Low Dose Radiation Biology: State-of-the art and future challenges

DEGRO 2023 – Refresherkurs Gutartige Erkrankungen

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Radiation Osteoimmunology Group

Translational Radiobiology
Head: Prof. Dr. U.S. Gaipl
Strahlenklinik
Head: Prof. Dr. R. Fietkau

Uniklinikum Erlangen

TOGETHER
[BMBF, 02NUK073]

GREWIS-Project
[BMBF, 02NUK017G]

GREWIS-alpha-Project
[BMBF, 02NUK050E]

Friedrich-Alexander-Universität
Medizinische Fakultät

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

Conflict of Interest

Berater- und Gutachtertätigkeiten
Nein

Honorare
Nein

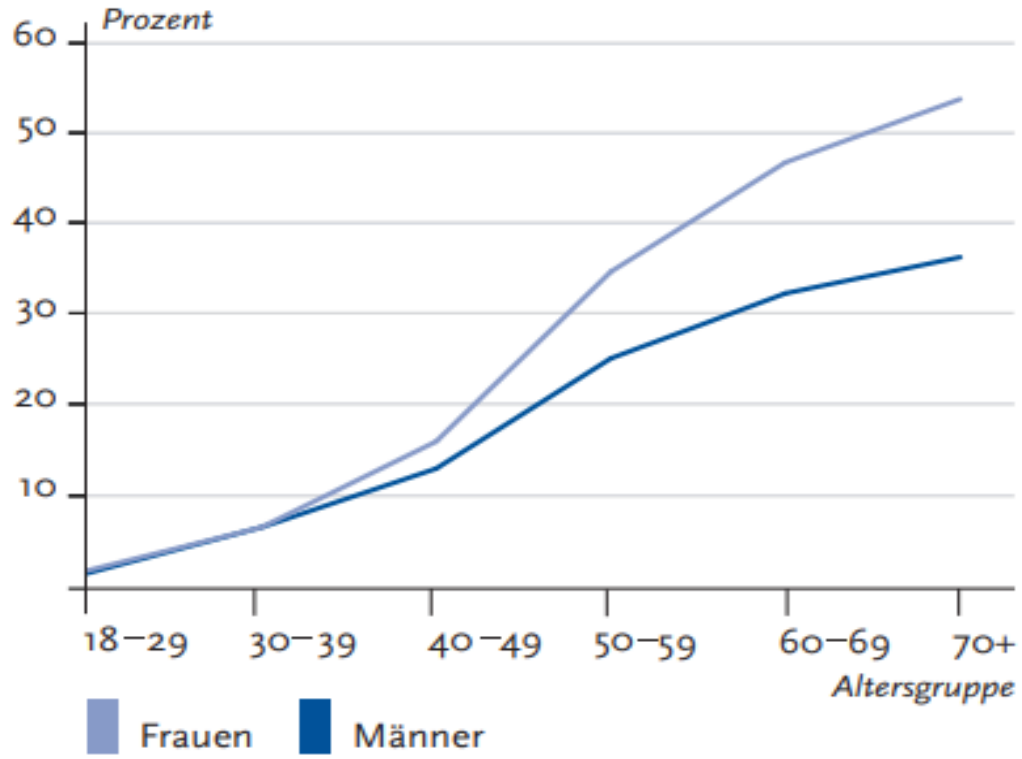
Forschungsfinanzierung
Nein

Eigentümerinteressen (Patent, Urheberrecht, Verkaufslizenz)
Nein

Geschäftsanteile, Aktien, Fonds
Nein

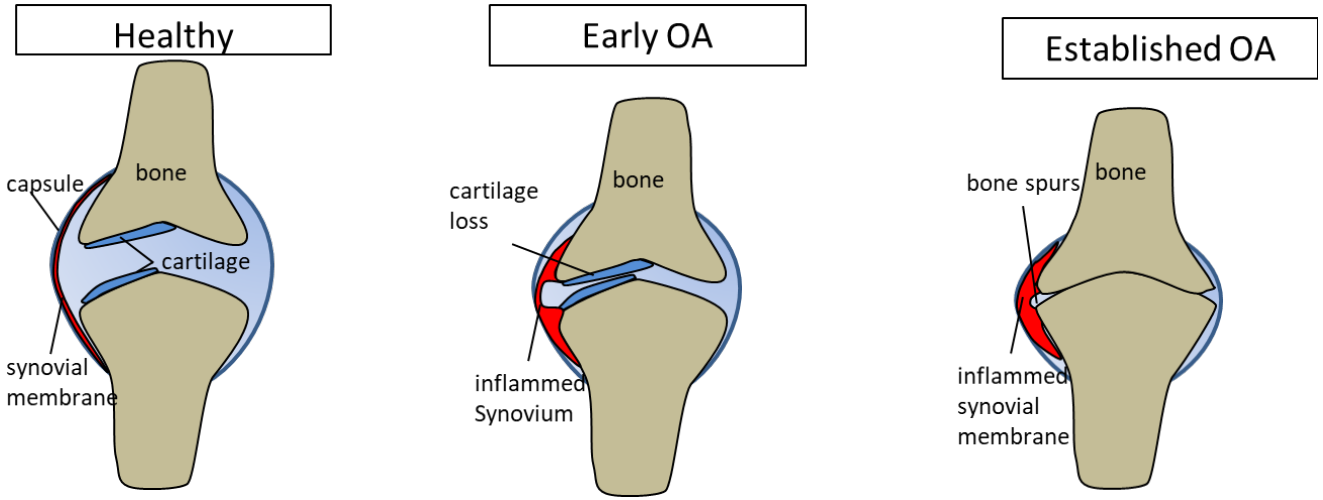
Arthroses as economically relevant disease

- Most common disease of the joints
- Most common reason for disability
- Increasing incidence and prevalence
- Cumulative direct and indirect costs of 7.6 billion Euro/year



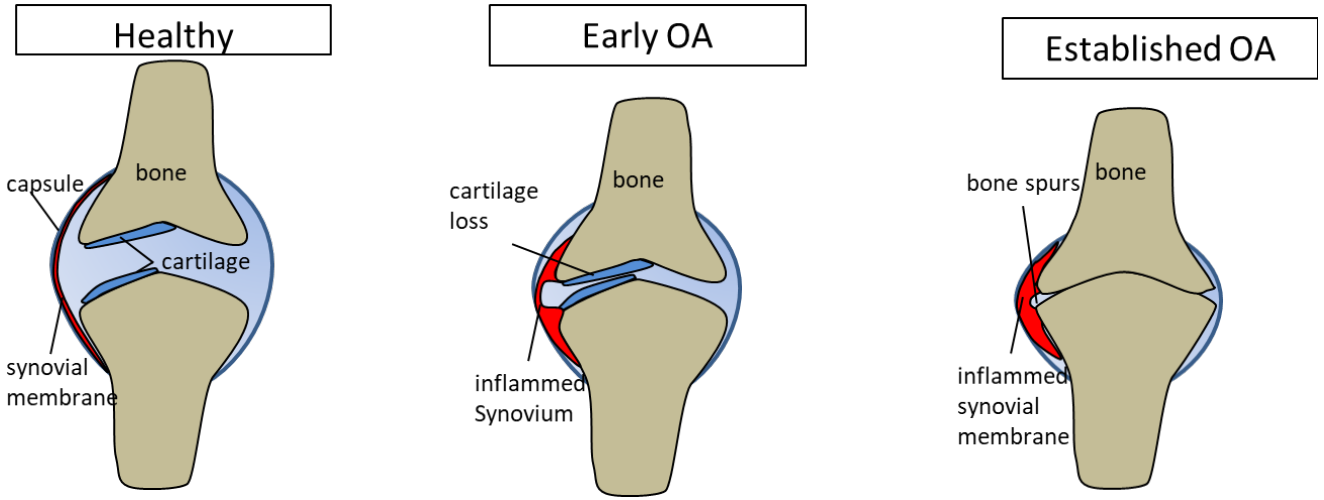
Arthroses/Osteoarthritis

- Complex, multifactorial condition affecting the entire joint
- **Mechanical** and **inflammatory** components (risk factors: age, obesity, hormones, genetic factors)
- **Leading degenerative joint disease**;
- Not only mechanical cartilage degradation → complex interaction of various tissue and cell types, strong involvement of the immune system



Treatment Options

- **Conservative measures**: Medication, physical therapy, ergotherapy orthopedic measures, ..
- **Surgical measures**: joint preserving surgery, joint replacement, …
- **But**: **~20% non-responders**



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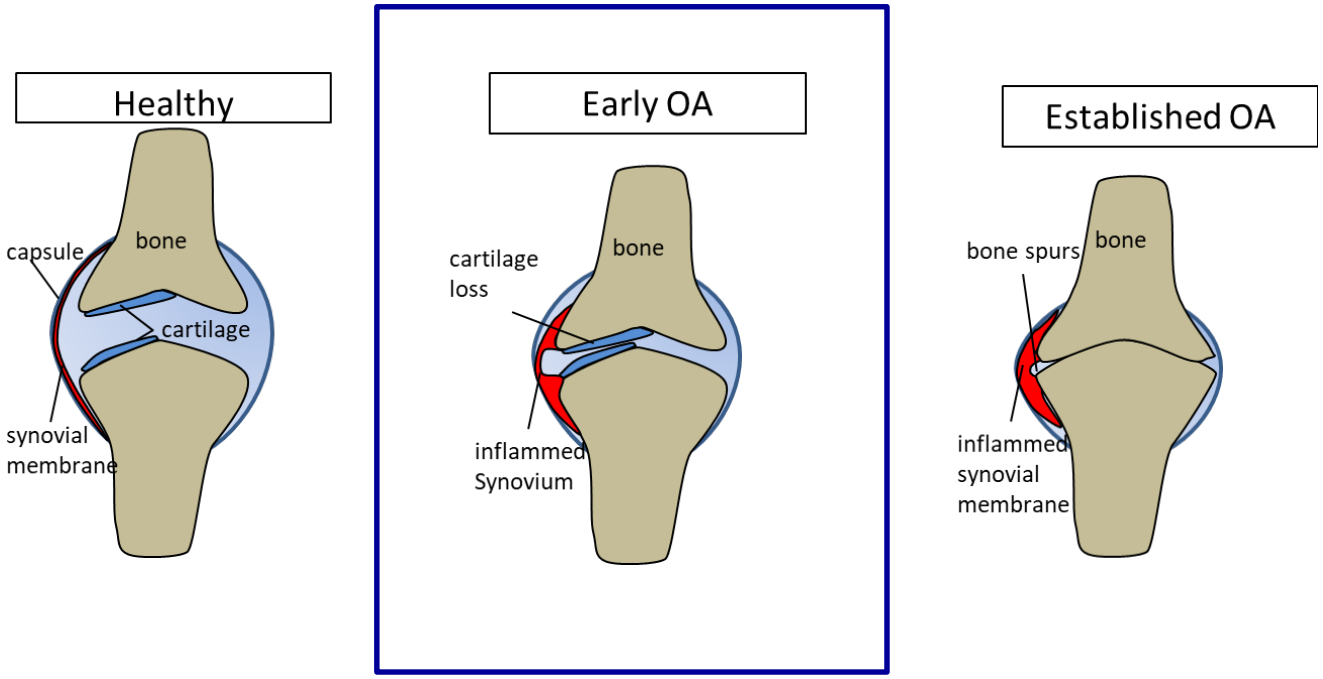


- **„Window of opportunity“**: Early treatment essential

→ LD-RT!

Low-dose Radiotherapy – Current usage in Germany

In Germany:

- Up to 50.000 LD-RT patients/year

- Chronic, degenerative, musculoskeletal disorders:
  → **improved pain management**
  → **improved mobility**

- Data: in patients → mostly **empirical** and/or **not supported by placebo-controlled** studies
  preclinical → exact mechanisms unknown, involvement of the **immune system**

→ often: **Hesitation to use LD-RT** as some existing treatment strategies are **better examined**

LD-RT as Effective Targeted Therapy

Multicenter Study > Strahlenther Onkol. 2020 Aug;196(8):715-724.
doi: 10.1007/s00066-019-01563-1. Epub 2019 Dec 23.

Radiotherapy for osteoarthritis-an analysis of 295 joints treated with a linear accelerator

Matthias G Hautmann [1], Philipp Rechner [2], Ulrich Neumaier [3], Christoph Süß [4], Barbara Dietl [4], Franz Josef Putz [5], Michael Behr [6], Oliver Kölbl [4], Felix Steger [4]

Low Dose Radiation Therapy, Particularly with 0.5 Gy, Improves Pain in Degenerative Joint Disease of the Fingers: Results of a Retrospective Analysis

Anna-Jasmina Donaubauer,[1,†] Jian-Guo Zhou,[1,2,†] Oliver J. Ott,[1] Florian Putz,[1] Rainer Fietkau,[1] Ludwig Keilholz,[3] Udo S. Gaipl,[1,‡] Benjamin Frey,[1,‡] and Thomas Weissmann[1,*,‡]

Multicenter Study > Strahlenther Onkol. 2021 Oct;197(10):895-902.
doi: 10.1007/s00066-021-01816-y. Epub 2021 Aug 3.

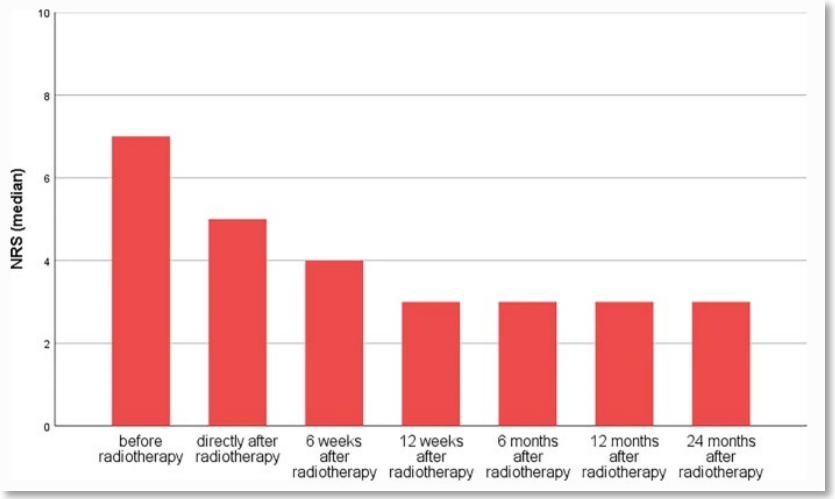
Low-dose radiotherapy for painful osteoarthritis of the elderly: A multicenter analysis of 970 patients with 1185 treated sites

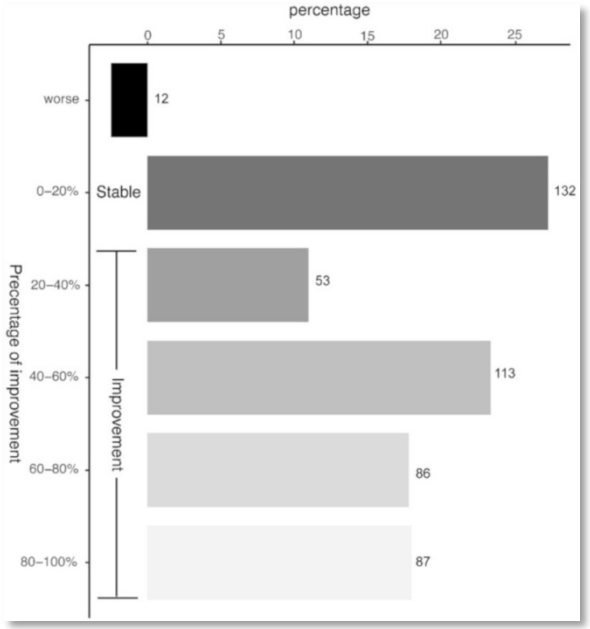
Alexander Rühle [1 2 3], Elisabeth Tkotsch [1], Rainer Mravlag [4], Erik Haehl [1 2], Simon K B Spohn [1 2], Constantinos Zamboglou [1 2], Peter E Huber [3 4], Jürgen Debus [4], Anca-Ligia Grosu [1 2], Tanja Sprave [1 2], Nils H Nicolay [1 2 3]

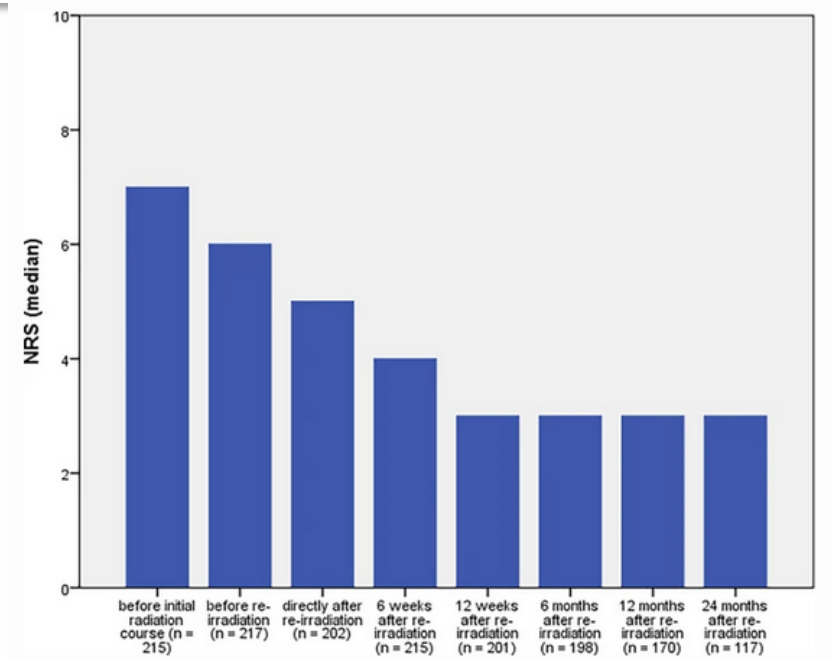
Multicenter Study > Strahlenther Onkol. 2019 Dec;195(12):1060-1067.
doi: 10.1007/s00066-019-01500-2. Epub 2019 Jul 25.

