Low Dose Radiation Therapy (LD-RT):

A Potential Novel Immunomodulatory Treatment for RT-induced Toxicities

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Outline

Introduction to LD-RT (< 1-2 Gy single dose RT)

Diseases have been treated historically by LDRT including COVID19

Mechanism of LDRT

Challenges historically using LDRT for benign disease

New opportunities/applications of LDRT

Trial design

Introduction

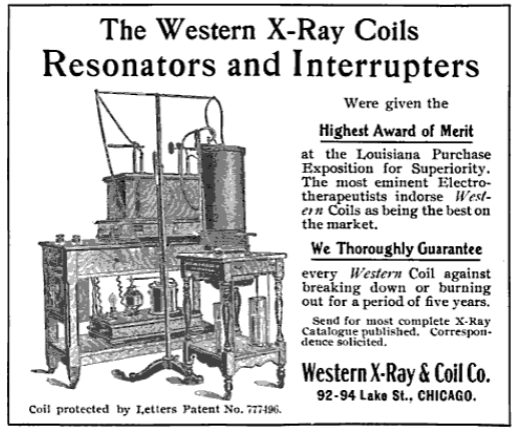
Low dose radiation therapy (LD-RT) has been recently resurrected and identified as a potentially life-saving treatment which was used prior to the “age of antibiotics” in the treatment of seriously ill patients with bacterial and/or viral pneumonia (Calabrese and Dhawan 2013a, b; Calabrese et al. 2014, 2015, 2019; Dhawan et al. 2019, 2020).

LD-RT (X-ray therapy) was used to treat pneumonia during the first half of the 20th century. Fifteen studies report that approximately 700 cases of bacterial (lobar and bronchopneumonia), sulfanilamide non-responsive, interstitial, and atypical pneumonia were effectively treated by low doses of X-rays, leading to disease resolution, based on clinical symptoms, objective disease biomarkers, and mortality incidence. (Calabrese and Dhawan 2013)

The capacity of the X-ray treatment to reduce mortality was similar to serum therapy and sulfonamide treatment during the same time period. Studies with four experimental animal models (i.e., mice, guinea pig, cat, and dog) with bacterial and viral pneumonia supported the clinical findings.

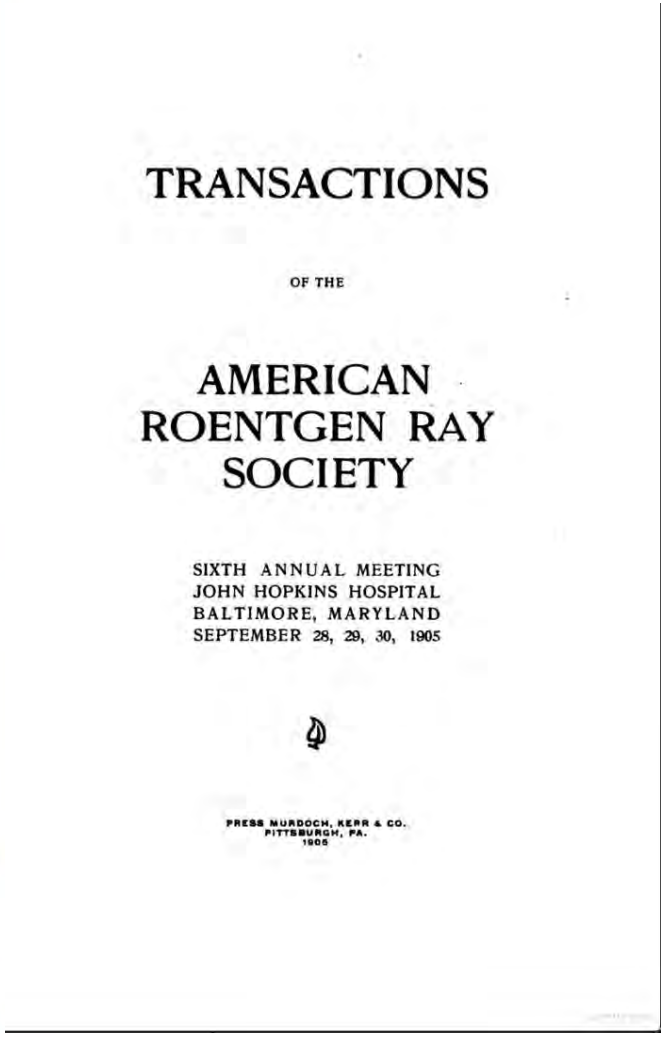
Benign disease treated by LD-RT historically

Bacterial and atypical pneumonia
Shoulder tendonitis/bursitis
bronchial asthma
carbuncles and furuncles (boils)
gas gangrene
sinus infections
inner ear infections and prevention of deafness
Pertussis
Lupus
Acne
Eczema
Keloids



Transactions of the American Roentgen Ray Society 1905

RT treating unresolved pneumonia



TRANSACTIONS

OF THE

AMERICAN ROENTGEN RAY SOCIETY

SIXTH ANNUAL MEETING
JOHN HOPKINS HOSPITAL
BALTIMORE, MARYLAND
SEPTEMBER 28, 29, 30, 1905

PRESS MURDOCH, KERR & CO.
PITTSBURGH, PA.
1905

The initial report using X-rays to treat patients with pneumonia was in 1905 by Musser and Edsall at the University of Pennsylvania.

They believed that X-rays may be useful in the treatment of unresolved pneumonia, that is, when the disease resolution process fails to proceed to a cure, with lung exudate material showing consolidation, enhanced bacterial infestation, and risk of prolonged serious illness.

Hypothesis: the X-ray treatment may accelerate autolytic processes and enhance the "fementation" (metabolism) of conditions that had been slowed down, including unresolved pneumonia. X-ray treatment would increase the metabolic digestion of the exudative material, leading to a resolution of the pneumonia.

RUDIS-JICINSKY, J., M.D., Cedar Rapids, Iowa.

SALTER, ALLEN, M.D., Lena, Ill.
SAUERBERING, D., M.D., Nassau, Wis.
SAYBERT, F. T., M.D., Council Bluffs, Iowa.
SCHEIDEL, W., 171 E. Randolph St., Chicago, Ill.
SCOTT, J. N., M.D., 214 New Ridge Bldg., Kansas City, Mo.

