

Trento Institute for Fundamental Physics and Applications



Neutron radiobiology: medicine and space

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Outline

- Introduction to radiobiology
 - Survival
 - Transformation
- Neutron radiobiology
 - Cell killing
 - Late effects
- Neutron therapy
 - Fast neutron therapy
 - Contamination in charged particle therapy
- Neutrons in space
 - Contribution in dose
 - Shielding
 - Facilities



How does radiation injure people?



Direct ionization of biological molecules

Indirect effect through formation of free radicals in water





The most unkindest cut of all

(W. Shakespeare, Julius Caesar)



How does this damage from ionizing radiation effect our bodies?



Sufficient Cell Killing



Radiation Sickness



Sufficient Genetic Alterations



Cancer



Survival after X- or γ-rays



 β [Gy⁻²]: bending of curve α/β [Gy]: dose, at which contribution from linear term = contribution from quad. term

Relative Biological Effectiveness

Comparison of dose values at Isoeffect-Level!



Radiation Biophysics - Cell Inactivation

Dose dependence of RBE



$$RBE_{\alpha} = \frac{D_X}{D_I} = \frac{\alpha_I}{\alpha_X}$$

Oxygen Effect



Oxygen effect: LET dependence



Radiation carcinogenesis



FAP = Familial Adenomatous Polyposis 🗇 HCV = Hepatitis C virus 🗇 HPV = Human papillomavirus 🗇 CLL = Chronic lymphocytic leukemia 🗇 AML = Acute myeloid leukemia

Evidence of radiation carcinogenesis





Figure 19–5. Thyroid cancer incidence per person year (PY) as a function of the radiation dose in the thyroid. Rates adjusted for sex, ethnicity, and interval after irradiation. Error bars represent 90% confidence limits. (From Shore RE, Woodard E, Hildreth N, et al: J Natl Cancer Inst 74:1177–1184, 1985)

In vitro dose-response curve

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Dose-response curve for the frequency of transformant/ surviving cell using linearquadratic, but plateaus at high doses

Animal studies



Figure 19-3. Incidence of myeloid leukemia in RF male mice exposed to whole-body x-irradiation. (From Upton AC: Cancer Res 21:717-729, 1961)



The elephant paradox



Nature, 8.10.2015

- Cancer is an aging disease, and depends on the number of divisions of the stem cells
- Large, old animals should get more cancers
- However, elephants do not get cancer
- Same is true for other large animals, such as humpback whales
- Recent studies show that elephants have approximately 20 copies of the p53 gene
- As a consequence, their blood cells are very radiosensitive and go into apoptosis
- Instead of repairing DNA damage, injured elephant cells kill themselves to nip nascent tumors in the bud



Neutron radiobiology: an old story

Neutrons: secondary charged particle spectra



14 MeV



Caswell & Coyne 1972

Neutrons: Survival Curves



Figure 3. Survival curves obtained for cultured cells of human origin irradiated with different beams of fast neutrons and with 250 kVp x-rays.

Neutron: Energy dependence of RBE





Broerse et al. 1968

"how much" or when"?



Induction of acute myeloid Iuekemia in mice





RBE~1 for Fe-ions

RBE ~ 10 for neutrons

Colorado State University, 2009

Neutron quality factor



Radiotherapy



Side-effects of Radiotherapy

Acute (<1 month)

- •Depend on area(s) being treated
- •Often fatigue can occur
- •mucositis/esophagitis, nausea, diarrhea and redness of skin

Late (>1 month)

Pneumonitis/fibrosis of lungs

Hypothyroidism

Xerostomia

Enteritis

Infertility/menopause

Long-term (10-20 years)

Increased risk of secondary cancers

Increased heart disease if chest region treated



Therapeutic window



Where is the Energy Deposited?