Re-irradiation for osteoarthritis-retrospective analysis of 217 joints

Matthias G Hautmann [1], Philipp Rechner [2], Matthias Hipp [3], Ulrich Neumaier [4], Felix Steger [5], Fabian Pohl [5], Markus Weber [6], Oliver Kölbl [5], Christoph Süß [5]







Median pain on the numeric rating scale (*NRS*) during the follow-up

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LD-RT Predicament- Lack of Prospective, Sham-controlled Studies

Randomized Controlled Trial > Ann Rheum Dis. 2019 Jan;78(1):83-90.
doi: 10.1136/annrheumdis-2018-214104. Epub 2018 Oct 26.

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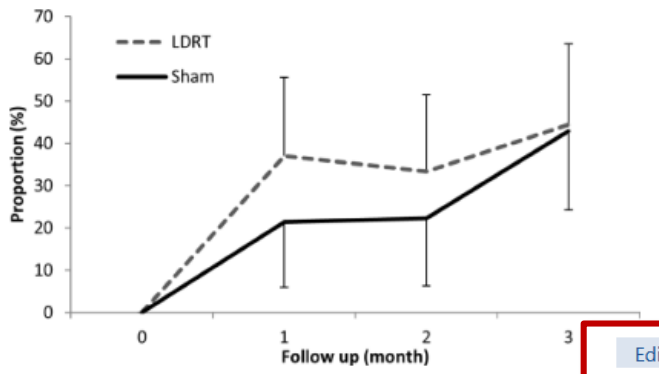

Figure 2 Proportion of responders over 3 months, with its 95% LDRT and sham intervention. LDRT, low-dose radiation therapy.

Editorial > Strahlenther Onkol. 2019 Apr;195(4):285-288. doi: 10.1007/s00066-018-1412-1. Epub 2018 Dec 18.

Low-dose radiotherapy: Mayday, mayday. We've been hit!

Oliver J Ott [1], Oliver Micke [2], Ralph Mücke [3], Marcus Niewald [4], Franz Rödel [5], Ulrich Schäfer [6], M H Seegenschmiedt [7], Meritxell Arenas [8], Benjamin Frey [9], Udo S Gaipl [9];
German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD)

Randomized Controlled Trial > Osteoarthritis Cartilage. 2018 Oct;26(10):1283-1290.
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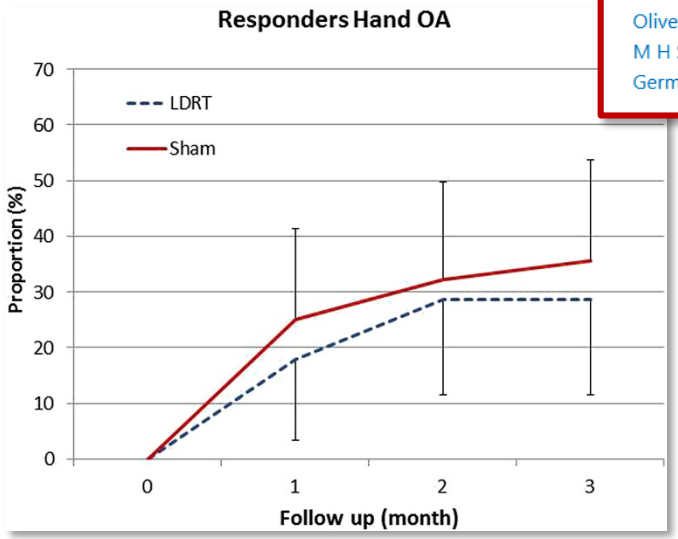

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- **Current study limitations:**
  - Applied dosage
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Need for biological data as proof of effectiveness!

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Classical Inflammatory Process

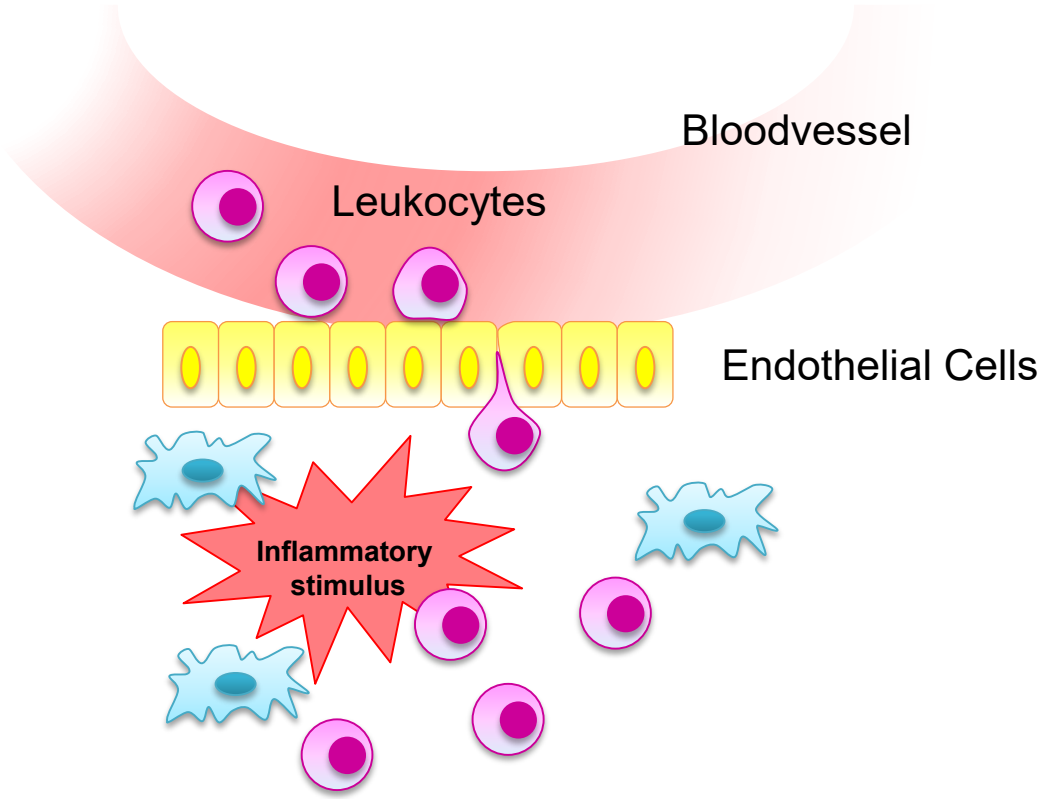
- Inflammatory stimulus

→ Enlargement and increased permeability of blood vessels

→ Alteration of adhesion properties of endothelial cells

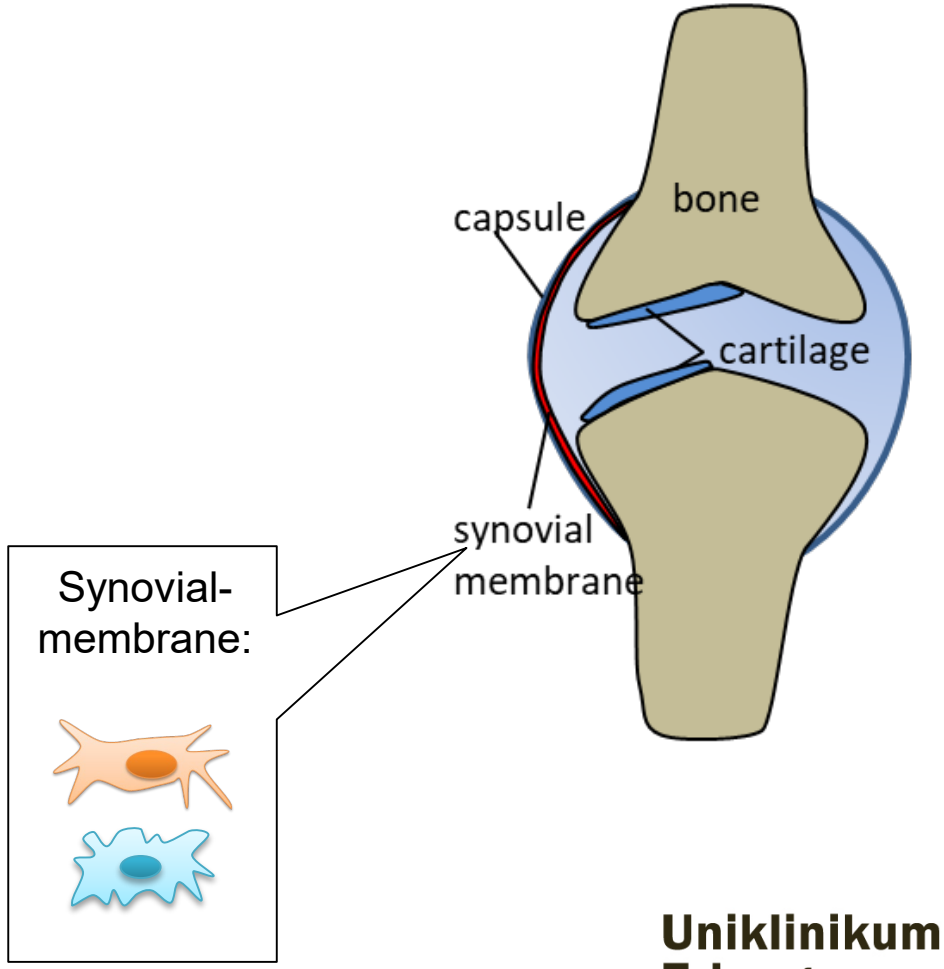
→ Attachment and tissue migration of leukocytes

→ Resolved inflammatory stimulus



Joint-specific Cell Types Involved in Inflammatory Processes

- Synovialfibroblasts and Macrophages→ **Initiiation** and **upkeep** of inflammation

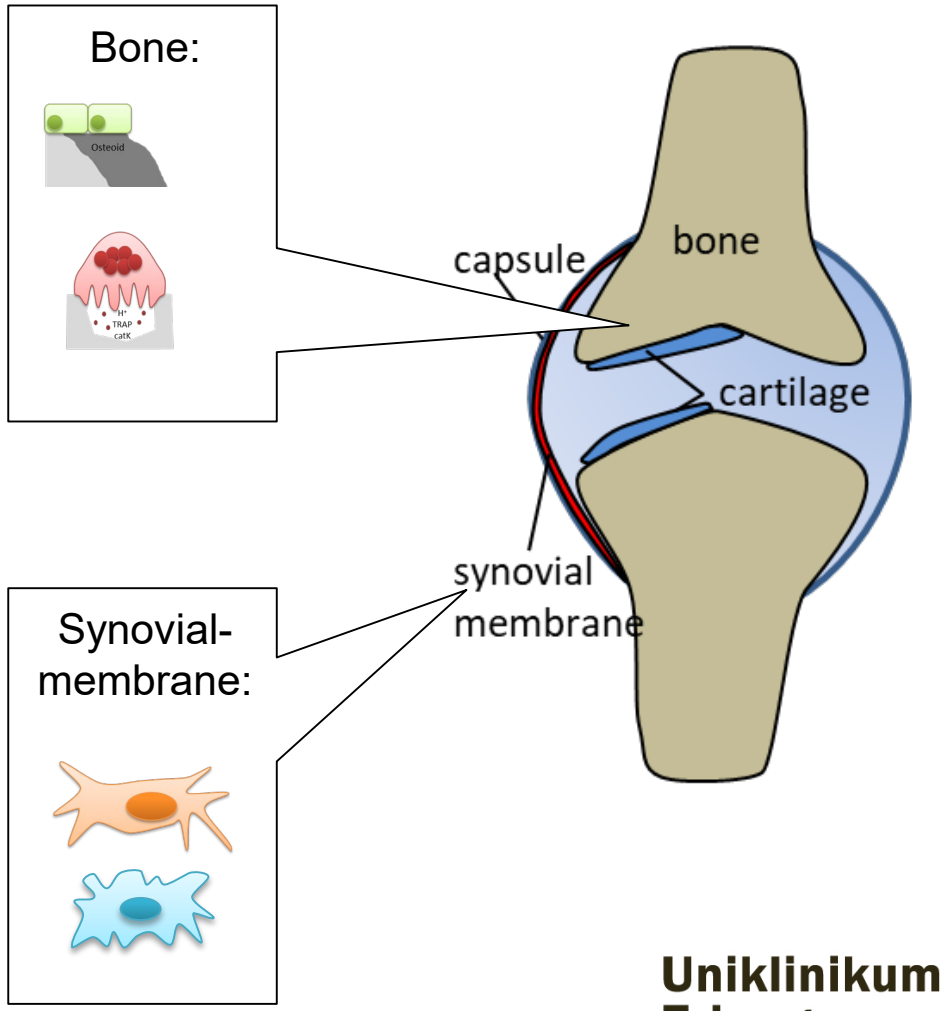


Joint-specific Cell Types Involved in Inflammatory Processes

- Synovialfibroblasts and Macrophages→ **Initiiation** and **upkeep** of inflammation

- **Disturbed bone metabolism** → more bone loss (Osteoclasts) than build up (Osteoblasts)

→ **Progressive destruction of joints**



LD-RT-mediated Cellular Effects – Dose Range 0.3 – 0.7 Gy

Endothelial Cells

Modulation of secreted cytokines (pro-inflammatory↓; anti-inflammatory↑)

Hampered attachment of leukocytes

Reduced levels of ROS

LD-RT-mediated Cellular Effects – Dose Range 0.3 – 0.7 Gy

Endothelial Cells	Leukocytes
	
Modulation of secreted cytokines (pro-inflammatory↓; anti-inflammatory↑) **Hampered attachment of leukocytes** **Reduced levels of ROS**	**Hampered attachment to endothelial cells** **Anti-inflammatory modulation of the cytokine milieu** **Increased rate of apoptosis**

LD-RT-mediated Cellular Effects – Dose Range 0.3 – 0.7 Gy

Endothelial Cells	Leukocytes	Macrophages
		
Modulation of secreted cytokines (pro-inflammatory↓; anti-inflammatory↑) **Hampered attachment of leukocytes** **Reduced levels of ROS**	**Hampered attachment to endothelial cells** **Anti-inflammatory modulation of the cytokine milieu** **Increased rate of apoptosis**	**Reduced migration and enhanced chemotaxis** **Reduction of inflammatory molecules and cytokines** **No effect on phagocytosis and survival** **No significant modulation of macrophage phenotypes** **Modulation of T cell mediated immune reactions**

LD-RT-mediated Cellular Effects – Dose Range 0.3 – 0.7 Gy

Endothelial Cells	Leukocytes	Macrophages	Fibroblast-like Synoviocytes
			
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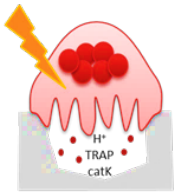
LD-RT-mediated Cellular Effects – Dose Range 0.3 – 0.7 Gy

Endothelial Cells	Leukocytes	Macrophages	Fibroblast-like Synoviocytes	Osteoclasts
				
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				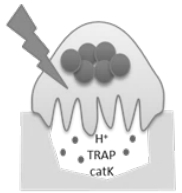	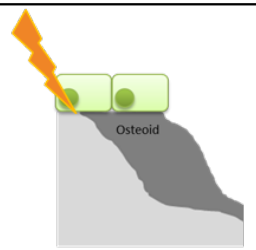
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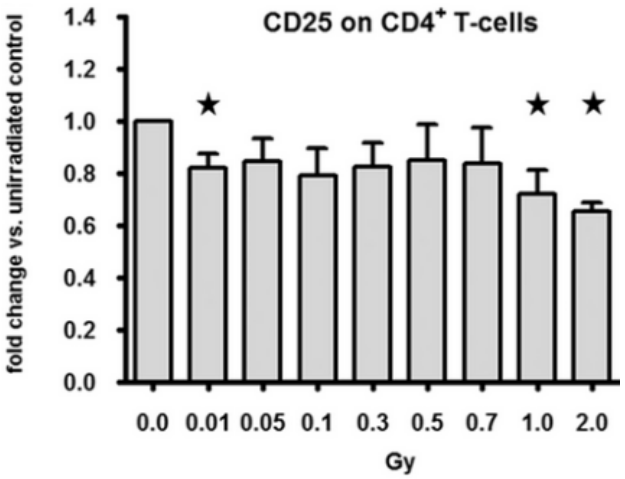
- Response to therapy often only judged on a clinical basis/imaging

- **Current study limitations:**
  - Applied dosage
  - Patient selection
  - Number of series

Can‘t we just use a lower dose as control instead of a placebo group?