DR. J. RUDIS-JICINSKY, Cedar Rapids, Ia.: When in 1897 I read a paper before the Nebraska State Medical Society on the X-ray diagnosis of pulmonary tuberculosis, they all laughed at me. I wish those gentlemen could see the beautiful negatives that Dr. Pfahler showed us today.

X-ray therapy in the treatment of pneumonia

Reference	Types of Pneumonia	Case Number	Cases Cured
Musser and Edsall, 1905 [14]	Unresolved pneumonia	1	1
Edsall and Pemberton, 1907 [37]	Unresolved pneumonia	2	2
Quimby and Quimby, 1916 [15]	Unresolved pneumonia	12	11
Krost, 1925 [20]	Unresolved pneumonia	12	11
Fried, [72]	Post-operative pneumonia	40	32
Fried [73]	Post-operative pneumonia	57	N/A
Merritt and McPeak, 1930 [22]	Unresolved pneumonia	7	6
Powell, 1936, 1938, 1939 [3,28,33]	Lobar pneumonia and bronchopneumonia	231	215
Scott, 1939 [24]	Lobar pneumonia	138	111
Solis-Cohen and Levine, 1939 [25]	Lobar pneumonia	42	40
Settle, 1941 [26]	Lobar pneumonia	34	32
Rousseau et al. 1942 [27]	Lobar pneumonia	104	98
Rousseau et al. 1942 [27]	Viral pneumonia	29	22
Correll and Cowan, 1943 [34]	Acute atypical pneumonia (not pneumococcal)	23	22
Correll and Cowan, 1943	Unresolved pneumonia	9	7
Oppenheimer, 1943 [32]	Interstitial pneumonia (children)	36	33
Oppenheimer, 1943 [35]	Virus pneumonia	56	45
Torbett, 1936 (see Abstract of Discussion in Powell [3])	N/A	30	29
Total		863	717

Calabrese and Dhawan 2013

Efficacy of LDRT in inflammatory conditions

RT studies are identified[6–13] that were conducted on more than 37,000 patients in the first part of the last century, ranging in time from about 1910 to the early 1950s. Each ailment had its own historical foundation as was described in prominent medical journals of the era. The strengths and limitations of the studies were assessed in each review publication according to the specific ailment, as cited above.

Early researchers/physicians including Dr. Samuel Stern, noted that in many cases, the crisis occurred within 24 hours after X-ray treatment and often were followed by complete recoveries. This observation suggested that the recovery process was causally related to the X-ray treatment.

Conclusions:

In general, the clinical successes of RT were not only substantial for each type of ailment but also repeatedly confirmed by independent studies.

Dosing of LD-RT

Early studies used X-rays dose of 0.1-0.75 skin erythema dose (SED), an emperically but not precisely defined concept.

During 1920s and 1930s, the SED varied in the carbuncle literature by author, typically being in the 350-500 Roentgen (R) range. The therapeutic responses to a single RT treatment consistently improved as the dosing decreased over time to **between 30 r and 100 r**

One roentgen deposits 0.00877 grays (0.877 rads) of absorbed dose in dry air, or 0.0096 Gy (0.96 rad) in soft tissue. **(1R in air is roughly 1 rad in human tissue)**

These doses are in agreement with a number of contemporary reports from Germany where RT has been commonly and successfully employed in treating ailments with an inflammatory origin, achieving this with the application of relatively low doses **(0.3-1.0 Gy)**

Calabrese et al., 2019

Table 2. Optimal radiotherapeutic dose range to treat human inflammatory conditions, injury, infectious disease, and other cases.

Clinical conditions	Optimal human dose range (total dose)	Comment	References
Arthritis	150–250 r	Similar optimal dose ranges were reported in mouse arthritic models—see table III, page 292, Calabrese and Calabrese[15]; this exposure was given on a weekly basis. Depending on the patient the treatment could be limited to single treatment or repeated up to three times.	Trott[16,17]
Bronchial asthma	250 r—and possibly lower—see comment	Report on 1000 cases: 850 improved with 250 r total dose; the therapeutic dose decreased from the mid-1920s to the 1940s; in 1949 Leddy and Maytum were recommending further lowering the dose to 100 r or less; in their experience most patients required only one treatment and reported relief within 24 h.	Leddy and Maytum[18]
Bursitis	100–150 r	Multiple independent studies (see table 2, page 1505); beneficial responses were reported over a broad dose response, depending on the subject, ranging from as low as 0.1 of the SED to multiples of this value, depending on the subject. According to Laltomus and Hinter[31] many patients were relieved of symptoms after the first 100 r treatment.	Calabrese et al.[11]
Cervical adenitis (massively swollen lymph nodes, neck area)	60 r	75–90% markedly improved/cured (see tables 5 and 6, page 550); dosing evolved to approximately 0.1 SED over two decades.	Calabrese and Dhawan[10]
Carbuncles	35–50 r	See table 5, page 822; the initial optimal treatment in the 1920s was 0.5–0.75 SED, dropping to 0.1–0.2 a decade later.	Calabrese[6]
Furuncles	35–50 r	See table 5, page 822; see explanation for carbuncles which is directly relevant for furuncles.	Calabrese[6]
Gas gangrene	120–150 r	Based on Bowen,[46] treatment given immediately after admitted to hospital.	Calabrese and Dhawan[7]
Otitis media	~20–50 r	Very high rate of clinical (>90%) improvement; chronically affected patients tended to receive multiple treatments; treatment dose was reported as 0.10–0.20 SED. This dose (i.e. 20–50 r) was administered over the affected ear.[19] These figures are in general agreement with the 62 r dose of McLaurin.[20]	Calabrese and Dhawan[10]
Mastoides	~70–75 r	Similar to findings with otitis media; dosing was reported to be approximately 0.25 SED; Lucinian[21] reported that 0.20 SED with a single dose was effective.	Calabrese and Dhawan[10]
Pneumonia	50–125 r	The dosing was based initially on that used for the treatment of carbuncles.	Calabrese and Dhawan[8]
Sinus infections	50–100 r	Effective in children and adults; therapeutic doses decreased markedly from the early 1930s to mid–1940s, from 900 r to 50–100 r.[14,15,22] Improvement with a single treatment occurred in 25–50% of patients, with some claiming cures. Extensive lead shielding employed.	Calabrese and Dhawan[9]
Tendonitis, shoulder	100–150 r	Based upon multiple independent studies; progressive decrease from 350–400 r to 100 r over two decades; see comment for bursitis.	Calabrese et al.[11]
Pertussis	37.5–50 r	Treatments were purposely low dose due to the young age of many patients; the dose was about 0.1 SED; the treatments were often a single dose but could be given up to three times for initially less responsive subjects.	Calabrese et al.[13]

LDRT for benign painful elbow syndrome in Germany

All patients received RT in orthovoltage technique. One RT course consisted of 6 single fractions/3 weeks. In case of insufficient remission of pain after 6 weeks a second radiation series was performed.