Protons

X-ray dose decrease with depth We have to cross-fire on the tumor from many angles

Single field

Dose per field

Total dose







Excellent target conformity Large normal tissue volume irradiated

Courtesy B. Mijnheer







Kristjan Anderle, Ph.D. thesis, TU Darmstadt, 2014



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Treatment plan with protons: pleural mesothelioma

Courtesy of Marco Schwarz, AtrEP, Trento, Italy



- About 100,000 patients treated with H and 10,000 with C-ions
- >30 particle therapy facilities in operation (6 with heavy ions)
- Many more are under construction or planned

Potential advantages

High tumor dose, normal tissue sparing Effective for radioresistant tumors

Effective against hypoxic tumor cells

Increased lethality in the target because cells in radioresistant (S) phase are sensitized

Fractionation spares normal tissue more than tumor

Reduced angiogenesis and metastatization





Only in USA, 27 new centers expected by 2017

The Star

4 000 - 1 000 patients

<1 000 patients</p>

< 500 patients</p>

uPECC report "Nuclear Physics in Medicine", 2014 vailable online www.nupecc.org
ITALIAN NETWORK FOR HADRONTHERAPY

EXISTING CENTRES











Population – scaled

GPD-scaled

1st Neutron Patient Dr Stone and Dr Lawrence



Fast neutron production: d



Fast neutron production: p





Proton linear accelerator for Neutron therapy



Proton linear accelerator for neutron therapy



The cost of particle therapy



High energy neutron treatment for pelvic cancers: study stopped because of increased mortality

R D Errington, D Ashby, S M Gore, K R Abrams, S Myint, D E Bonnett, S W Blake, T E Saxton

BMJ VOLUME 302 4 MAY 1991



REVIEW OF THE LOCO-REGIONAL CONTROL RATES FOR MALIGNANT SALIVARY GLAND TUMOURS TREATED DEFINITIVELY WITH RADIATION THERAPY

FAST NEUTRONS				
Authors	Number of patients Loco-regional control (%)			
Saroja et al., 1987	113	71	(63 %)	
Catterall and Errington,1987	65	50	(77 %)	
Battermann and Mijnheer, 1986	32	21	(66 %)	
Griffin et al., 1988	32	26	(81 %)	
Duncan et al., 1987	22	12	(55 %)	
Tsunemoto et al. (in press)	21	13	(62 %)	
Maor et al., 1981	9	6		
Ornitz et al., 1979	8	3		
Eichhorn, 1981	5	3		
Skolyszewski, 1982	3	2		
Overall	310	207	(67%)	

STUDY RESULTS



* Photons * Neutrons

* Photons * Neutrons 17% ± 11% 67% ± 14%

25% ± 14% 62% ± 14%





European Results in Neutron Therapy of Salivary Gland Tumors Severe radiation related morbidity

Reference	No.	%	
Catterall 1987	8/65	11.8%	
Battermann 1986	4/32	12.5%	
Duncan 1987	4/26	15.4%	
Kovács 1987	2/15	13.3%	
Engenhart 1994	2/49	4.1%	
Krüll 1995	6/74	8.1%	
Lessel 1995	6/38	15.8%	
Overall	32/299	10.7%	



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TABLE 1 | Current status of operating neutron facilities worldwide [status as stated at the IAEA Technical Meeting 2013 (F1-TM-44771)].

Location	Source	Mean energy (MeV)	50% depth (cm)	Beam direction	Collimator type	First patient treated	Patients treated (n)
University of Washington Medical Center, Seattle, USA	Cyclotron p(50.5) + Be	20	14	Isocentric	Multi leaf	1984	2960
iThemba Laboratory for Accelerator Based Science (LABS), Cape Town, South Africa	Cyclotron p(66) + Be	25	16	Isocentric	Multi blade trimmer	1988	1788
Tomsk Polytechnic University, Tomsk, Russian Federation	Cyclotron d(13.6) + Be	6.3	6	Horizontal	Inserts	1983	1500
FRM II, Technische Universität München, Garching, Germany	Uranium converter	1.9	5	Horizontal	Multi leaf	2007	124

Frontiers in Oncology | www.frontiersin.org

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November 2015 | Volume 5 | Article 262

The BNCT Reaction

2.33 MeV of kinetic energy is released per neutron capture: initial LET 200-300 ke V/µm



Thermal cross-section = 3837 barns (that's very big...)