Why can’t we just use a lower dose as the control?



CD25 = Marker on activated CD4+ T cells

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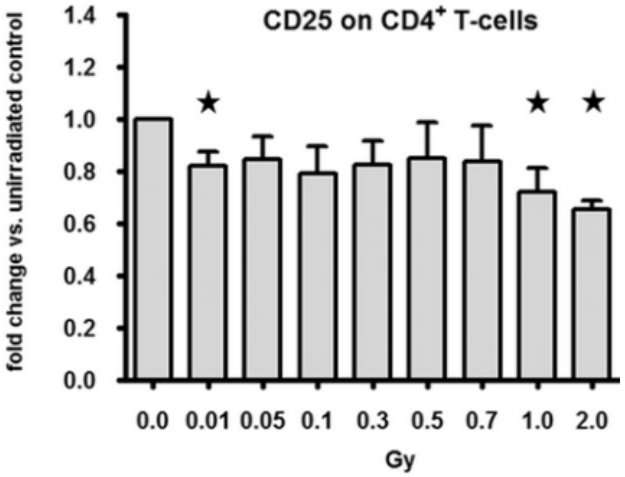

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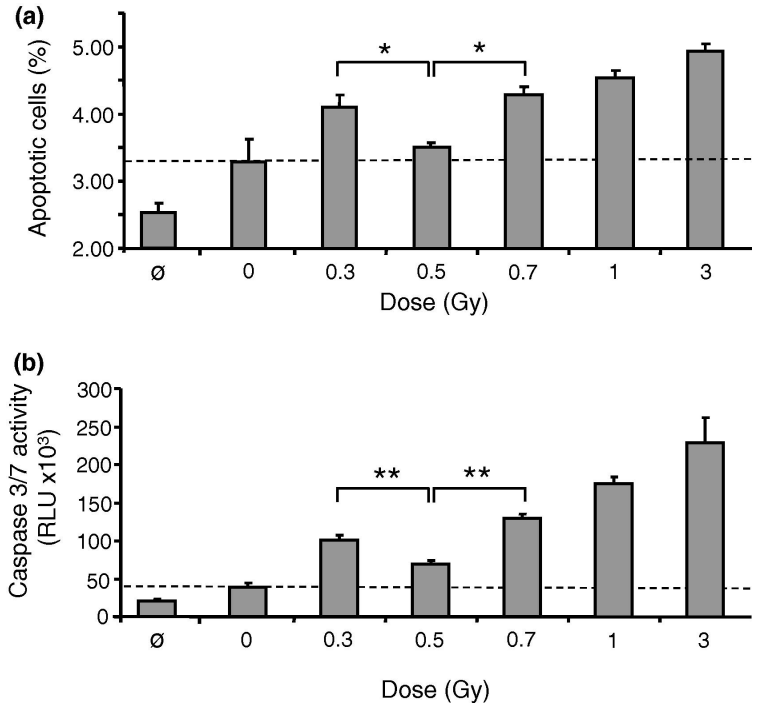

Cell death of endothelial cells after LD-RT

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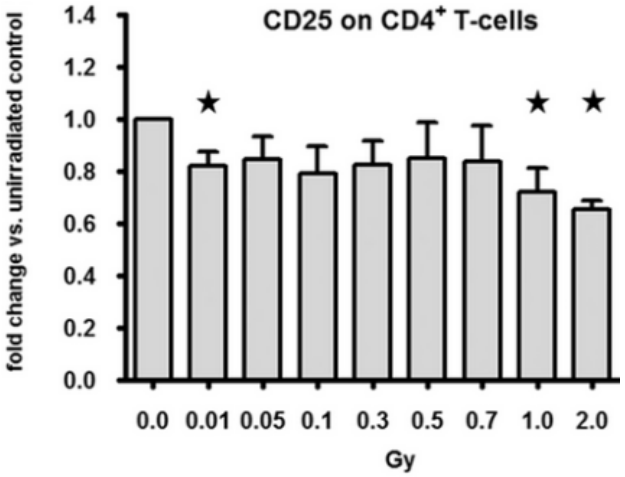

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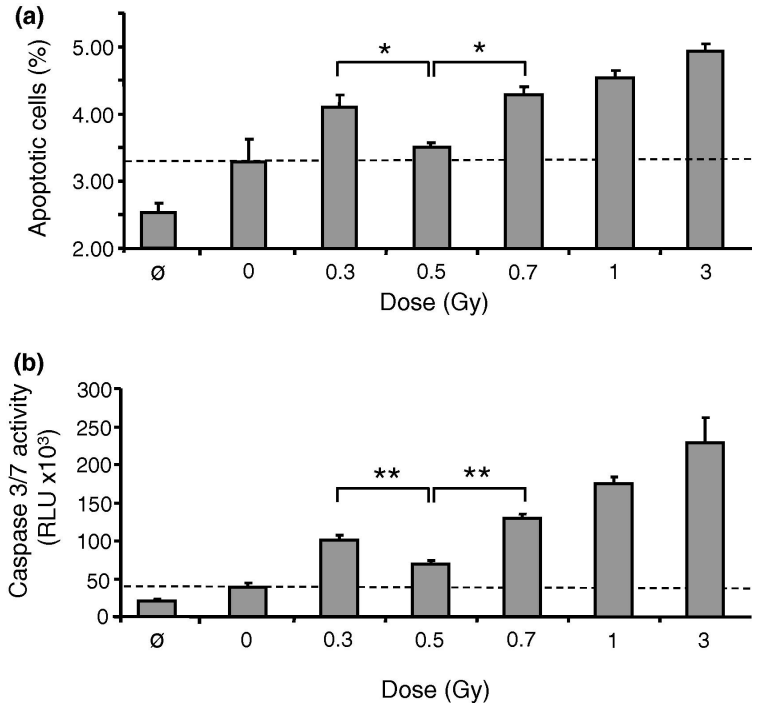

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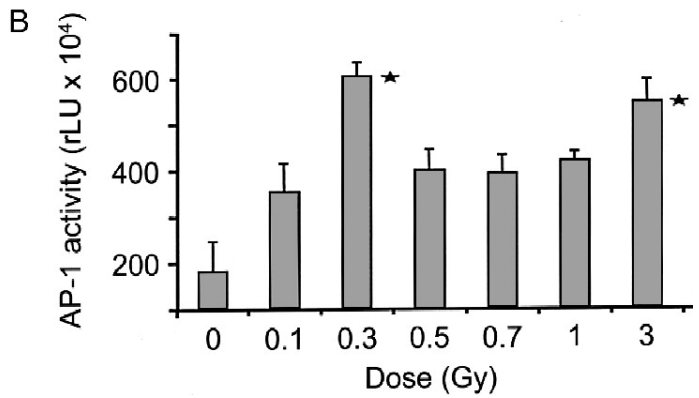

Activity of AP-1 as transcriptionfactor of Immun-effector molecules

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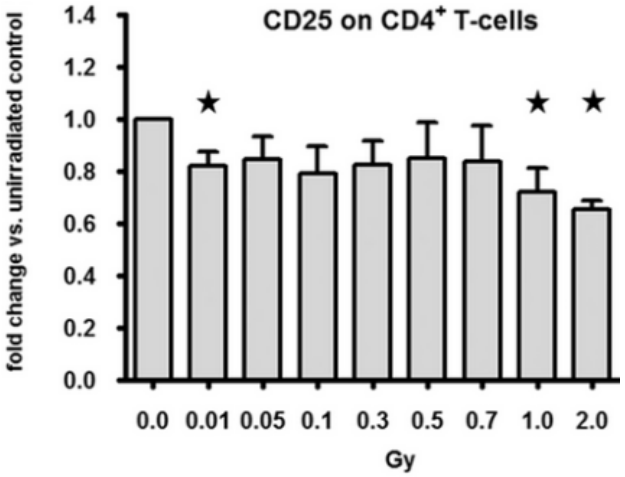

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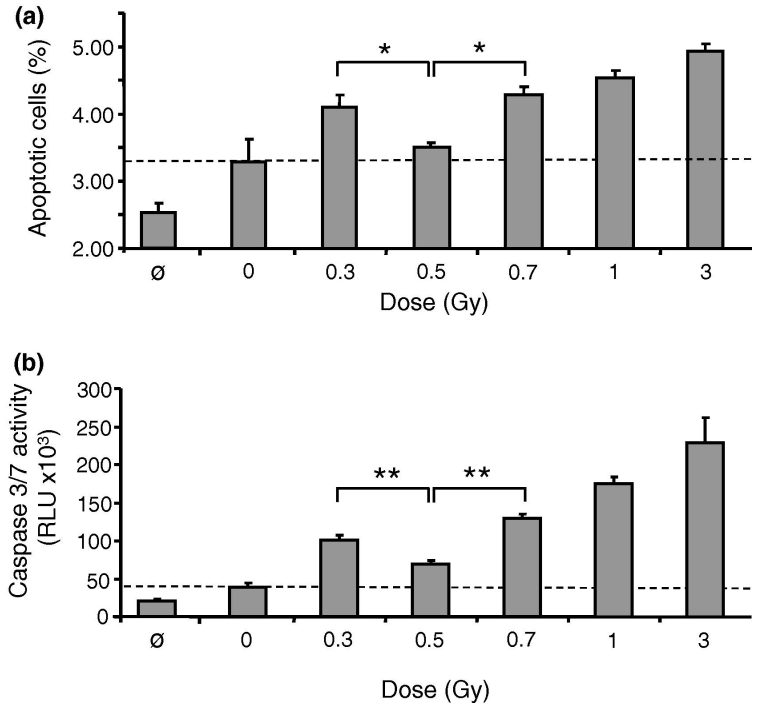

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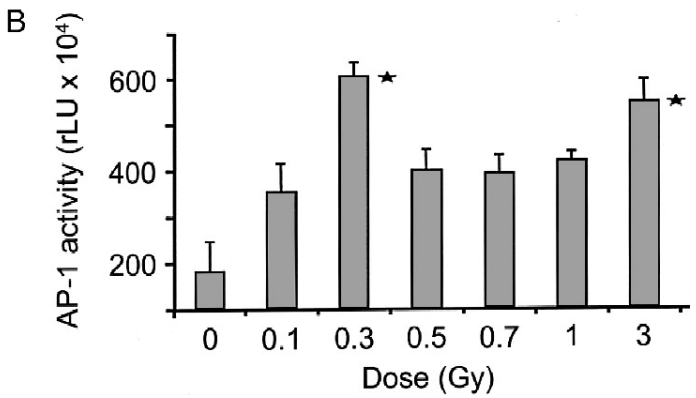

Activity of AP-1 as transcriptionfactor of Immun-effector molecules

→ NO linear dose-effect connection for cells (of the immune system)!

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Uniklinikum Erlangen

What dose should we be using? → Clinical Answer

Randomized Controlled Trial › Strahlenther Onkol. 2014 Jul;190(7):671-5.
doi: 10.1007/s00066-014-0618-0. Epub 2014 Mar 26.

Radiotherapy for benign calcaneodynia: long-term results of the Erlangen Dose Optimization (EDO) trial

Oliver J Ott [1], Carolin Jeremias, Udo S Gaipl, Benjamin Frey, Manfred Schmidt, Rainer Fietkau

Randomized Controlled Trial › Strahlenther Onkol. 2014 Mar;190(3):293-7.
doi: 10.1007/s00066-013-0504-1. Epub 2014 Jan 16.

The Erlangen Dose Optimization trial for low-dose radiotherapy of benign painful elbow syndrome. Long-term results

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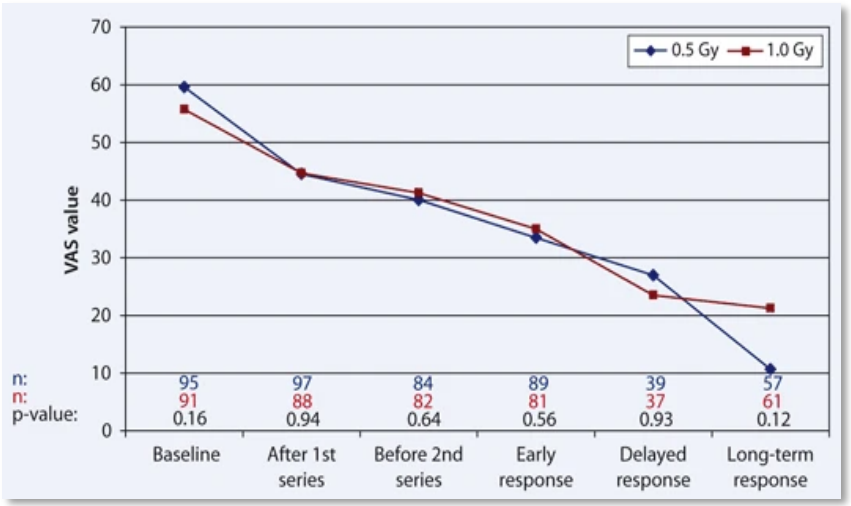
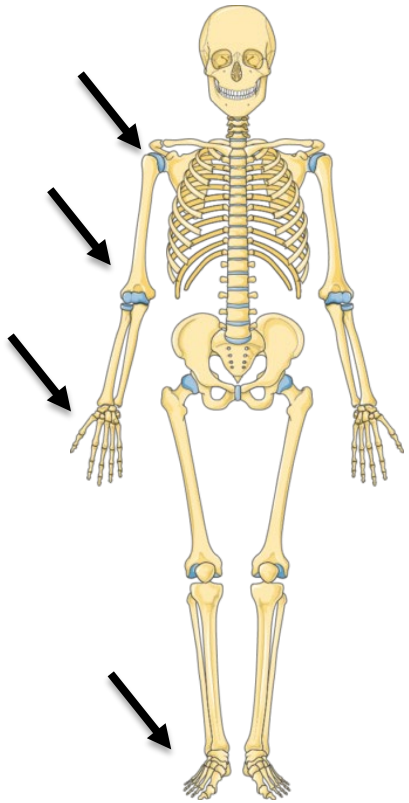


Randomized Controlled Trial › Strahlenther Onkol. 2012 Dec;188(12):1108-13.
doi: 10.1007/s00066-012-0237-6. Epub 2012 Nov 7.

Benign painful shoulder syndrome: initial results of a single-center prospective randomized radiotherapy dose-optimization trial

Radiotherapy 3 vs 6 Gy in Gonarthrosis and Coxarthrosis (RAGOCO)



Servier, Medical Art

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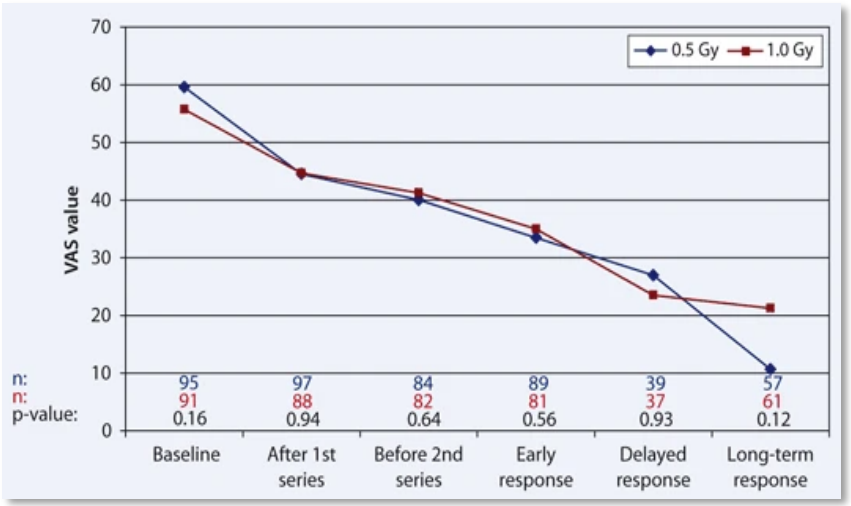
Randomized Controlled Trial › Strahlenther Onkol. 2014 Mar;190(3):293-7.
doi: 10.1007/s00066-013-0504-1. Epub 2014 Jan 16.

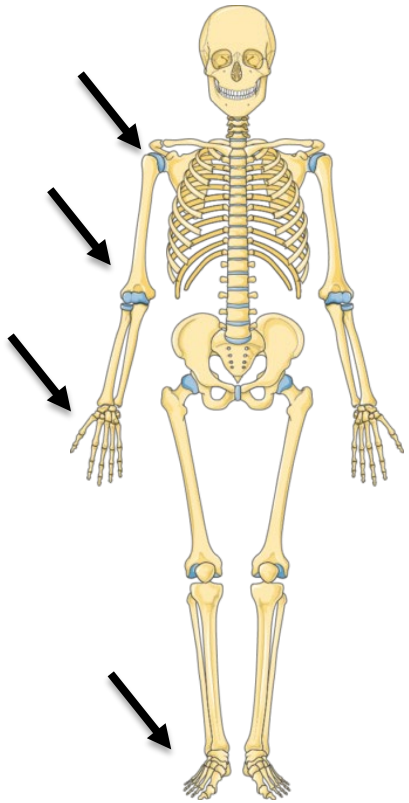
The Erlangen Dose Optimization trial for low-dose radiotherapy of benign painful elbow syndrome. Long-term results

O J Ott [1], S Hertel, U S Gaipl, B Frey, M Schmidt, R Fietkau



Randomized Controlled Trial › Strahlenther Onkol. 2012 Dec;188(12):1108-13.
doi: 10.1007/s00066-012-0237-6. Epub 2012 Nov 7.