Patients were randomly assigned to receive either single doses of 0.5 or 1.0 Gy.

Endpoint was pain reduction.

Pain was measured **before, right after, and 6 weeks after RT** by a visual analogue scale (VAS) and a comprehensive pain score (CPS).

Results: see table on right.

No statistically significant differences between the two single dose trial arms for early (p = 0.103) and delayed response (p = 0.246) were found.

Conclusion: RT is an effective treatment option for the management of benign painful elbow syndrome. For radiation protection reasons the dose for a RT series is recommended not to exceed 3.0 Gy.

		0.5Gy	1.0Gy	P values
VAS values	before	59.6 ± 20.2	55.7 ± 18.0	0.463
	Right after	32.1 ± 24.5	34.4 ± 22.5	0.256
	6 weeks after	27.0 ± 27.7	23.5 ± 21.6	0.818
CPS mean	before	8.7 ± 2.9	8.1 ± 3.1	0.207
	Right after	4.5 ± 3.2	5.0 ± 3.4	p = 0.507
	6 weeks after	3.9 ± 3.6	2.8 ± 2.8	0.186

Ott et al., Strahlentherapie bei Ellenbogensyndrom 2012

Fact

The use of LDRT has continued for the treatment of arthritis in Germany with 50,000 people treated annually.

Timing of response

RT was reported to be frequently effective after only a single treatment, with a rapid (within 24 h) and often long-lasting (from months to years) relief from symptoms.

Interstitial pneumonia:
The X-ray treatment for interstitial pneumonia was very successful when the duration of illness prior to the therapy was 2 to 5 days and nearly as successful when duration of illness prior to the radiotherapy was 6 to 14 days. After 14 days, the successful response rate dropped by about 50 percent. The so-called failure in the cure rate meant that the symptoms did not completely disappear within a period of a few days.

Arthritis (Sautter_Bihl et al., 1993):
Between 1980 and 1991, ionizing radiation was applied for analgesic purposes to 181 patients (97 men, 84 women, mean age 54 [29-81] years) with degenerative-inflammatory skeletal disease. The long-term effects were evaluated by questionnaire.

Radiation of **2.5 to 6.0 Gy** achieved lasting pain relief in 21 of 30 patients (70 %) with arthritis of the shoulder or humeroscapular periarthritis, 15 of 21 (71 %) with arthritis of the hip, in 12 of 15 (80 %) with heel spurs or Achilles tendon bursitis and 10 of 11 (91 %) with epicondylitis.

Pain relief lasted for longer than two years in 41 of the 77 patients (53 %).

There were no side effects at the stated dosage.

Sautter-Bihl et al., 1993

Mechanism of LDRT

Within this context, several studies have indicated that ionizing radiation induces macrophage polarization, with the capacity to polarize macrophages toward either M1 (pro-oxidative) or M2 (anti-inflammatory) phenotypes depending on the radiation dose.[4,5]

These observations are potentially significant since they help explain the dual capacity of ionizing radiation to be effective in both treating inflammatory conditions (i.e. M2 mediated) and killing microbes and tumor cells (i.e. M1 mediated).

The immunosuppressive effects of LD-RT

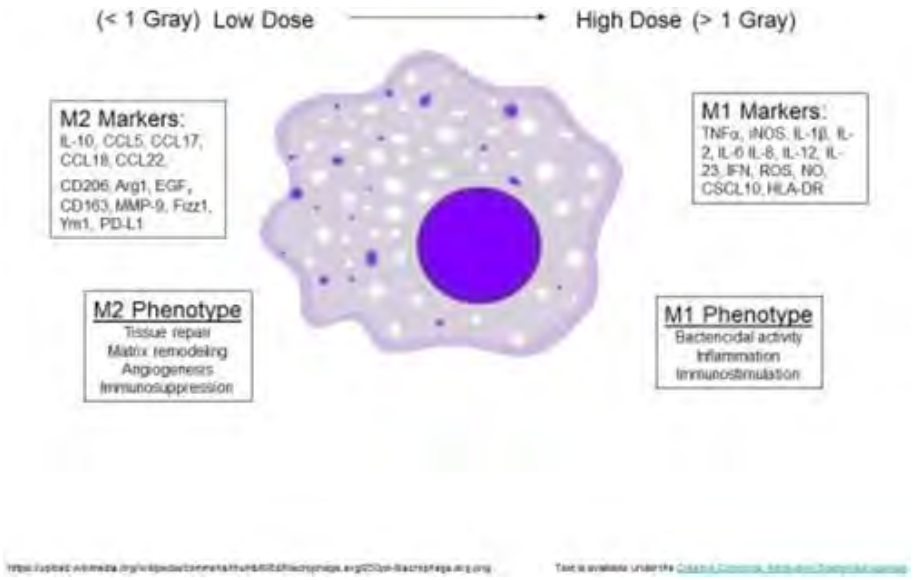
Substantial research has revealed that LD-RT induces an anti-inflammatory phenotype in a wide range of systems