The figure shows that the maximum dose rate in healthy tissue of 0.13 Gy/min is reached at 2.6 cm of depth. The tumour tissue would experience the same dose-rate value at 9.8 cm of depth. Deeper tumours would receive lower dose then the healthy tissue maximum dose. At the AD the advantage-depth dose-rate (ADDR in the figure) is 0.13 Gy/min. Clearly, the AD value depends on the tumour-to-healthy-tissue ¹⁰B concentration ratio (BR). A thumb rule is to use guasi-thermal neutrons for depths less than 2 cm and epithermal neutrons for deeper depths.

Possible applications: melanoma (shallow tumors) and GBM (boron accumulate in tumor rather than in normal brain)

From NuPECC, Nuclear Physics in Mediicine, 2014..

Boron neutron capture therapy (BNCT) for glioblastoma multiforme: A phase II study evaluating a prolonged high-dose of boronophenylalanine (BPA)[☆]

Roger Henriksson^{a,*}, Jacek Capala^{b,c}, Annika Michanek^d, Sten-Åke Lindahl^e, Leif G. Salford^f, Lars Franzén^a, Erik Blomquist^g, Jan-Erik Westlin^h, A. Tommy Bergenheimⁱ



Adverse events obtained during the study period in 19 of 29 patients

Type of AE	No. of events	No. of patients
Skin/mucosa	13	8
Seizures (epilepsies)	12	7
Thrombosis	8	6
Abdominal	5	4
Depression	3	3
Aphasia	2	2
CVS	2	2

Conclusion: Although, the efficacy of BNCT in the present protocol seems to be comparable with conventional radiotherapy and the treatment time is shorter, the observed side effects and the requirement of complex infrastructure and higher resources emphasize the need of further phase I and II studies, especially directed to improve the accumulation of ¹⁰B in tumour cells.

Operative BNCT centers

CENTER	STATES	NEUTRON SOURCE	NEOPLASM	T R E A T E D PATIENTS
Helsinki University Central Hospital, Helsinki, Finland	Europe	FIR-1, VTT Technical Reserch Centre, Espoo	GB and HN	50 GM 2 AA 31 HN
Faculty Hospital of Charles University, Prague, Czech Republic	Europe	LVR-15 Reactor, Nuclear Reserch Institute Rez	GB	5 GM
University of Tsukuba, Tsukuba City, Ibaraki	Japan	JRR-4, Japan Atomic Energy Agency, Tokai, Ibaraki	GB	20 GM 4 AA
University of Tokushima, Tokushima	Japan	JRR-4 (Kyoto University Research Reactor, Osaka)	GB	23
Osaka Medical College and Kyoto University Research Reactor, Kyoto University, Osaka and Kawasaki Medical School, Kurashiki	Japan	KURR	GB, HN, CM	30 GBM 3 AA 7 Men 124 HN
Taipei Veterans General Hospital, Taipei, Taiwan	Republic of China	THOR, National Tsing Hua University, Hsinchu, Taiwan	HN	10
Inst de Oncol. Angel H, Buenos Aires	Argentina	Bariloche Atomic Center	CM and AT	7CM 3 AT

Neutrons as a contamination in radiotherapy



Secondary Neutron Spectra Measured for Varian 18MV



Howell et al. Medical Physics, Vol. 36, No. 9, 4027-4038 (2009)

NEUTRON ENERGY SPECTRUM

<u>18 MV X-rays, 5x5 cm2 field, BDS</u> Direction: GT, Energy: 18 MV Field size: 5x5 cm²



NEUTRON EQUIVALENT DOSE

Direction: GT, Energy: 18 MV Field size: 5x5 cm², BDS



• Neutrons are the major contributors to the equivalent dose measured outside the field at the surface, but negligible at 10 cm depth