Benign painful shoulder syndrome: initial results of a single-center prospective randomized radiotherapy dose-optimization trial

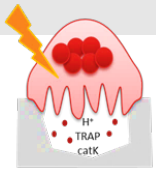


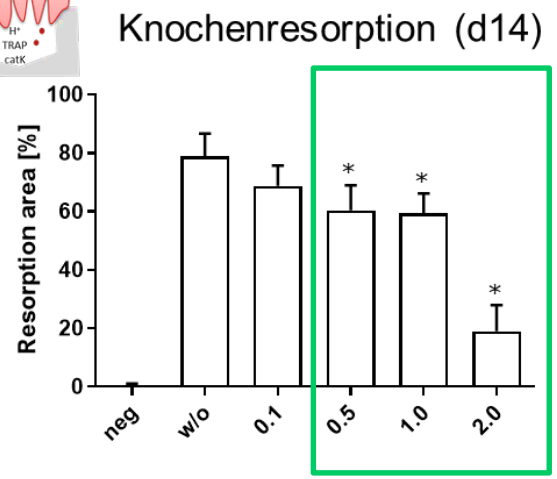
Servier, Medical Art

Radiotherapy 3 vs 6 Gy in Gonarthrosis and Coxarthrosis (RAGOCO)

→ No superiority in 1.0 vs. 0.5 Gy (single dose) → 0.5 Gy!

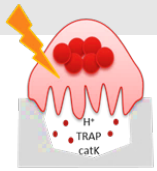
Ideal dose for patient treatment? → Biological Answer

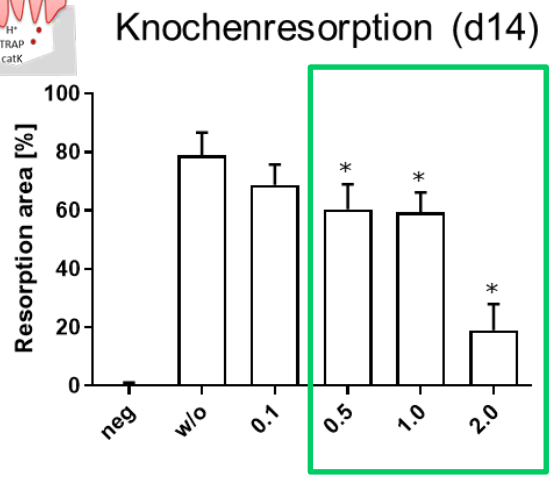




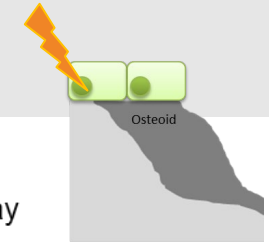
Bone resorption ↓

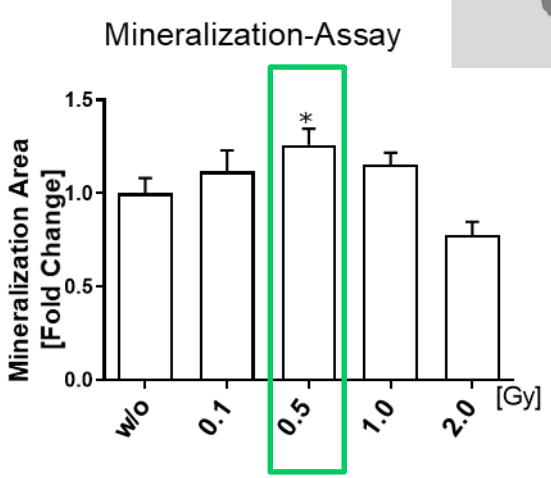
Ideal dose for patient treatment? → Biological Answer

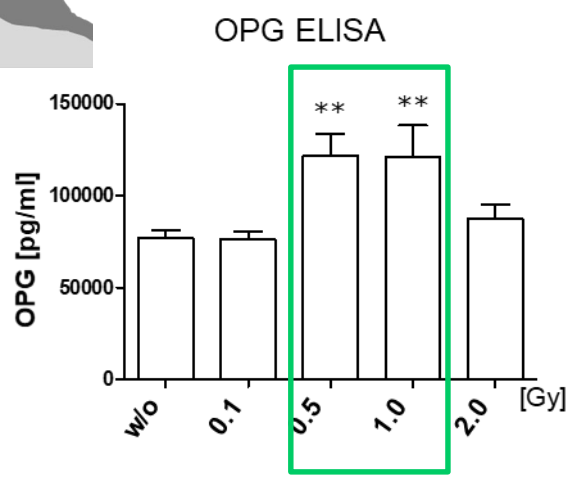




Bone resorption ↓

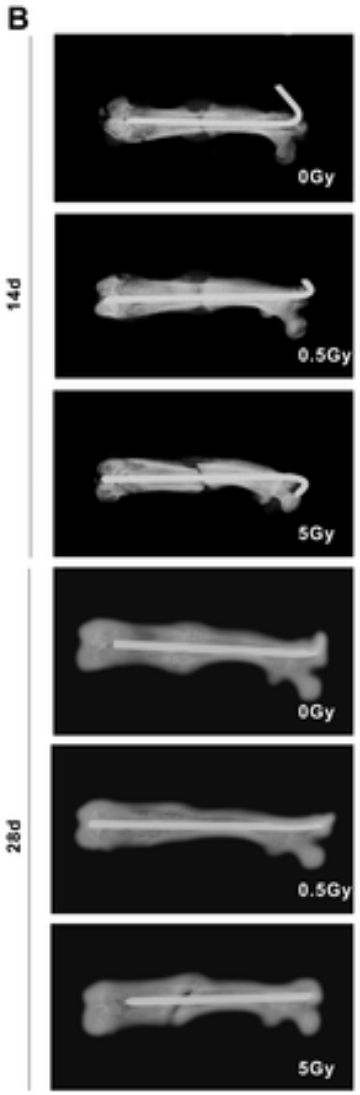


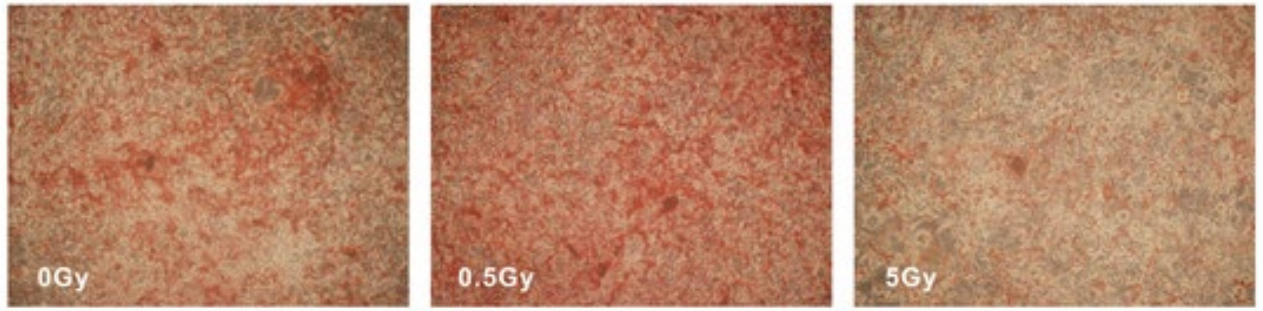




Bone build up ↑

Ideal dose for patient treatment? → Biological Answer



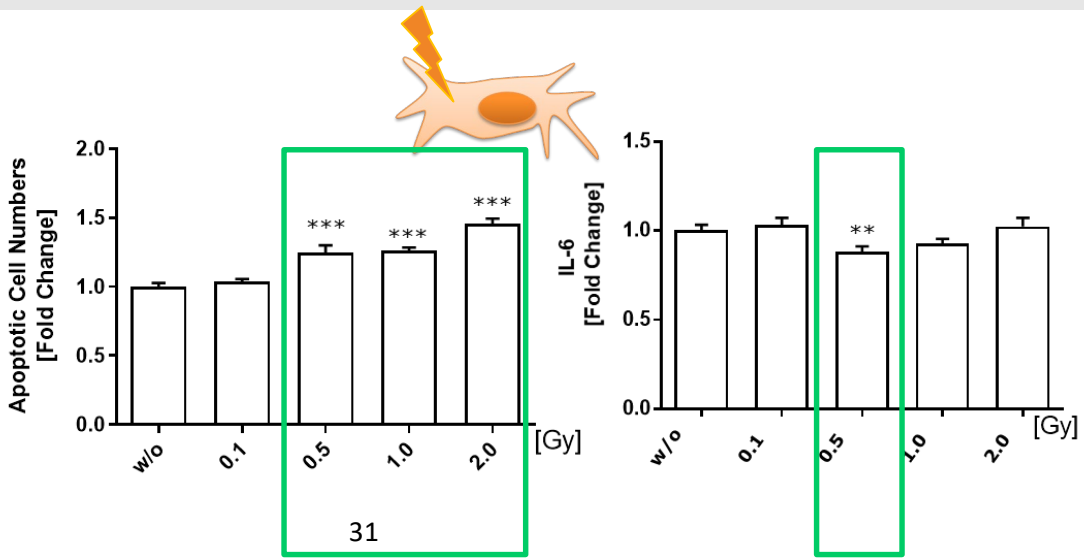


0.5 Gy increased proliferation and viability in osteoblasts

0.5 Gy: Increased fracture healing

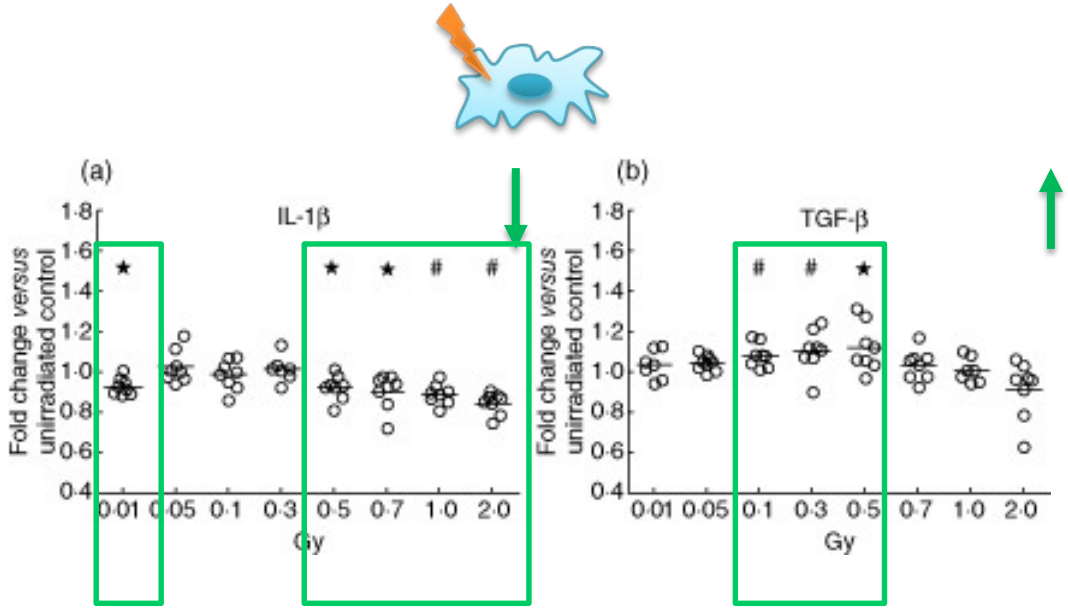
Uniklinikum Erlangen

Ideal dose for patient treatment? → Biological Answer



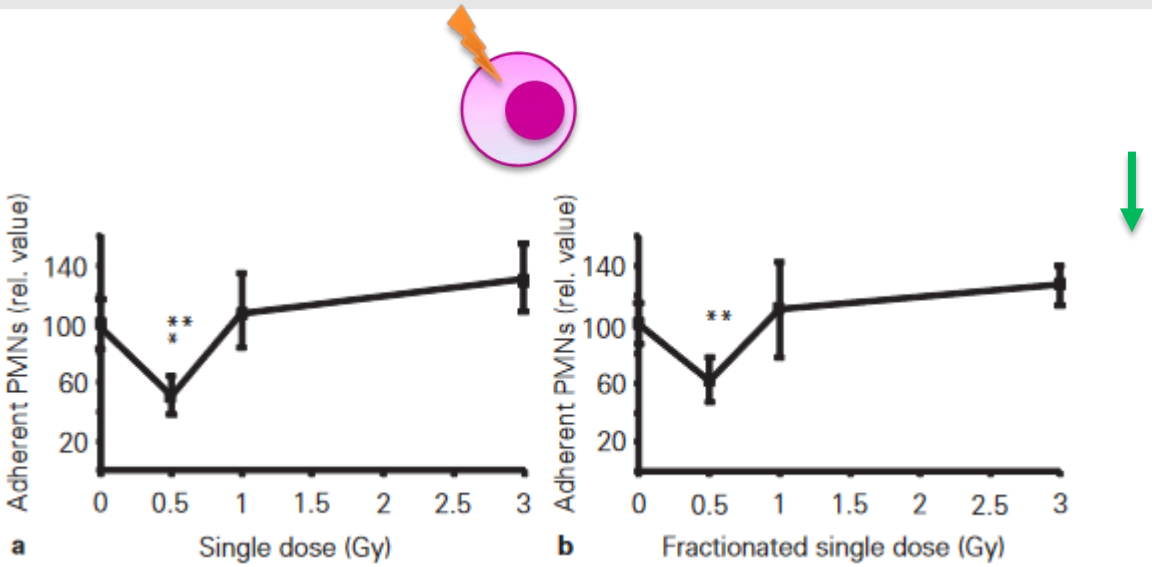
Cell numbers
Inflammatory cytokines ↓

Ideal dose for patient treatment? → Biological Answer



0.1 and 0.5 Gy increased chemotaxis
Reduced IL1β levels, increased TGF-β levels

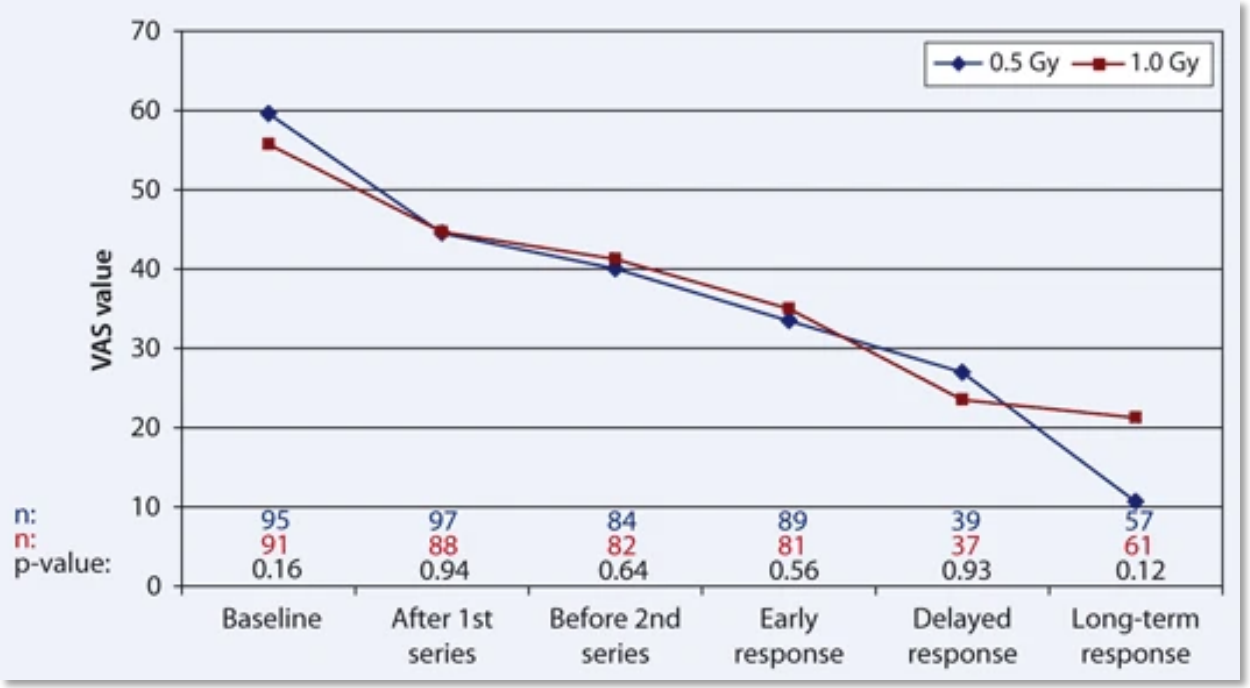
Ideal dose for patient treatment? → Biological Answer



0.5 Gy reduced leukocyte adhesion

Ideal Dose within the Joint?

Clinical Data Biological Data



In line with patient data:
No benefit for higher doses
→ 0.5 Gy biological most effective dose

LD-RT Predicament- Lack of Prospective, Sham-controlled Studies

Randomized Controlled Trial > Ann Rheum Dis. 2019 Jan;78(1):83-90.
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Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial

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M J M Minten [1], M M Leseman-Hoogenboom [2], M Kloppenburg [3], M C Kortekaas [4], J W Leer [5], P M P Poortmans [6], F H J van den Hoogen [7], A A den Broeder [8], C H M van den Ende [9]

- Response to therapy often only judged on a clinical basis/imaging

- **Current study limitations:**
  - Applied dosage
  - **Patient selection**
  - Number of series

Need for biological data as proof of effectiveness!