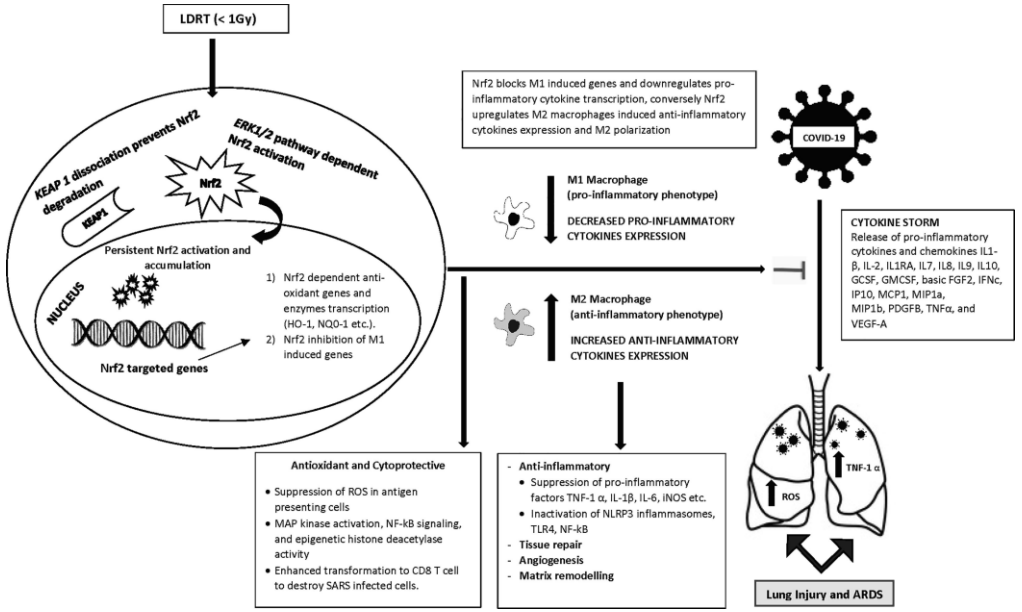
- ***in vitro* cell lines** e.g., activated murine macrophages-RAW 264.7 cells, mouse resistant peritoneal macrophages, adult human peripheral blood mononuclear cells, primary cultures of human umbilical vein endothelial cells, HC 60 cells [i.e., leukocytes], the hybrid endothelial cell line EA-hy.926, and the murine endothelioma cell line mlEnd) and
- ***in vivo* models** (e.g., murine air pouch models with Tuck mice, NMRI mice, Lewis Rats, C57 BC/6 mice, DBA mice, BALB/C mice, human tumor necrosis factor 2 transgenic mice).

- The mechanism(s) accounting for the anti-inflammatory phenotype(s) in the broad range of biological models also displays a common strategy with similar patterns and sequences of biochemical/molecular events, including
    - NO/iNOS decrease [50-52], reduction in reactive oxygen species [53],
    - enhancement of heme-oxygenase 1 (HO-1) [51,54,55],
    - induction of apoptosis [56-62],
    - suppression of TGFα, enhancement of TGFβ1 [54,55],
    - activation of transcription factors NFkB and activating protein 1 (AP-1) [63,64],
    - decreased adhesion of leukocytes and PMN to endothelial cells (EC) [47,48,65-69], and
    - enhancement of T regulatory cells [55,70,71].
    - Nrf2 activation

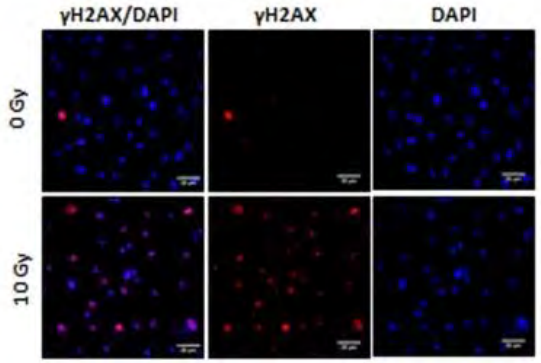
The immunosuppressive effects of LD-RT

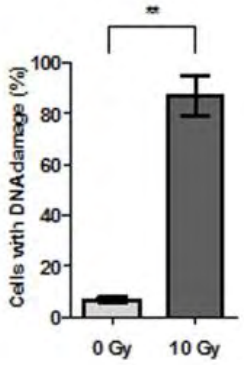
Data from previous study suggest that macrophages are polarized more toward M2 and the anti-inflammatory state when doses descend below 1.0 Gy and, conversely, more toward M1 and the pro-inflammatory state when doses ascend above 1.0 Gy.

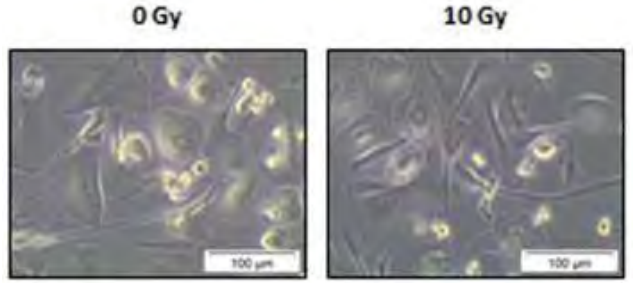


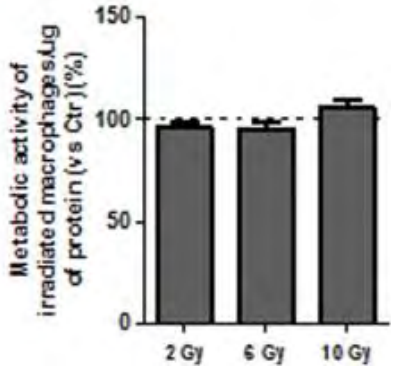


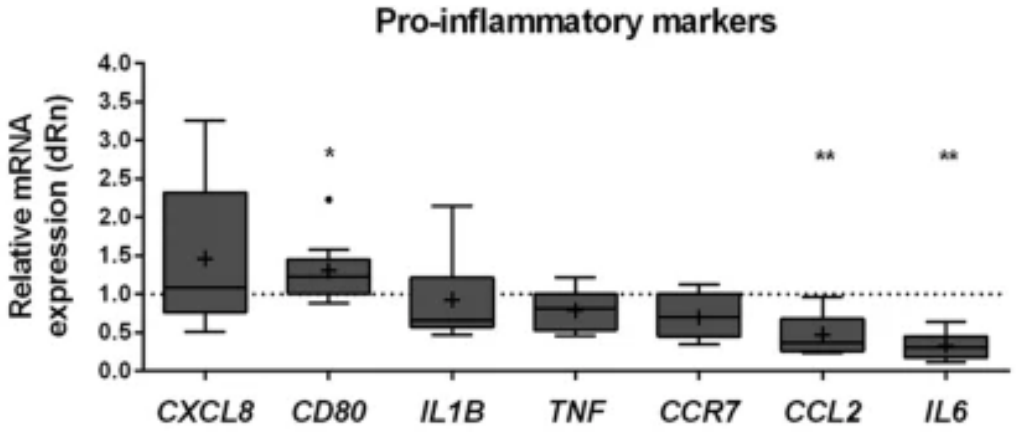
RT at 2Gy/fraction induces pro-inflammatory macrophage differentiation