• Data from Kaderka et al. Phys. Med. Biol. 2012 support calculations by Howell et al. Med. Phys. 2009 and Ongaro et al. Phys. Med. Biol. 2000

Radiotherapy and SMN

- Cancer survivors represent about 3.5% of US population
- Second primary malignancies in this high-risk group accounts for about 16% of all cancers
- Three possible causes: Continuing lifestyle;Genetic predisposition:treatment of the primary cancer (SMN)



CCSS study, St. Jude et al. 2008-2015 Retrospective cohort of 14,000 survivors of childhood cancer diagnosed between 1970 and 1986

Fast neutrons: second cancers in radiotherapy





Radiation Absorbed Dose



Risk of SMN Incidence



Secondary Malignant Neoplasms (SMN) in particle therapy

Comparison of relative radiation dose distribution with the corresponding relative risk distribution for radiogenic second cancer incidence and mortality. This 9-year old girl received craniospinal irradiation for medulloblastoma using passively scattered proton beams. The color scale illustrates the difference for absorbed dose, incidence and mortality cancer risk in different organs.

MDAnderson Cancer Center

Making Cancer History*

Newhauser & Durante, *Nat. Rev. Cancer* 2011

The MATROSHKA facility

- Standard RANDO phantom of property of DLR (German Aerospace center)
- > 850 mm high divided into 34 slices
- Holders for detectors in several slices
- Currently used for space radiation dosimetry inside the ISS























Protons (PSI)









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Rod Slice #1 Slice #4 (tumor) Belt Slice #3 Slice Slice #5 Slice #7 Slice #9 Slice #11 Slice #13 Belt Slice #14 (Slice #14) Slice #17 Slice #20 Slice #21 Belt = (Phantom main axis)

Inner dose

TLD 700

 Highest out-of-field dose for photons • Higher lateral dose for passive modulation dose than scanning delivery Higher lateral dose for portons than carbon ions
Collimator produces ions

sharper field edges



La Tessa et al., Radiother. Oncol. 2012

Neutrons produced by charged particles



slow neutrons for photons • Passive delivery enhances the production of slow neutrons compared to scanned beams • Scanned carbon ions produce the lowest amount of low-energy neutrons

• Highest production of

La Tessa *et al., Phys. Med. Biol.* 2014



In patient dosimetry (uterus dose for a pregnant woman)





TABLE 1						
Measured doses in the pelvic region during the treatment.						
	Photon dose (μSv/fraction)	Neutron dose (μSv/fraction)	No. of fractions	Total dose (μSv)		
Normal field Boost field Total treatment	3.0 ^a 2.2 ^b	1.4 1.0	15 5 20	66 16 82		

^a Calculated assuming a factor of 1.4 between normal and boost fields as in neutron dose.

^b Measured by the TOL/F gamma dose rate meter. The passive thermoluminescence dosimeter films did not measure any significant dose above the normal background.

Münter. Heavy ion radiotherapy during pregnancy. Fertil Steril 2010.

Total dose < 0.3 mSv

Very low stray radiation reduced risk of secondary cancers or teratogen effects

Münter et al., Fertil Steril. 2010



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Neutrons in space

The Space Radiation Environment

Solar particle events (SPE) (generally associated with Coronal Mass Ejections from the Sun):

- medium to high energy protons
- largest doses occur during maximum solar activity not currently predictable
- MAIN PROBLEM: develop realistic forecasting and warning strategies

pped Radiation:

medium energy protons and electrons effectively mitigated by shielding v shielding mainly relevant to ISS MAIN PROBLEM: develop accurate dynamic model

Galactic Cosmic Rays (GCR)

high energy protons

highly charged, energetic atomic nuclei (HZE particles)

not effectively shielded (break up into lighter, more penetrating pieces) abundances and energies quite well known MAIN PROBLEM: biological effects poorly understood but known to be most significant space radiation hazard
Solar particle events



Galactic Cosmic Radiation



"Best" shielding materials



Projectile interactions per unit target mass: Ionization ~ Z/A (Bethe-Bloch formula) Fragmentation ~ A^{-1/3} (Bradt-Peters formula)

Is shielding a solution?