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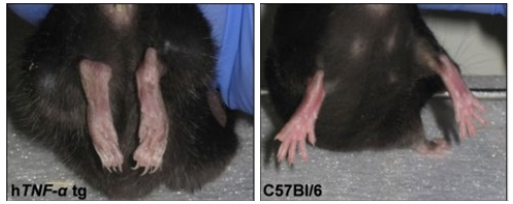
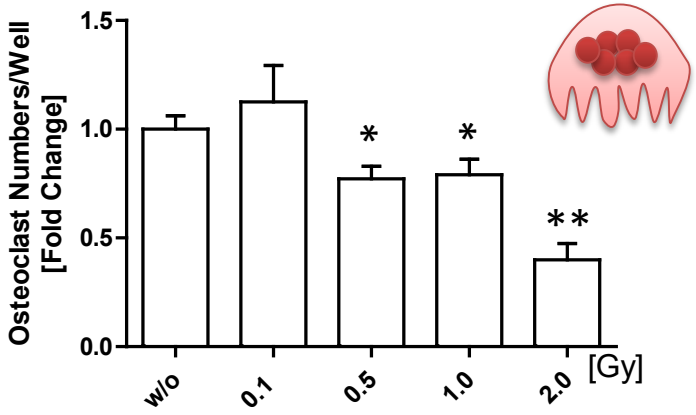
Patient Selection? – Inflammatory Status

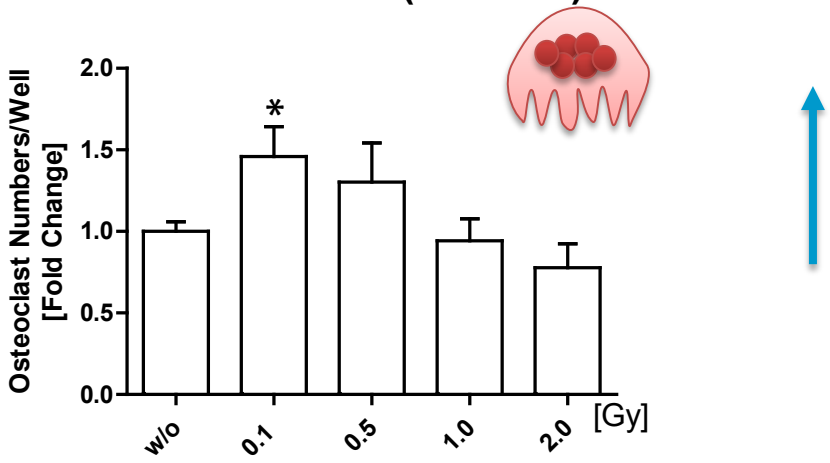


hTNFα tg – Rheumatoide Arthritis
C57Bl/6 – gesunde Maus

Entzündet (h*TNFα* tg)



Gesund (C57Bl/6)

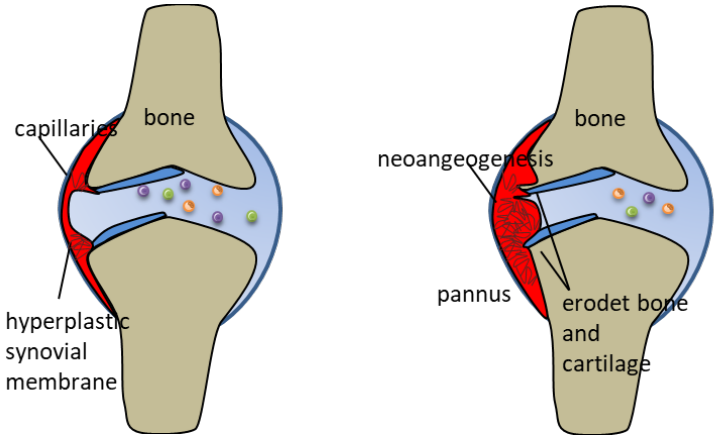


→ The inflammatory background has an influence on cellular responses after LD-RT

Image adapted from: Choy EH, Panayi GS. 2001 N Engl J Med 344: 907-16

Considerations for LD-RT – Patient Selection

Rheumatoid Arthritis



- Complex, chronic **inflammatory** autoimmune disease with mostly unknown etiology
- **Higher risk in women** than in men
- Immune cell infiltration in the synovial layer, Progressive joint and bone destruction; **Systemic inflammation**

Uniklinikum Erlangen

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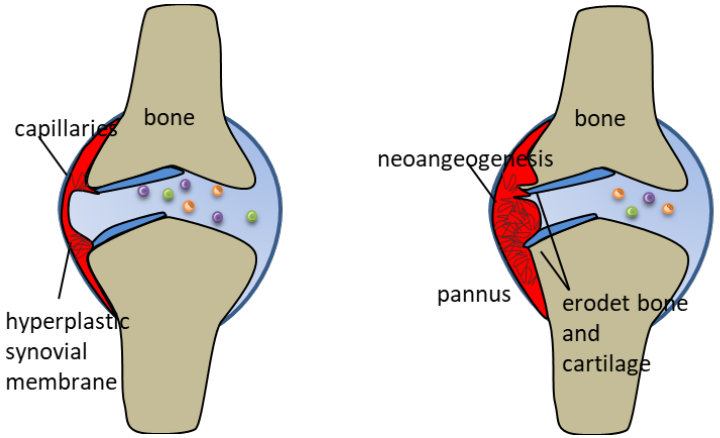
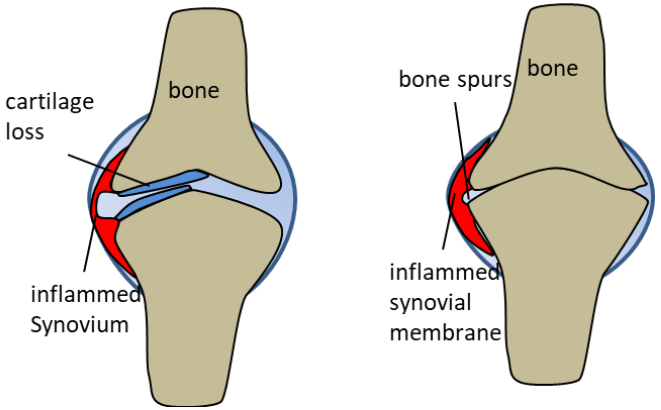
Considerations for LD-RT – Patient Selection

Rheumatoid Arthritis



Arthroses



- **Mechanical** and **inflammatory** components
- **Higher risk in women** than in men
- Synovial inflammation; Joint and bone destruction; **Possible association with systemic inflammation in some patients**

Uniklinikum Erlangen

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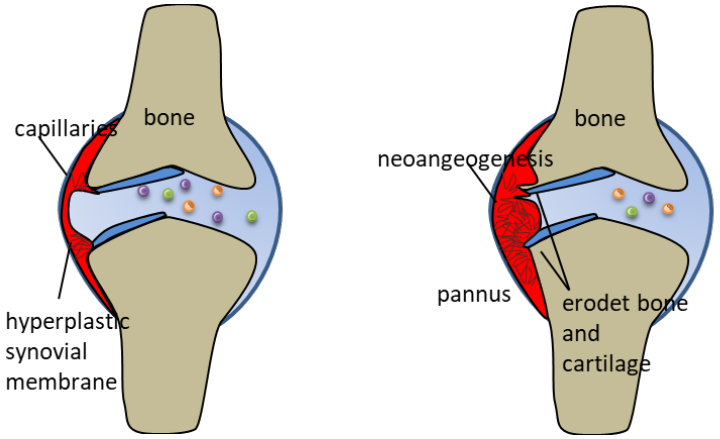
Considerations for LD-RT – Patient Selection

Rheumatoid Arthritis



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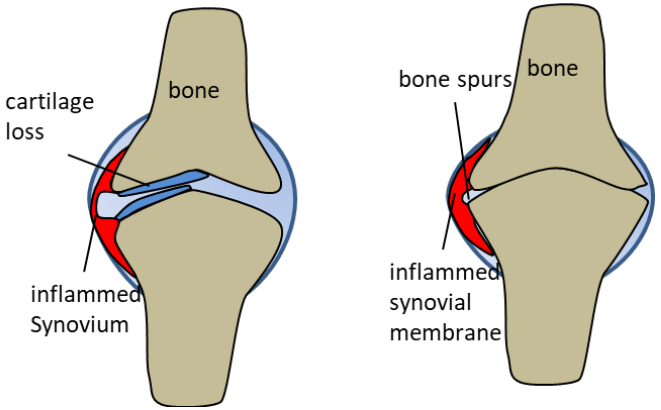
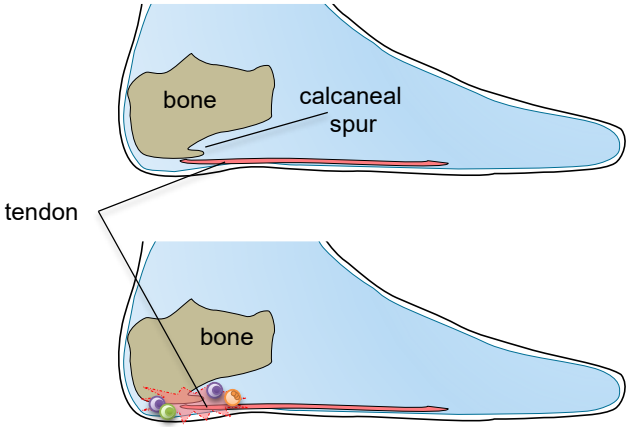


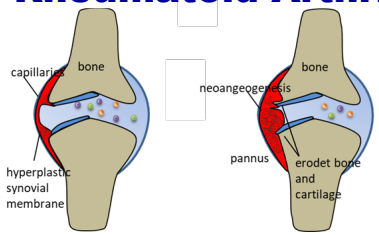
Heel Spur

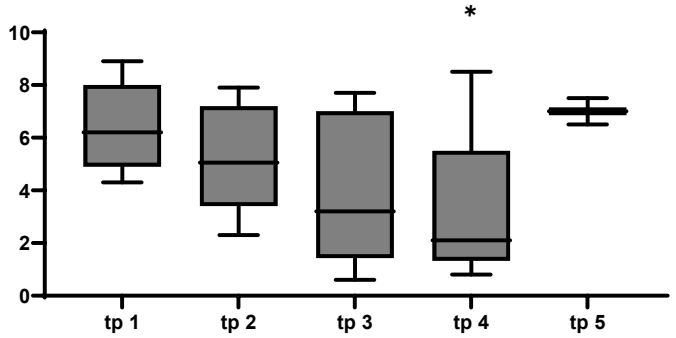


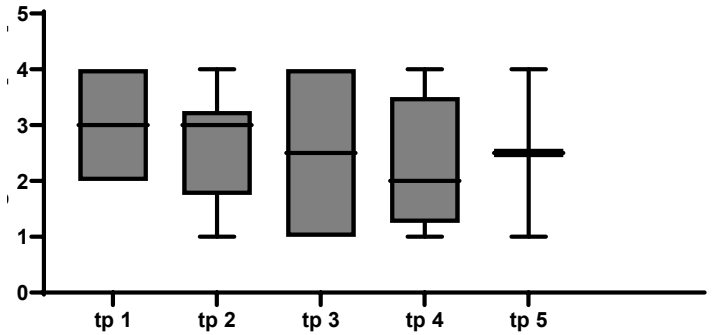
- **Discrepancy about gender aspect** (younger cohorts female > males)
- **Discrepancy inflammation** → MRI 8% inflammatory changes

Considerations for LD-RT – Patient Selection

Rheumatoid Arthritis







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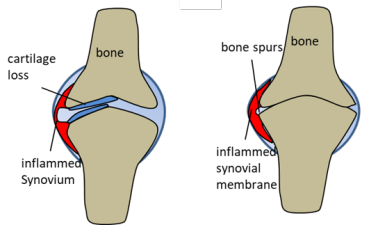

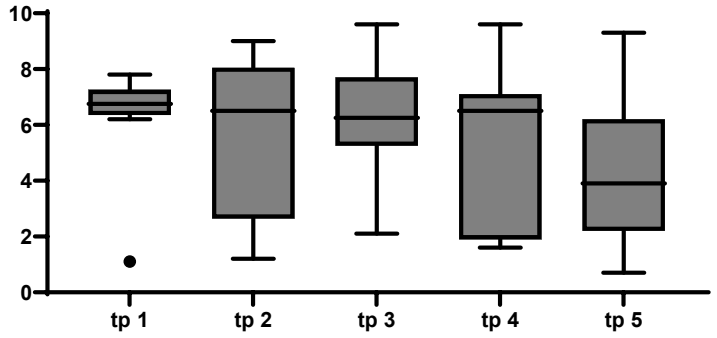

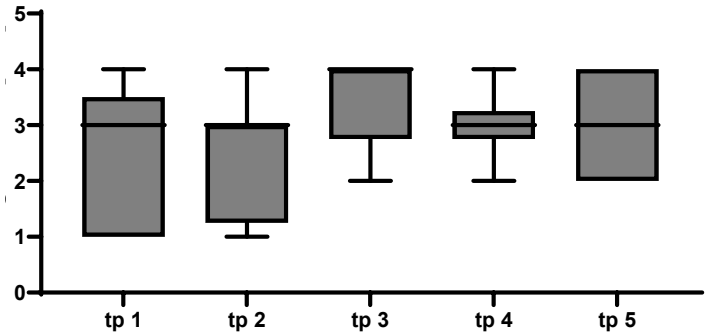

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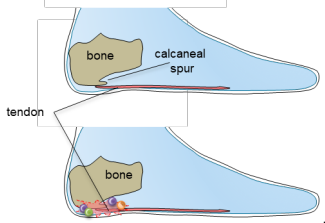
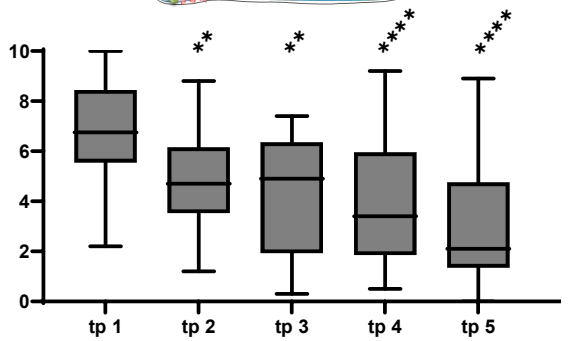
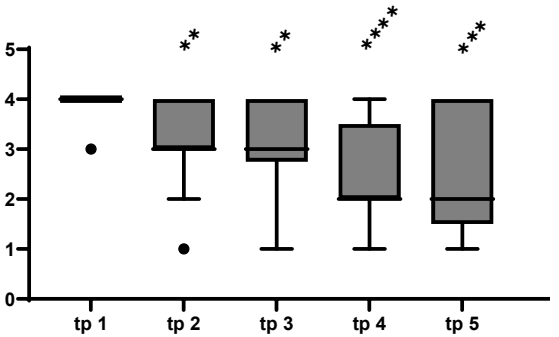
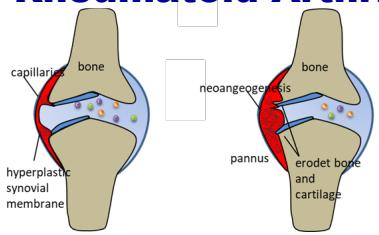




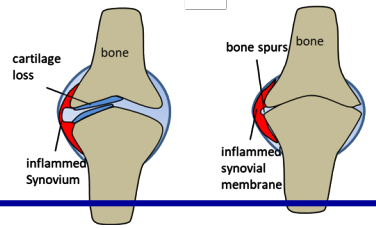


Considerations for LD-RT – Patient Selection

Rheumatoid Arthritis



Arthroses



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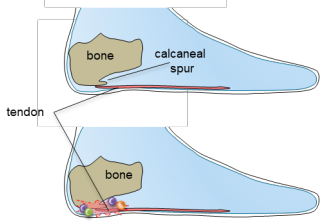
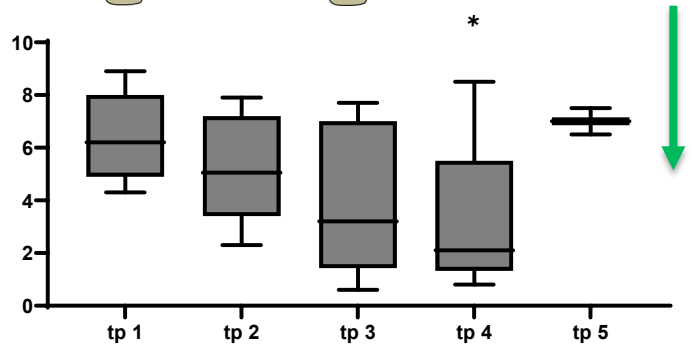
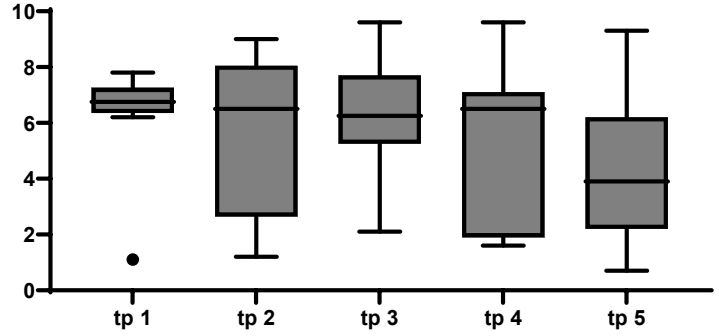
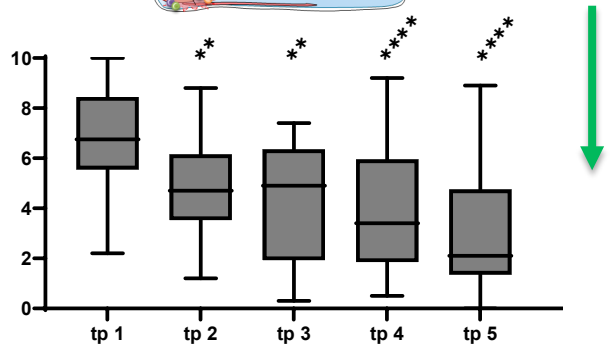