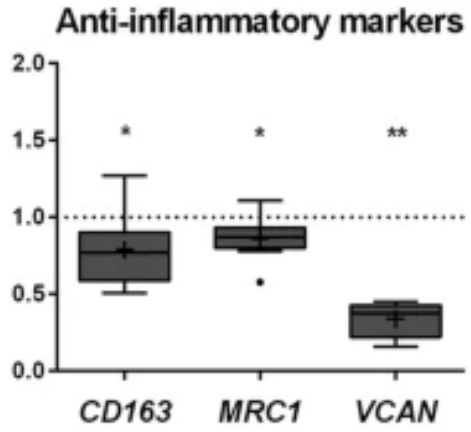








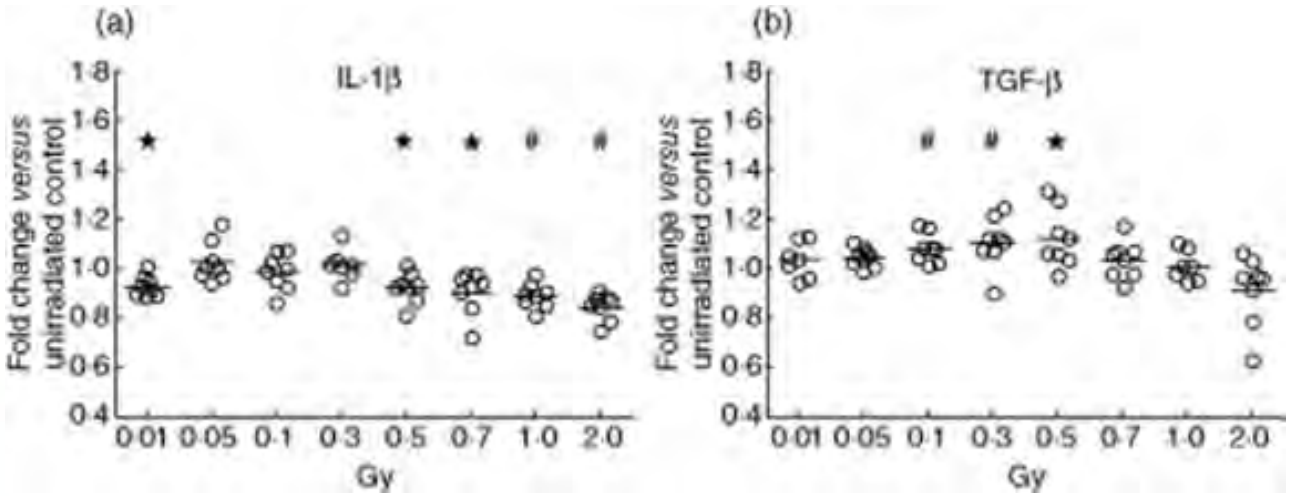


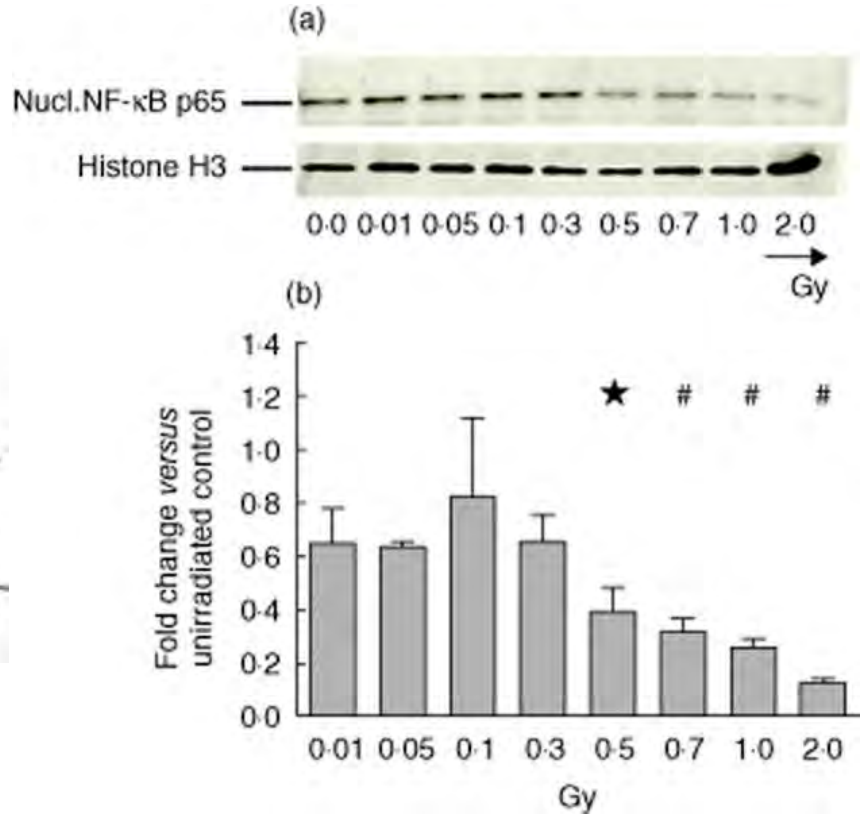


Pinto et al., 2016

LD-RT (<1-2Gy) induces immunosuppressive macrophage

Peritoneal macrophages activated by LPS:





Wunderlich et al., 2015

Challenges using LD-RT in benign disease
-Secondary cancer risks of LD-RT

According to dose measurements the theoretical risk of malignant tumor induction is 20-40/million radiated patients and thus four orders of magnitude below the spontaneous malignant tumor incidence rate (

>10% for age 60-69 or higher for elder age population; ~450/100,000 or **4,500/million** in all ages

Probability (%) of Developing Invasive Cancer during Selected Age Intervals by Sex, US, 2013-2015*