Free Space at 1 AU

Max GCR dose

reduction

Lunar Surface

Martian Surface



Aluminum ~ 30% Polyethylene ~ 50% Liquid hydrogen ~ 90%

Cosmic ray damage to microelectronics

Radiation damage is caused by electron-hole pairs created in SiO₂ or other insulators

Single event upsets (SEU), total dose effects (TDE), and displacement damage (DD)

Special Redesign of 2901 Microprocessor for Galileo

- Problem identified during design and evaluation
- Potential "show stopper" for Galileo mission
- Resets in Hubble Space Telescope after Upgrade in 1996
- Caused by transients from optocouplers
- Occurred when spacecraft flew through South Atlantic anomaly
- Failures of Optocouplers on Topex-Poseidon
- Resets in Power Control Modules on Cassini
- High Multiple-Bit Error Rate in Cassini Solid-State Recorder









Norbury and Slaba, *Life Sciences in Space Research*, 2014

Level











Effective Dose

Dose Eq in ICRP Phantom [cSv/y], QL ICRP60







Neutrons in space: LEO

- Dose contribution: 5-15%
- Dose equivalent contribution: 20-50%
- Spectra by Bonner balls (ISS) or nuclear emulsions (Mir)

	Altitude	Neutron	Charged particle	Neutron equivalent	Charged particle equivalent
		dose rate	dose rate	dose rate	dose rate
Mission	(km)	$(\mu Gy/day)$	$(\mu Gy/day)$	$(\mu Sv/day)$	$(\mu Sv/day)$
STS-55	302	5.9	57.2	52.0	120.1
STS-57	470	25.3	461.9	220.0	859.4
STS-65	306	11.0	75.2	95.0	157.8
STS-94	296	3.7	101.5	30.8	213.9

Durante and Cucinotta, *Rev. Mod. Phys.* 2011

Neutrons in space: MSL





Launched 26.11.2011 – on Mars since 6.8.2012







	GCR dose rate	GCR dose-equivalent	Inspiration	Mars sortie	Mars base
	(mGy/day)	rate (mSv/day)	Mars (Sv)	(Sv)	(Sv)
MSL cruise (Zeitlin et al., 2013) MSL on Mars (Hassler et al., 2014)	0.46 0.21	1.84 0.64	0.92	0.7	0.98

Neutrons in RAD



NASA



Neutrons in deep space



Dose rate and dose equivalent rate for the calculated neutron spectrum. The measurement covers an energy range of 12–436 MeV, the simulation extends this range to 0.1–1000 MeV.

	Measurement	Simulation
Dose equivalent rate Dose rate	$19\pm5~\mu Sv/day$ $3.8\pm1.2~\mu Gy/day$	$30\pm10~\mu Sv/day$ $6\pm2~\mu Gy/day$

Charged particle doserate 1840 µSv/day

Koehler *et al., Life Sci. Space Res.* 2015

Neutrons on Mars



Dose equivalent rate := $61 \pm 10 \ \mu$ Sv/d Doserate : $14 \pm 3 \ \mu$ Gy/d

Charged particle doserate 640 μSv/day

Koehler *et al., J. Geophys. Res.*2014



There is greater concern about high-energy neutron fields owing to the increasing number of highenergy accelerators in research and medicine and the special consideration given to the occupational exposure to cosmic radiation. In order to study the physics of neutron interactions in these applications, in particular concerning dosimetry, radiation protection monitoring of workplaces, and radiation effects in electronics, particularly those used in aircraft and in spacecraft, wellcharacterized neutron fields for high energies are needed.

- Louvain, Belgium: closed
- Uppsala, Sweden: closed
- NPI, Czech Republic: max 30 MeV
- NFS, Ganil, France: under construction, max 40 MeV

(....)QMN beams with energies above 40 MeV will be available only in South Africa and Japan, with none in Europe.



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Grazie! Thank you! Vielen Dank! 89