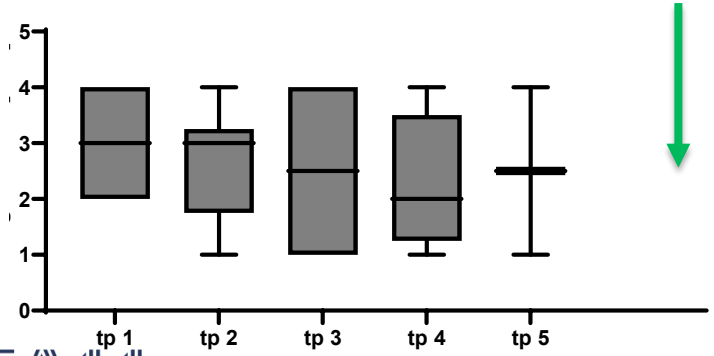
General pain level [VAS]

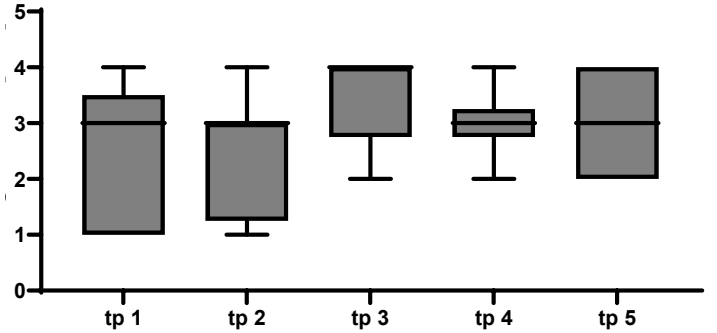


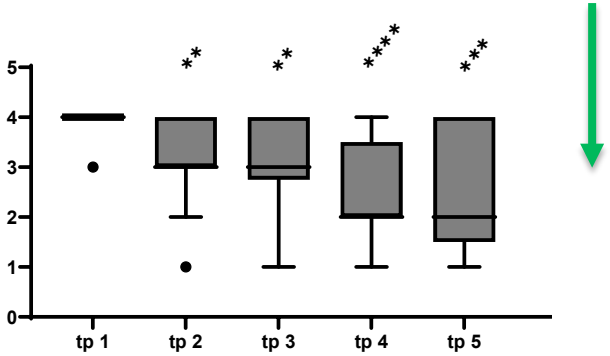




Morning stiffness [VAS]



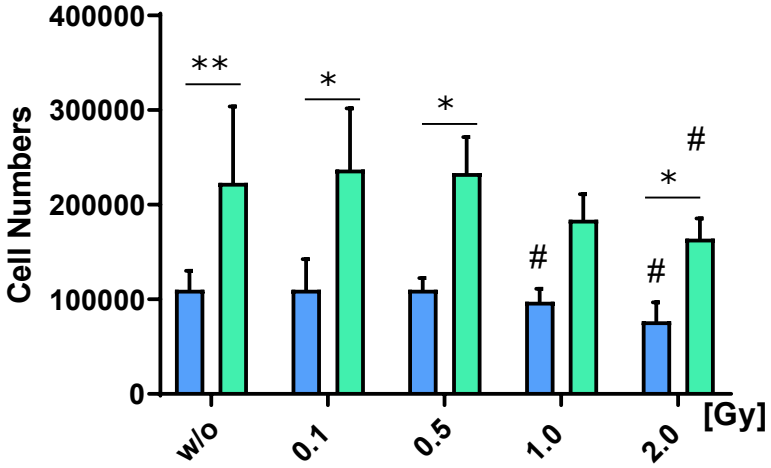


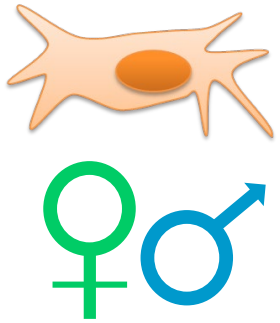


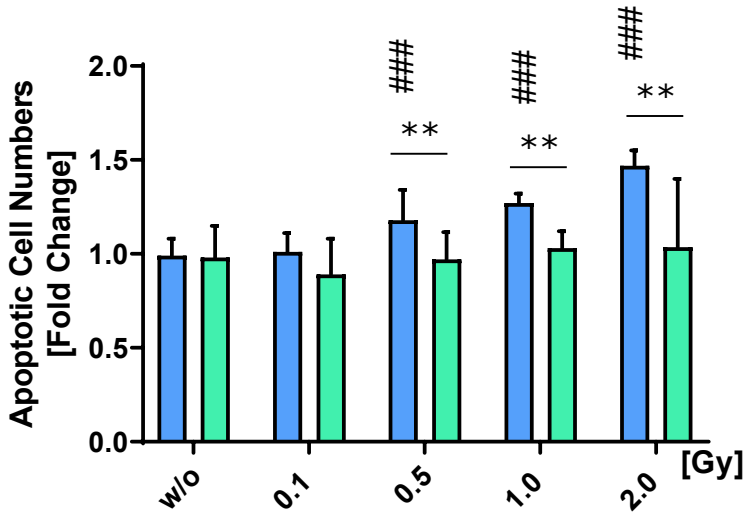
Outcome differs on type of disease!

Friedrich-Alexander-Universität
Medizinische Fakultät

Patient Selection? – Gender

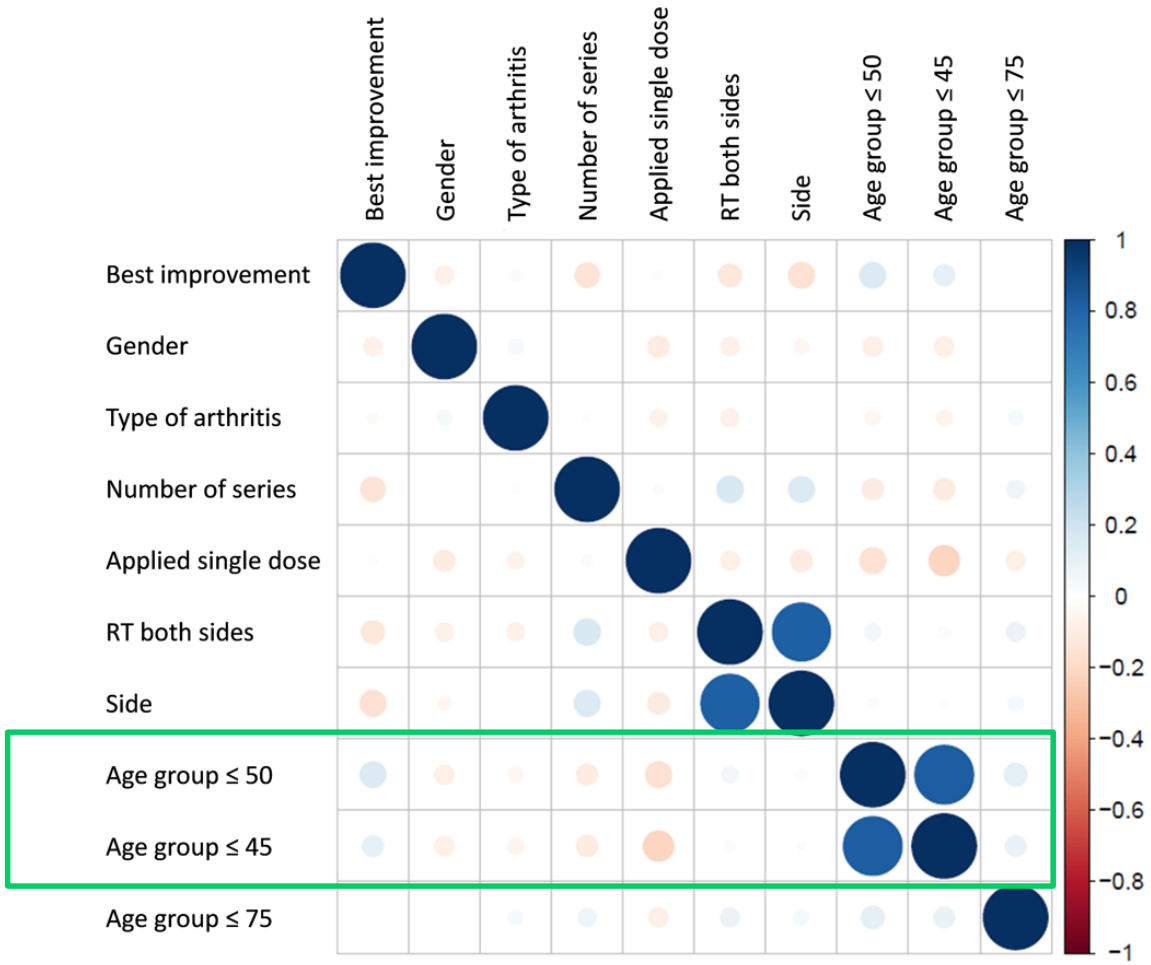






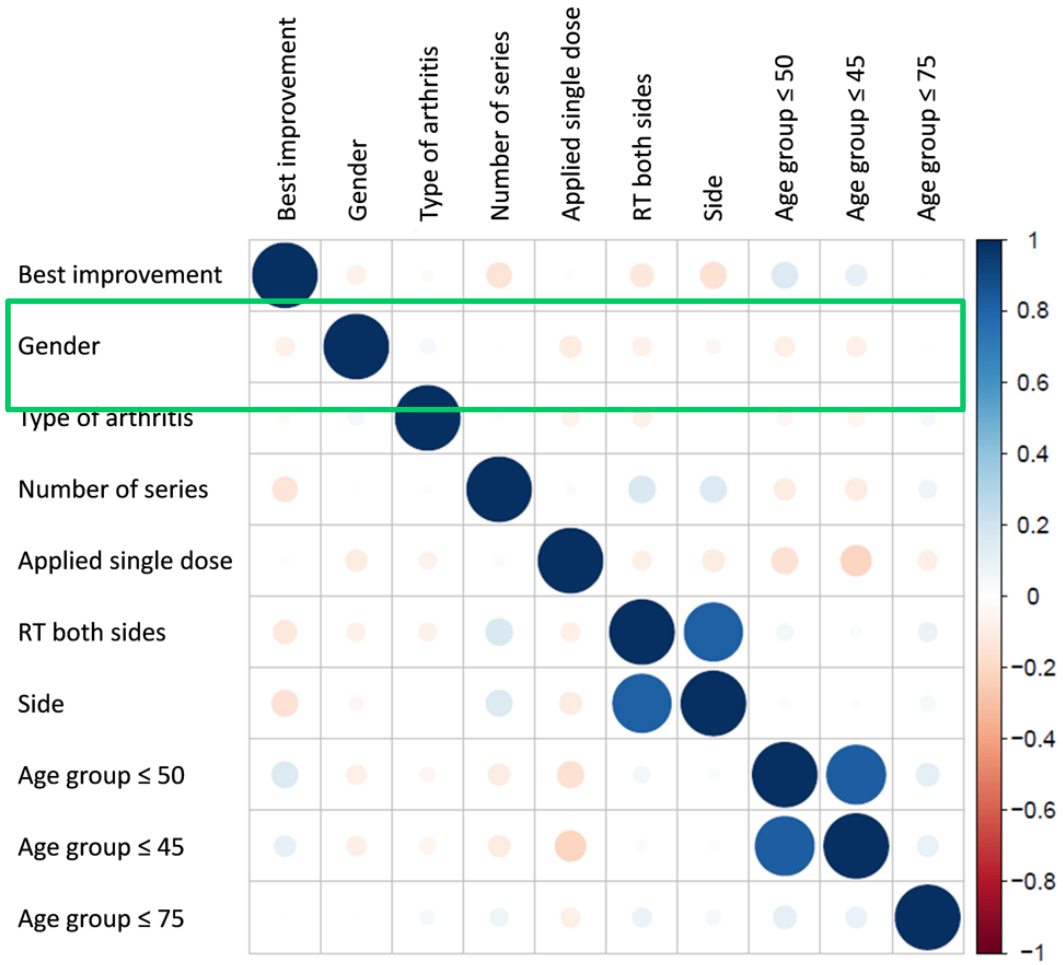
→ **LD-RT results in sex specific differences**

Considerations for LD-RT – Patient Selection



OA patients < 50 years: significant better outcome

Considerations for LD-RT – Patient Selection



OA patients < 50 years: significant better outcome

No significant influence on gender

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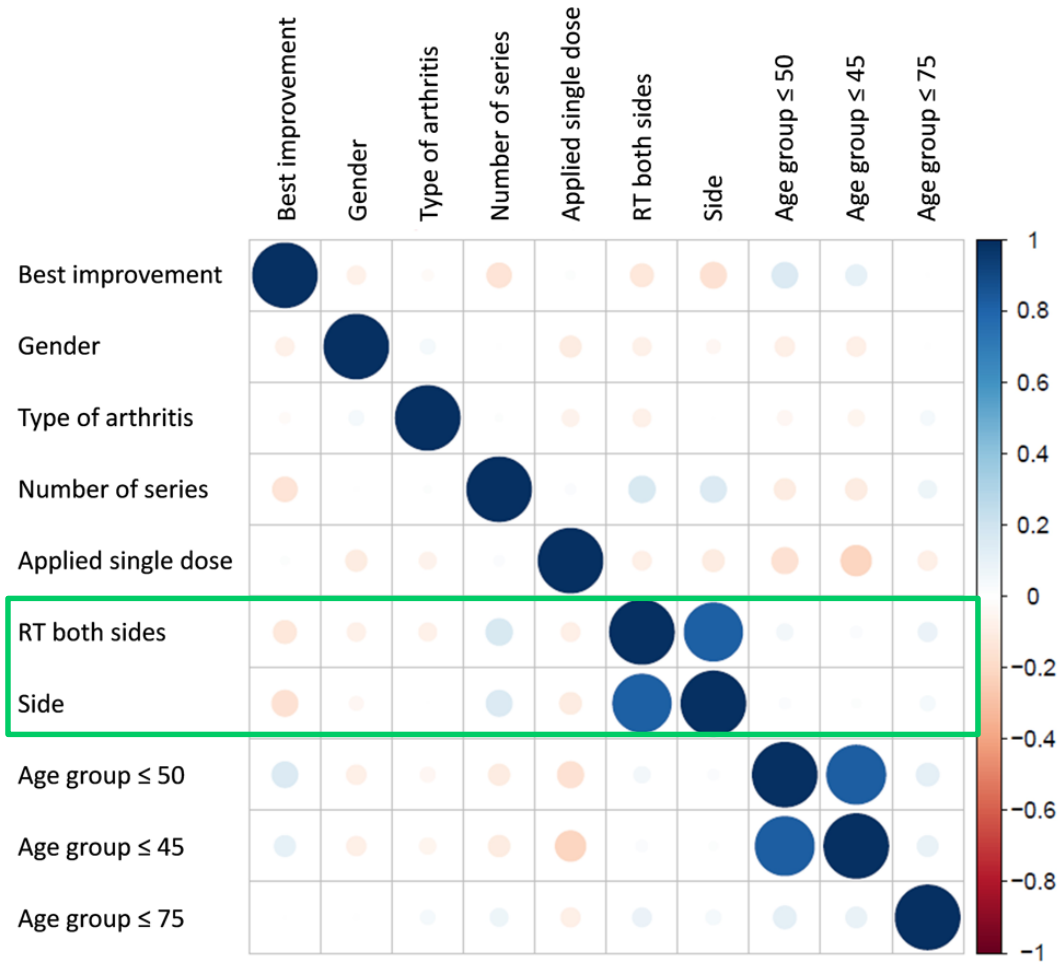

OA patients < 50 years: significant better outcome

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BUT: Significant impact of localization

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  - **Number of series**

Need for biological data as proof of effectiveness!