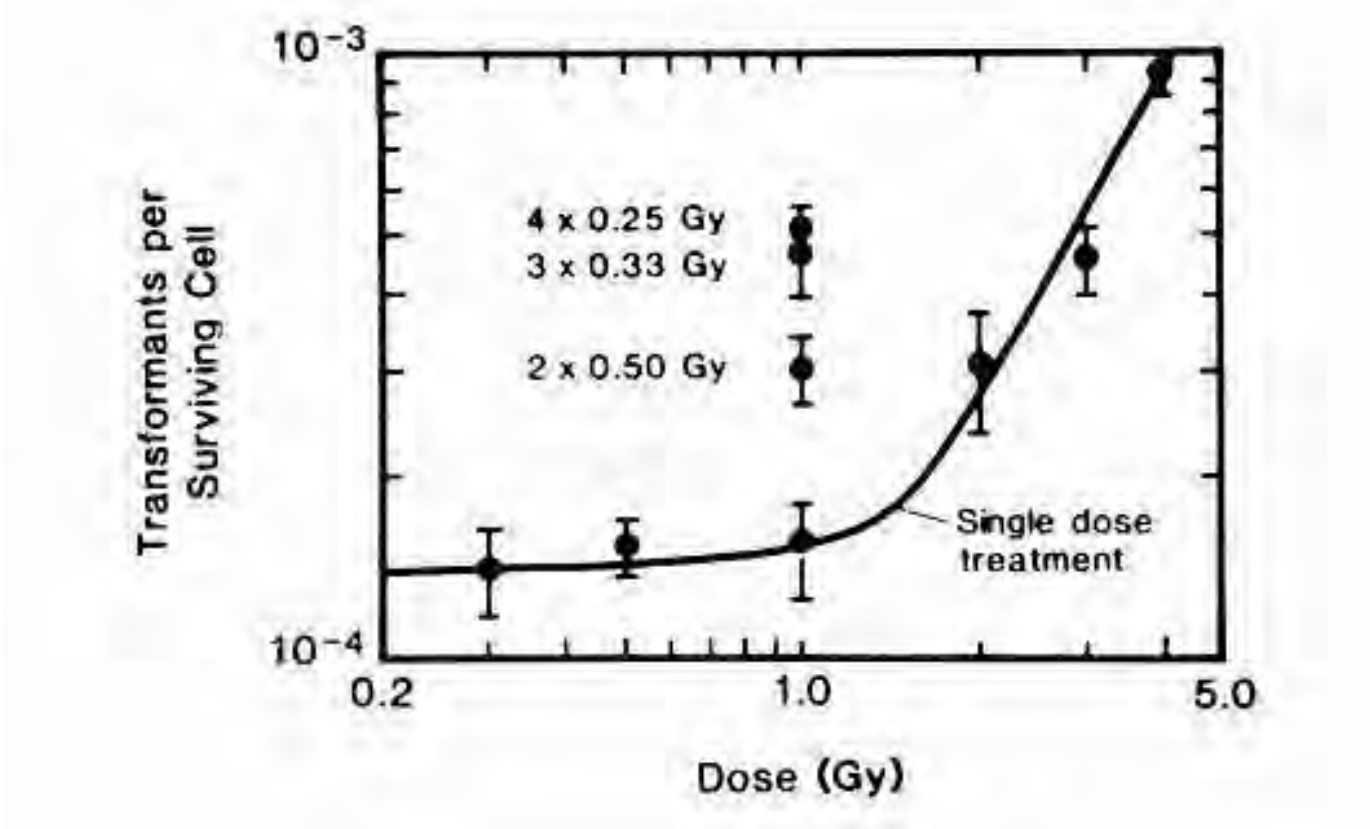
		Birth to 49	50 to 59	60 to 69	70 and older	Birth to death
All sites†	Male	3.4 (1 in 30)	6.1 (1 in 16)	13.2 (1 in 8)	31.9 (1 in 3)	39.3 (1 in 3)
	Female	5.6 (1 in 18)	6.2 (1 in 16)	10.0 (1 in 10)	26.0 (1 in 4)	37.7 (1 in 3)
Breast	Female	2.0 (1 in 51)	2.3 (1 in 43)	3.5 (1 in 29)	6.7 (1 in 15)	12.4 (1 in 8)
Colon & rectum	Male	0.4 (1 in 272)	0.7 (1 in 143)	1.2 (1 in 87)	3.3 (1 in 30)	4.4 (1 in 23)
	Female	0.3 (1 in 292)	0.5 (1 in 190)	0.8 (1 in 123)	3.0 (1 in 33)	4.1 (1 in 25)
Kidney & renal pelvis	Male	0.2 (1 in 440)	0.4 (1 in 280)	0.6 (1 in 155)	1.4 (1 in 73)	2.1 (1 in 47)
	Female	0.2 (1 in 665)	0.2 (1 in 575)	0.3 (1 in 319)	0.7 (1 in 135)	1.2 (1 in 82)
Leukemia	Male	0.3 (1 in 396)	0.2 (1 in 570)	0.4 (1 in 259)	1.4 (1 in 72)	1.8 (1 in 56)
	Female	0.2 (1 in 508)	0.1 (1 in 876)	0.2 (1 in 434)	0.9 (1 in 112)	1.3 (1 in 80)
Lung & bronchus	Male	0.1 (1 in 719)	0.6 (1 in 158)	1.8 (1 in 56)	6.0 (1 in 17)	6.7 (1 in 15)
	Female	0.1 (1 in 673)	0.6 (1 in 178)	1.4 (1 in 72)	4.7 (1 in 21)	5.9 (1 in 17)
Melanoma of the skin‡	Male	0.5 (1 in 215)	0.5 (1 in 186)	1.0 (1 in 104)	2.7 (1 in 37)	3.7 (1 in 27)
	Female	0.7 (1 in 150)	0.4 (1 in 238)	0.5 (1 in 191)	1.1 (1 in 87)	2.5 (1 in 40)
Non-Hodgkin lymphoma	Male	0.3 (1 in 382)	0.3 (1 in 350)	0.6 (1 in 176)	1.8 (1 in 54)	2.4 (1 in 42)
	Female	0.2 (1 in 548)	0.2 (1 in 484)	0.4 (1 in 247)	1.4 (1 in 74)	1.9 (1 in 54)
Prostate	Male	0.2 (1 in 437)	1.7 (1 in 59)	4.6 (1 in 22)	7.9 (1 in 13)	11.2 (1 in 9)
Thyroid	Male	0.2 (1 in 513)	0.1 (1 in 764)	0.2 (1 in 584)	0.2 (1 in 417)	0.6 (1 in 156)
	Female	0.8 (1 in 122)	0.4 (1 in 268)	0.3 (1 in 286)	0.4 (1 in 262)	1.8 (1 in 55)
Uterine cervix	Female	0.3 (1 in 366)	0.1 (1 in 835)	0.1 (1 in 938)	0.2 (1 in 628)	0.6 (1 in 162)
Uterine corpus	Female	0.3 (1 in 333)	0.6 (1 in 164)	1.0 (1 in 102)	1.3 (1 in 75)	2.9 (1 in 35)

All sites excludes basal and squamous cell skin cancers and in situ cancers except urinary bladder.

