace{1cm} \text{RBE} = 2.5
Developmental deterioration

Photon (6 MV)

Fission neutron (1 MeV)

Cycl. neutron (p(18 MeV+Be)}
Histopathology analysis

cb- ceratobranchials
yse- yolk sac edema/ szíkhólyag ödéma
hp-
Eye and brain tissue

Control 20 Gy- 6 MV Foton 2 Gy- Fission neutron (<EN=1 MeV> 8.12 Gy- Cyclotron neutron (p(18 MeV)+Be, <EN> =3.5 MeV)
Small intestine, liver, muscle tissue

Control

20 Gy- 6 MV Photon

2 Gy- Fissioni neutron <EN=1 MeV>

8.12 Gy- Cyclotron neutron (p(18 MeV)+Be, <EN> =3.5 MeV)
Collaboration with OncoRay, and HZDR

150 MeV proton source

6 MV photon (ref. Source)

Experiments on

- proton RBE at the plato and mid of SOBP
- laser driven proton irradiation
- FLASH effect
Feasibility experiment at the LION facility at LMU

Further technical improvements may open the possibilities for **micro beam irradiation** development.
Laser driven ionizing radiation

Pulsed mode/ Ultraintense beam /Ultrashort dose delivery

- short treatment time
  - without increased entrance (skin) dose
  - no need for internal organ motion management
    - immunoRT

  - high temporal resolution
    (adaptive response, FLASH RT)

  - high spatial resolution

  - Intensity modulation with higher resolution
    - Microbeam RT

Potential for charged particle/neutron and multiple particle beams

Improved dose distribution,

BNCT, BPCEPT

Dose and LET painting
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