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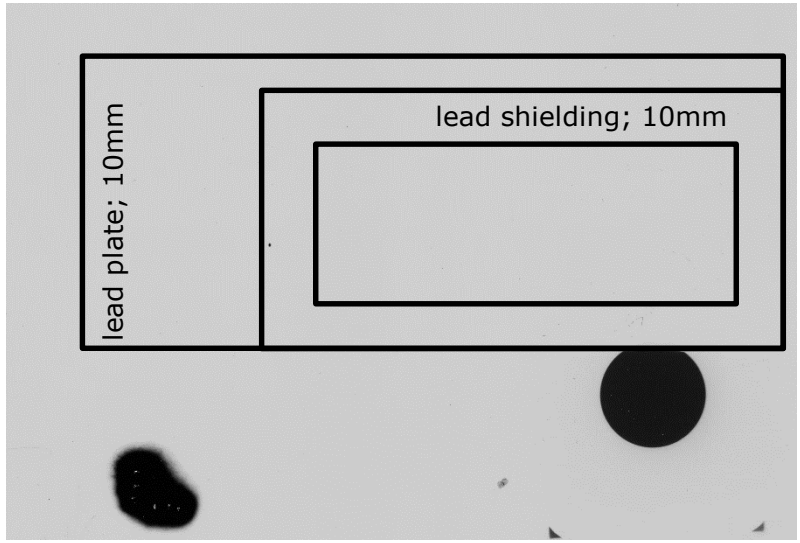
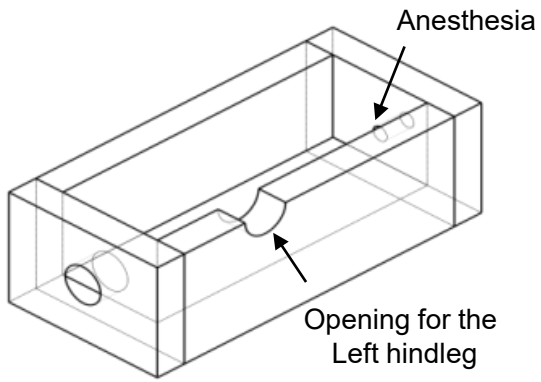
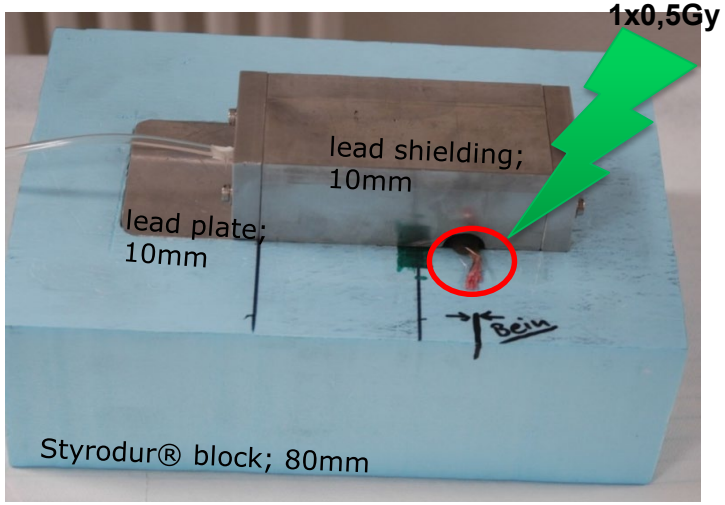
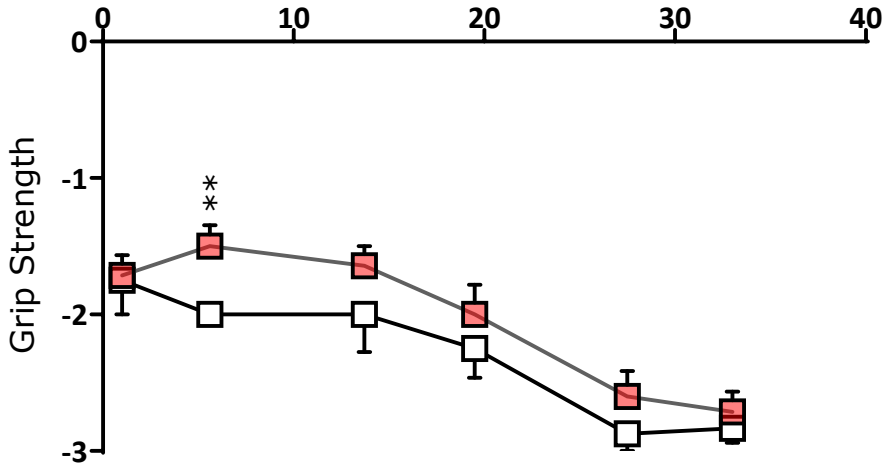
In vivo irradiation set-up

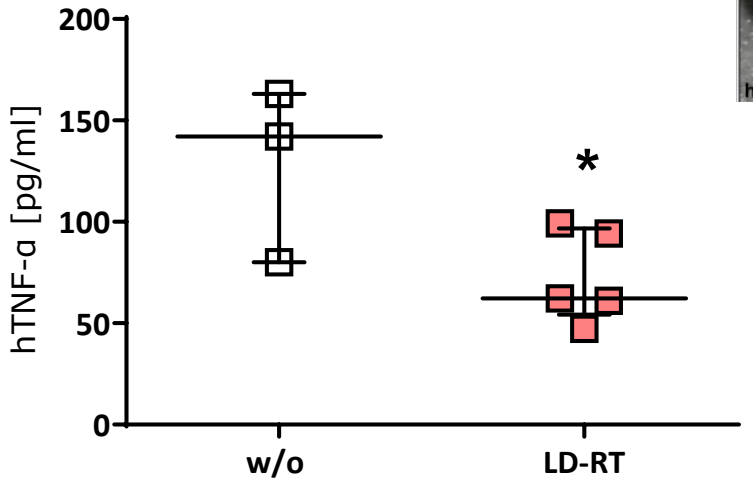






Local LD-RT with 1x0.5Gy enhances grip strength and reduces hTNFα levels in the serum of hTNFα tg animals





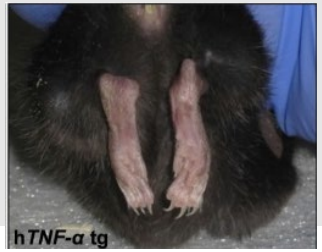
→ Significantly **enhanced grip strength** right after the treatment

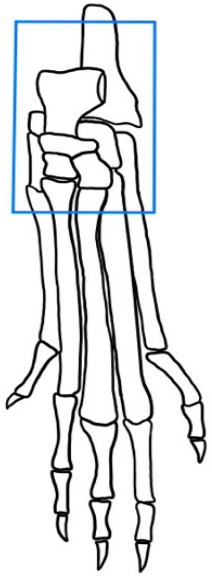
→ **Reduced hTNFα levels** in the serum of irradiated animals (d33)

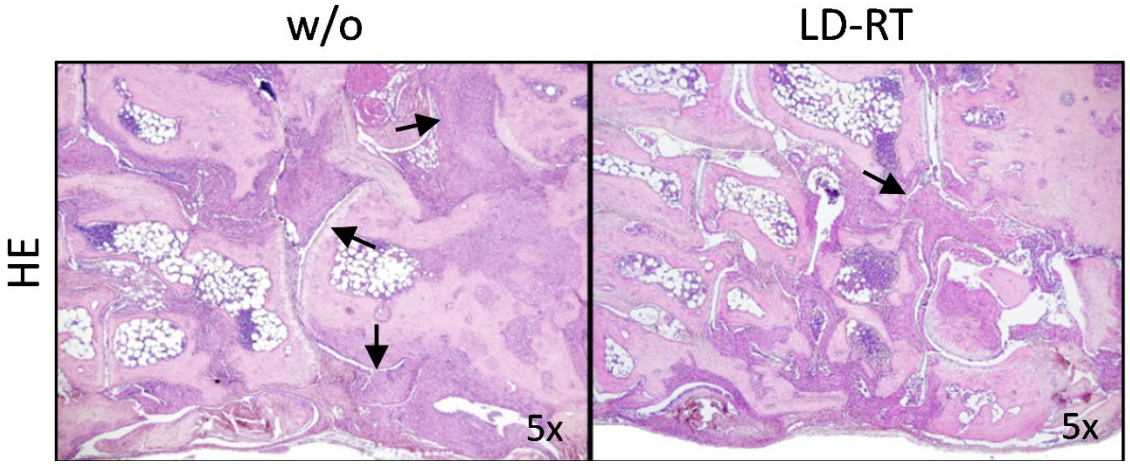
Shown are 3 independent experiments with in sum (w/o)=6 and n(local)=5 h*TNF-α* tg Mäusen. Data is presented as Mean ±SEM for grip strength and Median + IQR; Statistic was calculated using Whitney-U test in comparison to untreated controls (w/o) *p<0.05).

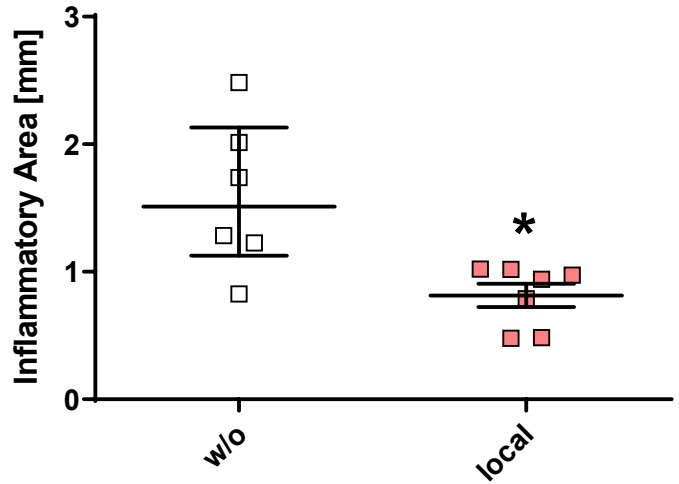
Deloch et al., *Frontiers Immunology*, 2018; Histological slices in Cooperation with Barbara Happich, Medical Clinic 3; Paw: modified after http://www.informatics.jax.org/cookbook/figures/figure43.shtml 26.11.2020;

Local LD-RT with 1x0.5Gy reduces systemic inflammation in h*TNFα* tg mice









→ Significantly **reduced inflammatory areas** after 1x 0.5Gy (d33) → Systemic reaction!!

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Shown are 3 independent experiments with in sum (w/o)=6 and n(local)=5 h*TNF-α* tg mice. Data is presented as Mean ±SEM for grip strength and Median + IQR; Statistic was calculated using Whitney-U test in comparison to untreated controls (w/o) *p<0.05).

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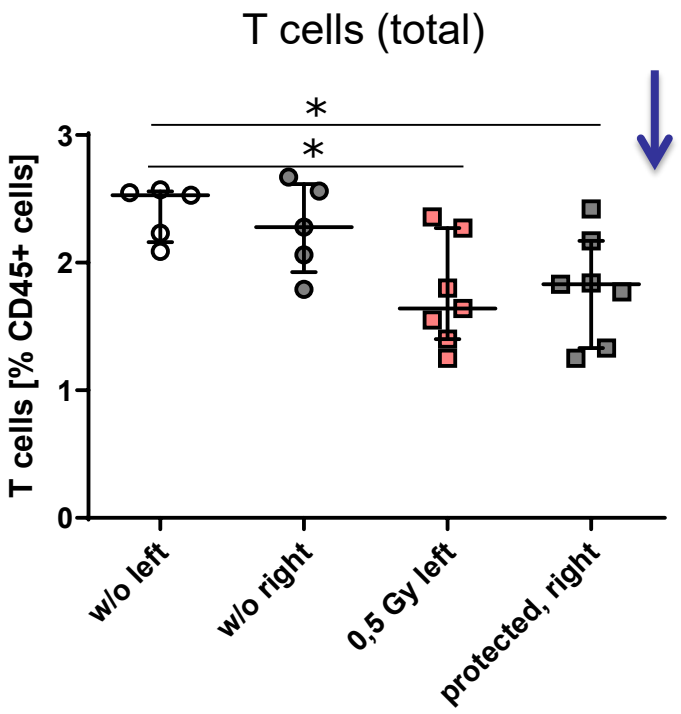
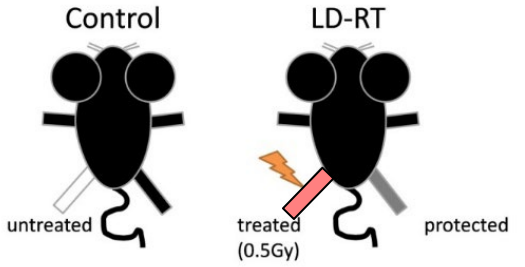
LD-RT with 1x0.5 Gy results in an anti-inflammatory T cell response (CD4+↑, CD8+↓)

Bone marrow





Data shows 2 independent experiments with in sum n(w/o)=5 and n(local)=7 mice; mice were age- and sex-matched. Data is presented as median+IQR and analyzed by two-tailed Mann-Whitney-U test in comparison to mock-treated (w/o) controls (*p<0.05)

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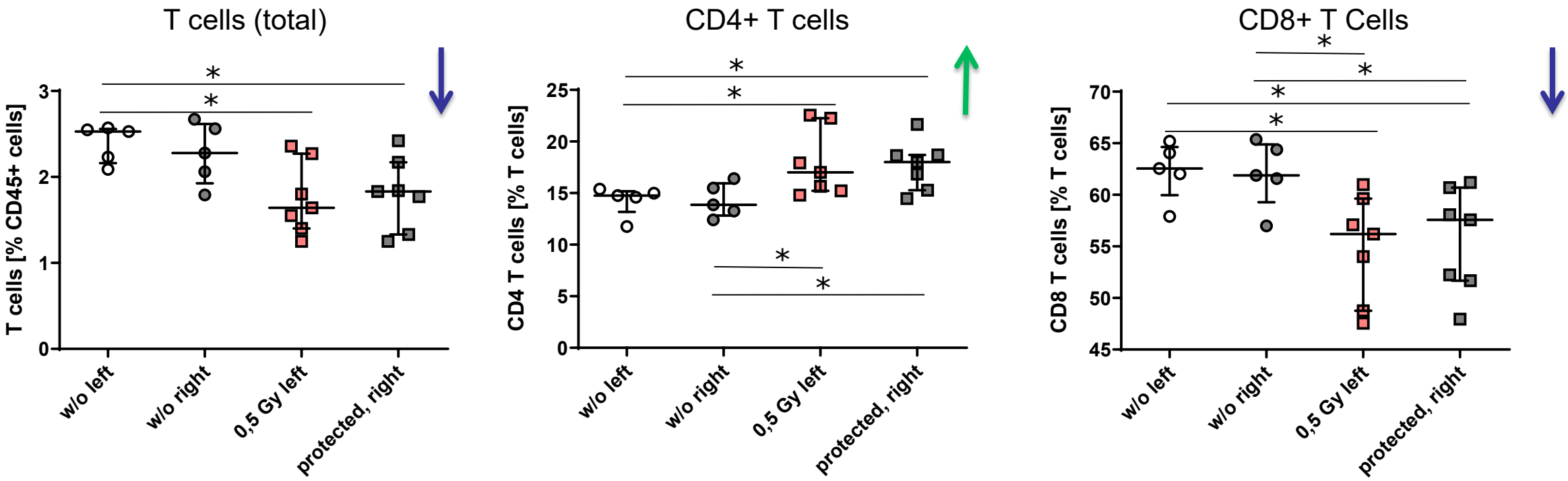
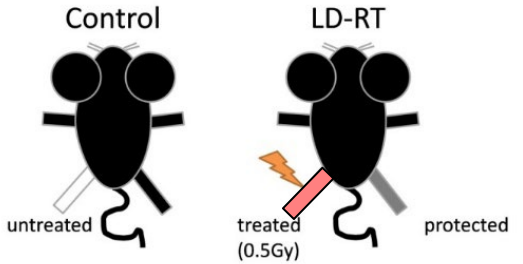


- Significant **increase** of rather **anti-inflammatory** CD4+ T cells
- Significant **decrease** of rather **inflammatory** CD8+ T cells