Incidence of cancers (per 100,000, age adjusted), US, 2011-2016, American Cancer Society

Incidence, 2011-2015	All races	Non-Hispanic white	Non-Hispanic black	Asian/ Pacific Islander	American Indian/ Alaska Native†	Hispanic/ Latino
All sites	449.8	465.3	463.9	291.7	398.5	346.6
Male	494.8	505.5	549.1	298.9	418.4	377.6
Female	419.3	438.4	407.0	290.3	386.9	329.9
Breast (female)	124.7	130.1	126.5	92.9	100.9	93.0
Colon & rectum	39.3	39.0	46.6	30.7	44.4	34.4
Male	45.2	44.6	55.2	36.1	49.8	41.7
Female	34.3	34.2	40.7	26.4	40.1	28.8
Kidney & renal pelvis	16.4	16.6	18.4	7.8	23.2	16.2
Male	22.2	22.5	25.4	11.1	29.9	21.1
Female	11.4	11.4	13.1	5.1	17.4	12.2
Liver & intrahepatic bile duct	8.1	6.7	10.7	13.0	14.8	13.3
Male	12.5	10.3	17.6	19.9	20.9	19.7
Female	4.3	3.6	5.2	7.4	9.5	7.8
Lung & bronchus	60.5	64.7	63.8	34.9	61.5	30.7
Male	71.3	74.3	85.4	44.5	69.3	39.2
Female	52.3	57.4	49.2	27.8	55.7	24.6
Prostate	109.2	101.7	179.2	56.0	73.1	91.6
Stomach	6.6	5.4	10.3	10.5	8.4	9.7
Male	9.1	7.8	14.1	13.7	11.2	12.5
Female	4.6	3.5	7.7	8.0	6.1	7.7
Uterine cervix	7.6	7.1	9.2	6.0	9.2	9.6

Transformation incidence of irradiated cells



Importance of age at exposure

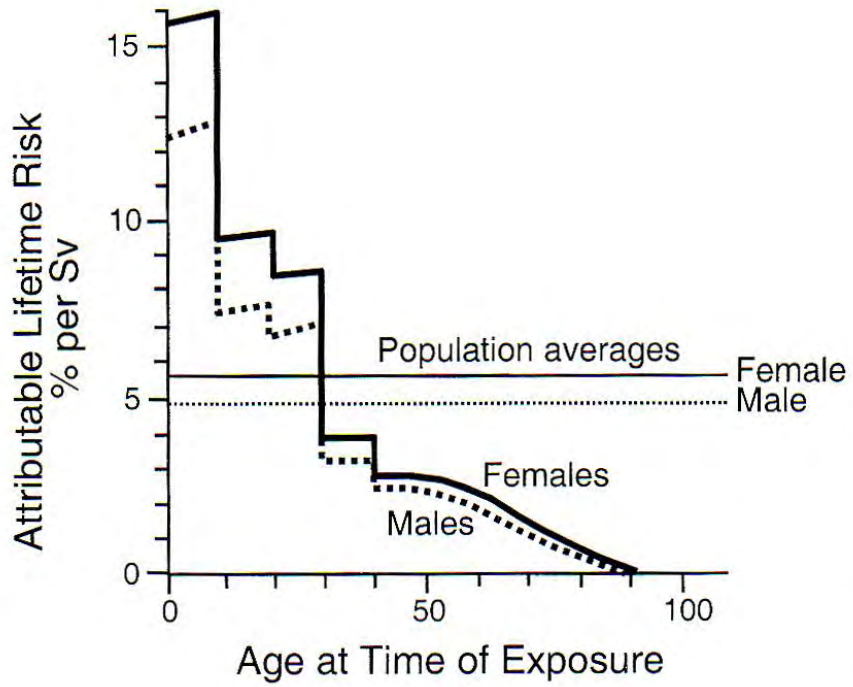


FIGURE 10.8 The attributable lifetime risk from a single small dose of radiation at various ages at the time of exposure. Note the dramatic decrease in radiosensitivity with age. The higher risk for the younger age-groups is not expressed until late in life. These estimates are based on a relative risk model and on a dose and dose-rate effectiveness factor (DDREF) of 2. (Adapted from ICRP: Recommendations. *Annals of the ICRP Publication 60*, Oxford, England, Pergamon Press, 1990.)

Children and young adults are much more susceptible to radiation-induced cancer than the middle- and old-aged.

Potential applications of LD-RT in modern medicine

Patients with cancer

Cancer treatment induced inflammatory conditions, such as

- Radiation pneumonitis
- Radiation necrosis
- Radiation-induced colitis/cystitis
- Immunotherapy related toxicities, ie, thyroiditis, pneumonitis, encephalitis, hypothesitis, nephritis, gastrointestinitis, etc.

Infectious disease with low virulent disease but acute high inflammatory response of body with mortality
COVID19

Other non-related benign inflammatory disease such as arthritis in patients with cancer

LOWRAD-Cov19 trial

A prospective, single-arm, phase 1/2 clinical trial conducted at Madrid, Spain.

Eligibility: Patients aged ≥50 years, coronavirus disease 2019 (COVID-19) positive, bilateral lung involvement at imaging study and oxygen requirement (O2 sat ≤ 93% via RA).

Treatment: Patients received 100 cGy to total lungs in a single fraction.

Primary outcome: radiologic response using severity and extension score on baseline computed tomography (CT), at days 3 and 7 after LD-RT.

Secondary outcomes were toxicity, duration of hospitalization, blood work evolution, and oxygen requirements using SatO2/FiO2 index (SAFI), at days 3 and 7 after LD-RT.

Median time to receive RT from the date of admission was 52 days (17-85) and from the last anti-COVID treatment (hydroxychloroquine, lopinavir/ritonavir, tocilizumab, or remdesivir) was 25 days (10-75).

Sanmamed et al., IJROBP 2020;
Radiother Oncol 2022

LOWRAD-Cov19 trial - Results

41 patients were included. Median age was 71 (interquartile range, 60-84).