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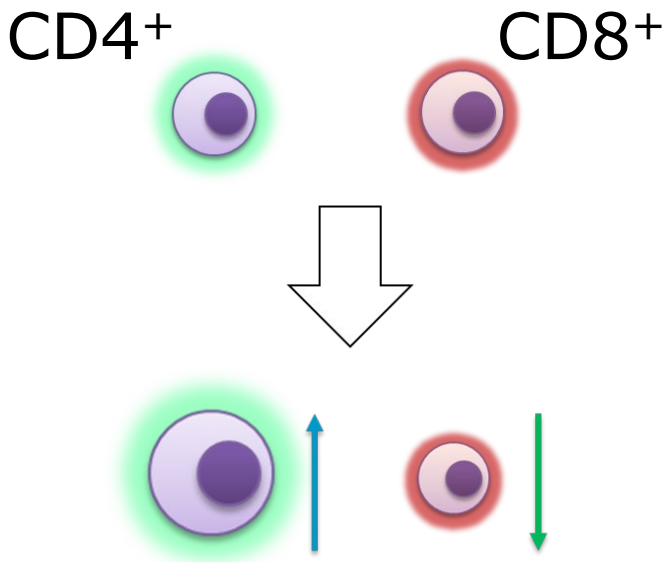
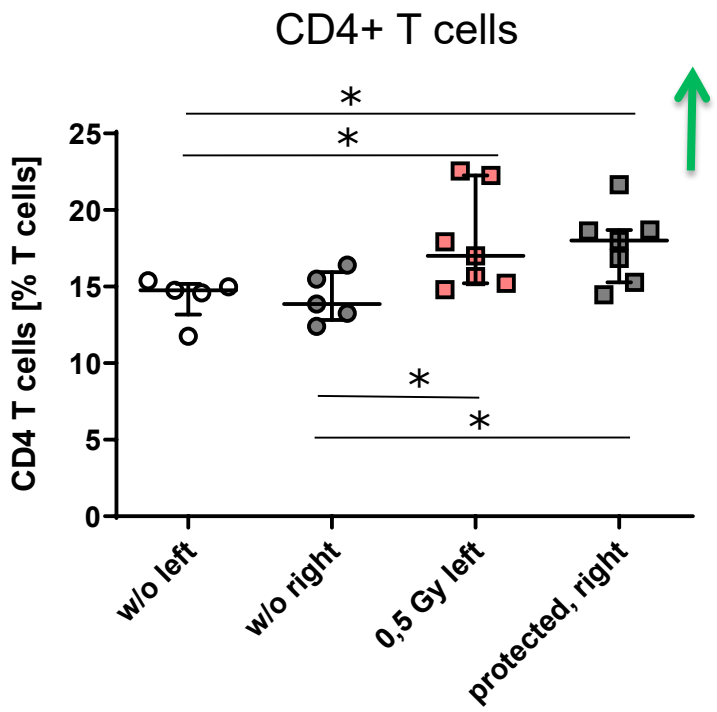
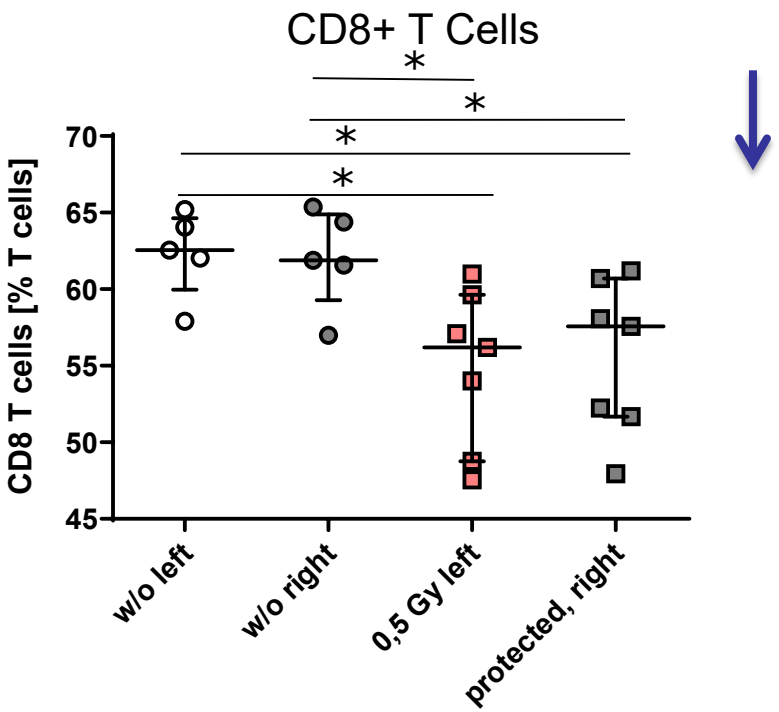
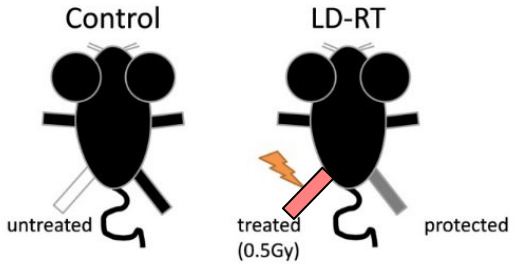






Rather anti-inflammatory response



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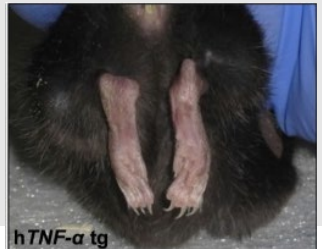
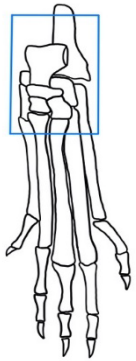
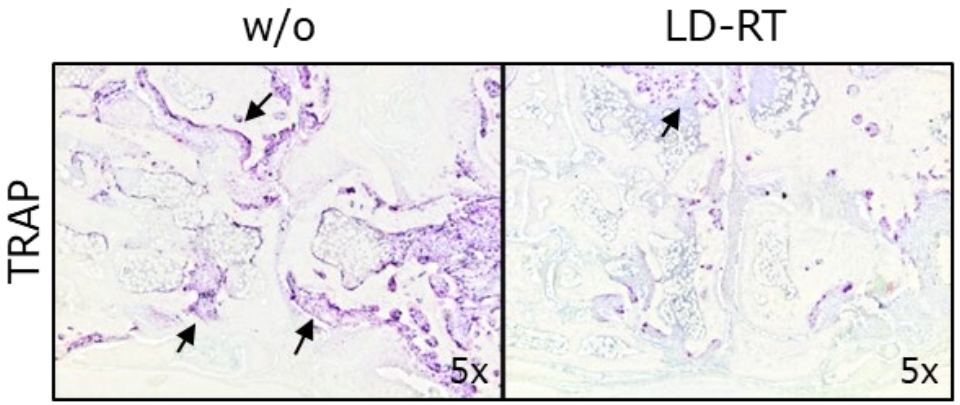
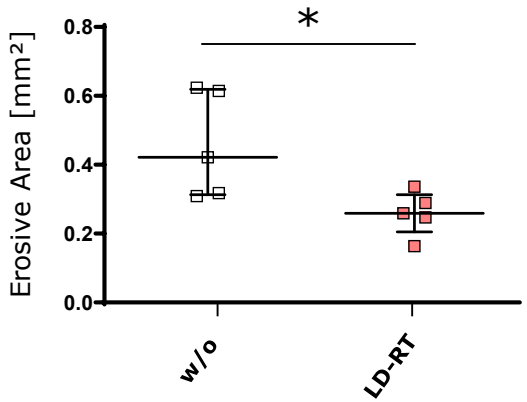
Deloch et al., *Frontiers Immunology*, 2018; Histological slices in Cooperation with Barbara Happich, Medical Clinic 3; Paw: modified after http://www.informatics.jax.org/cookbook/figures/figure43.shtml 26.11.2020;

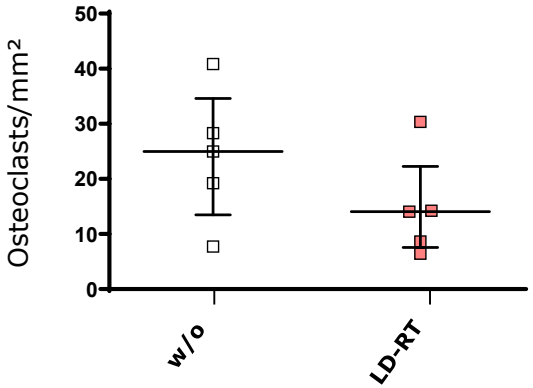
Locally applied LD-RT with 0.5 Gy reduces Bone Loss and Osteoclast Numbers in h*TNFα* tg mice











→ Significant **reduction of erosive areas** (d33) as well as a **reduction of osteoclast numbers** after 1x 0.5Gy

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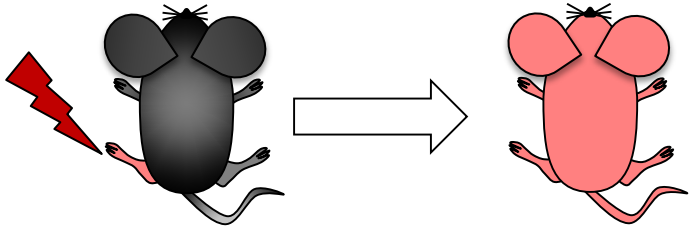
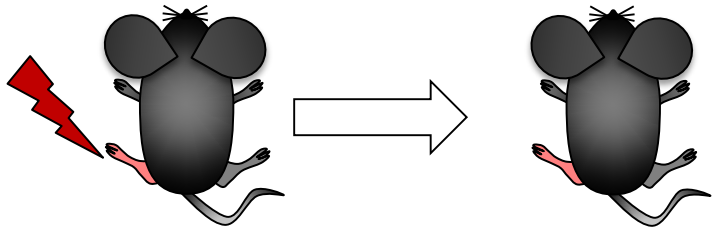
Local and systemic effects of LD-RT with 0.5 Gy



Local irradiation →
systemic anti-inflammatory effects in inflammation



Local irradiation →
local effects in bone

Reduction of erosive areas

LD-RT Predicament- Lack of Prospective, Sham-controlled Studies

Randomized Controlled Trial > Ann Rheum Dis. 2019 Jan;78(1):83-90.
doi: 10.1136/annrheumdis-2018-214104. Epub 2018 Oct 26.

Effectiveness of low-dose radiation therapy on symptoms in patients with knee osteoarthritis: a randomised, double-blinded, sham-controlled trial

Elien A M Mahler [1], Michiel Jm Minten [2], Mathilde M Leseman-Hoogenboom [3], Philip M P Poortmans [3 4], Jan Willem H Leer [3], Simone S Boks [5], Frank H J van den Hoogen [6], Alfons A den Broeder [2], Cornelia H M van den Ende [2]

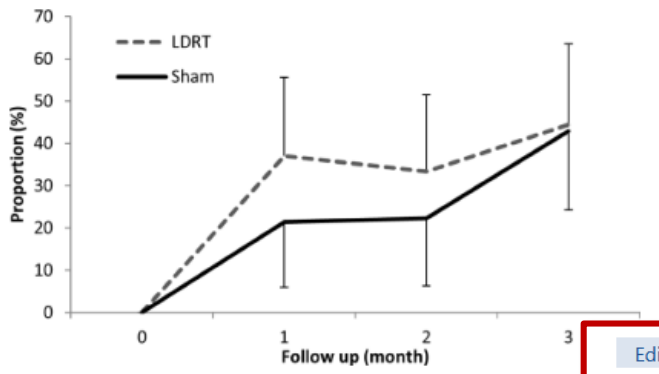


Figure 2 Proportion of responders over 3 months, with its 95% LDRT and sham intervention. LDRT, low-dose radiation therapy.

Editorial > Strahlenther Onkol. 2019 Apr;195(4):285-288. doi: 10.1007/s00066-018-1412-1. Epub 2018 Dec 18.

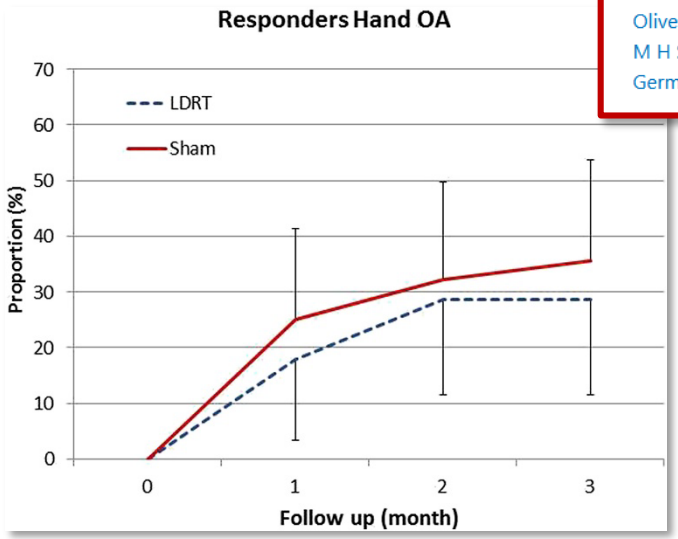
Low-dose radiotherapy: Mayday, mayday. We've been hit!

Oliver J Ott [1], Oliver Micke [2], Ralph Mücke [3], Marcus Niewald [4], Franz Rödel [5], Ulrich Schäfer [6], M H Seegenschmiedt [7], Meritxell Arenas [8], Benjamin Frey [9], Udo S Gaipl [9];
German Cooperative Group on Radiotherapy for Benign Diseases (GCG-BD)

Randomized Controlled Trial > Osteoarthritis Cartilage. 2018 Oct;26(10):1283-1290.
doi: 10.1016/j.joca.2018.06.010. Epub 2018 Jul 7.

Lack of beneficial effects of low-dose radiation therapy on hand osteoarthritis symptoms and inflammation: a randomised, blinded, sham-controlled trial

M J M Minten [1], M M Leseman-Hoogenboom [2], M Kloppenburg [3], M C Kortekaas [4], J W Leer [5], P M P Poortmans [6], F H J van den Hoogen [7], A A den Broeder [8], C H M van den Ende [9]



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Biological data in *in vitro* experiments does not support lack of effectiveness!

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Considerations for LD-RT – Research in Clinical and Pre-clinical Settings

Autoimmune disease or mechanical disease?

Inflammatory background?

Gender?

Age?

Localization of affected joints?

Applied dosage?

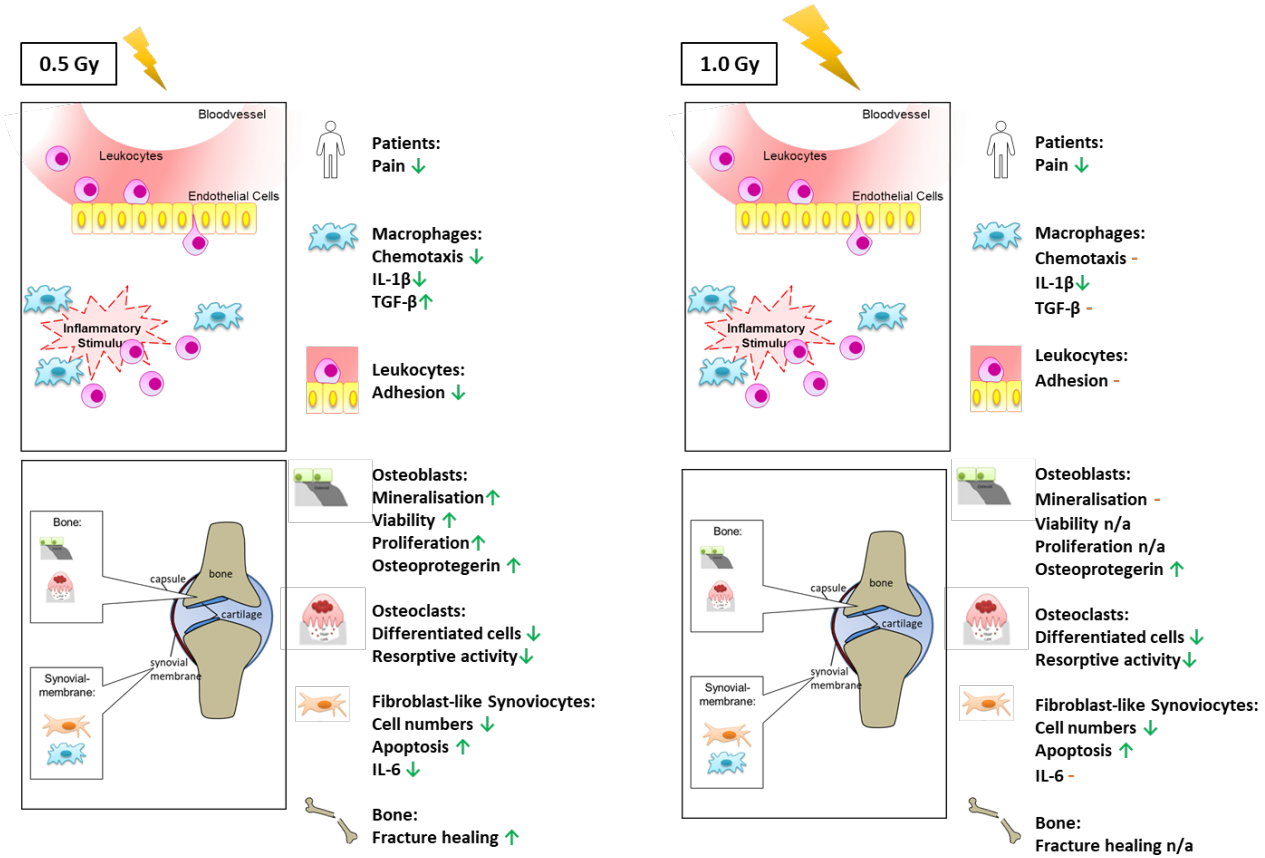
Summary and Outlook

We already know quite a lot!

Summary and Outlook

We already know quite a lot!

(and a lot more than what I have been able to share here is known)



Summary and Outlook

We already know quite a lot!
(and a lot more than what I have been able to share here is known)

BUT

There are still many open questions!

Thank you for your attention!

TOGETHER [BMBF, 02NUK073]
GREWIS-Project [BMBF, 02NUK017G]
GREWIS-alpha-Project [BMBF, 02NUK050E]

Department of Radiation Oncology
Prof. Rainer Fietkau


Translational Radiobiology
Prof. Udo Gaipl





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PTKA Projektträger Karlsruhe im Karlsruher Institut für Technologie

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