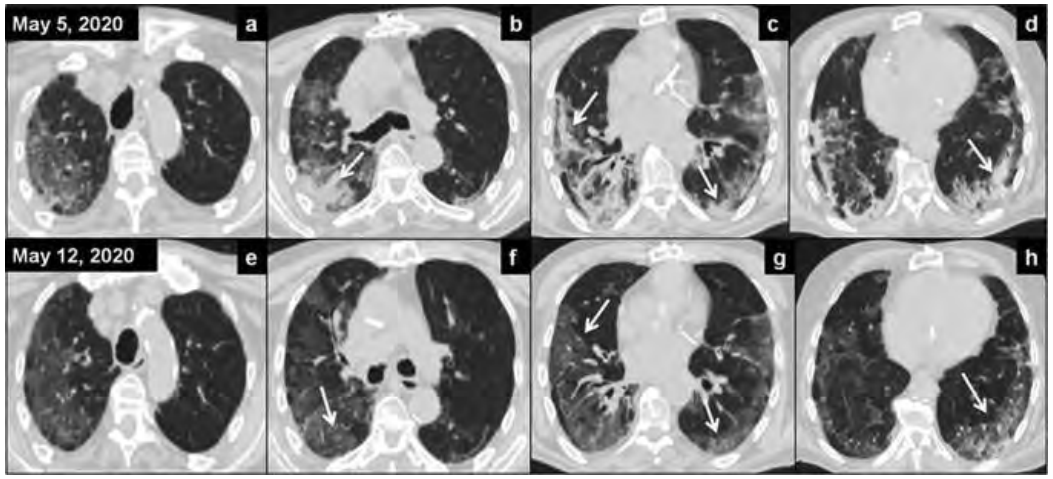
Severity score was stable or decreased in the third CT but was not statistically significant (P = .28); however, there were statistically significant changes in the extension score (P = .03). SAFI index significantly improved 72 hours and 1 week after LD-RT (P < .01).

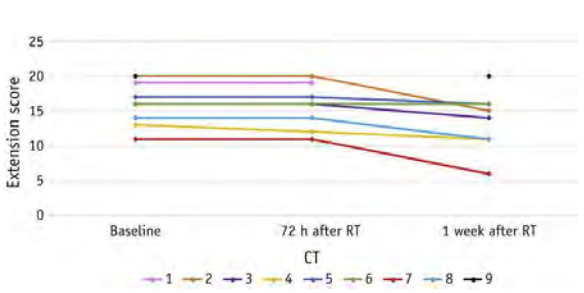
Inflammatory blood parameters decreased 1 week after RT compared with baseline; only C-reactive protein on day 7 and lymphocytes counts on day 3 and 7 decreased significantly (P = .02).

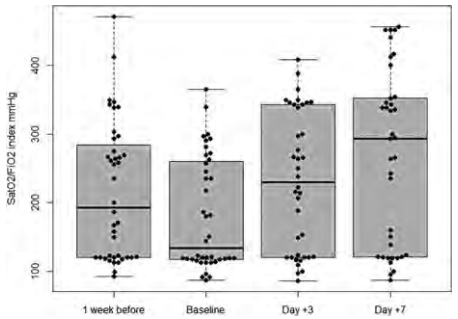
Two patients presented grade 2 lymphopenia after RT and another (with baseline grade 3) worsened to grade 4.

Overall, the median number of days of hospitalization was 59 (26-151). After RT the median number of days in the hospital was 11 (4-78).

With a median follow-up after RT of 60 days (), 63% patients were discharged and 37% patients died, (27% from COVID-19 respiratory failure; 10% from other causes).







Sanmamed et al., IJROBP 2020;
Radiother Oncol 2022

LDRT Studies on COVDI19	Design	Inclusion criteria	Dose (Gy)	Sample size	Median age	Primary endpoint	Key results
Ameri 2020	Phase II No randomized	>60 yo, SpO2 <93% or RR >30/min	0.5–1	**10**	75	SpO2 improvement	90% improved SpO2 one day after LDRT. 5 patients D/C, 4 died. Response rate better in 0.5Gy Rx (80% vs 40%).
Hess 2021	Phase I/II Matched controls	O2 requirement, Rx involvement	1.5	**20**	78	Time to clinical improvement	12 vs 3 days for RT (p = 0.05). Intubation rates: 14% vs 32% without (p=0.09). 28d OS 90%.
Arenas 2021	Phase I/II Multicentric Control group	Mod–severe, hospitalized with suppl. O2. Not ICU candidate <8 days of symptoms	0.5–1	**36**	84	Improvement in SpO2/FiO2	SpO2/FiO2 at 24 h improved in 50% patients. 64% survived, 22% died from Covid. No toxicity.
Ganesan 2021	Phase I/II Randomized	>40 yo, <10 days of symptoms, RR >24/min, SpO2 <94% and SpO2/FiO2 ratio >89 and <357	0.5	**25**	57	Improvement in SpO2/FiO2	SpO2/FiO2 improved at 48 h, 3 d and 7 d (p = 0.025). Rx improvement.
Sharma 2020	Phase II No randomized	Moderate to severe illness, RR >24/min and/ or SpO2 <94%	0.7	**10**	51	Clinical recovery	Clinical recovery ranging from 3 to 7 days. 9 patients survived and 1 died.
Papachristofilou 2021	Randomized Double-blind	ICU, Male>40yo, Female >50yo	1	**22**	75	Ventilator-free days at day 15	No differences VFDs. 28 d OS 63.6%.
Sanmamed 2022	Phase I/II No randomized	>50 yo, O2 requirement, Rx involvement	1	**41**	75	Radiological response	Extension score improved at 7d (p = 0.002). SpO2/FiO2 improved at 3d and 7d (p < 0.01). 63% patients D/C and 27% died from Covid.

Adapted from Sanmamed et al., 2022

Summary

Large number of patients with a variety of benign infectious/inflammatory disease have been treated with LD-RT historically with high efficacy.

Treatment effects usually take place within days after LD-RT and can have durable effects, ie. months to years.

New anti-inflammatory medications/antibiotics have largely replace the need of further research of LD-RT in these conditions.

Concerns of secondary cancer risks of RT for treating benign disease. But single fraction of <1Gy has very low risk of secondary cancer induction.

LD-RT (<1Gy) have immunosuppressive effects, particularly by promoting M2 subtype of macrophage differentiation. The best utilization of LD-RT might be treating therapy-induced hyperimmunostimulation in cancer patients.

Clinical trial design

Cancer patients with therapy-induced hyper-immunostimulation
- Radiation pneumonitis
- Radiation necrosis

Conditions not responding to steroids
- prolonged used of steroids
- requiring very high dose of steroids with side effects

Intervention: LD-RT of 1Gy x 1

Symptoms to be evaluated within the first week after LD-RT

Thank you!