Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia

Principi radiobiologici della re-irradiazione e applicazioni nella pratica clinica

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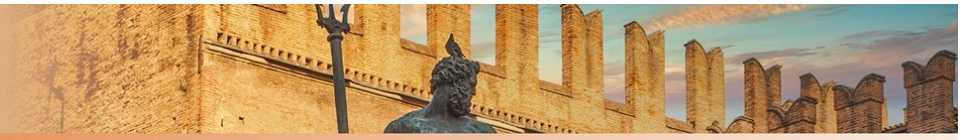


DICHIARAZIONE

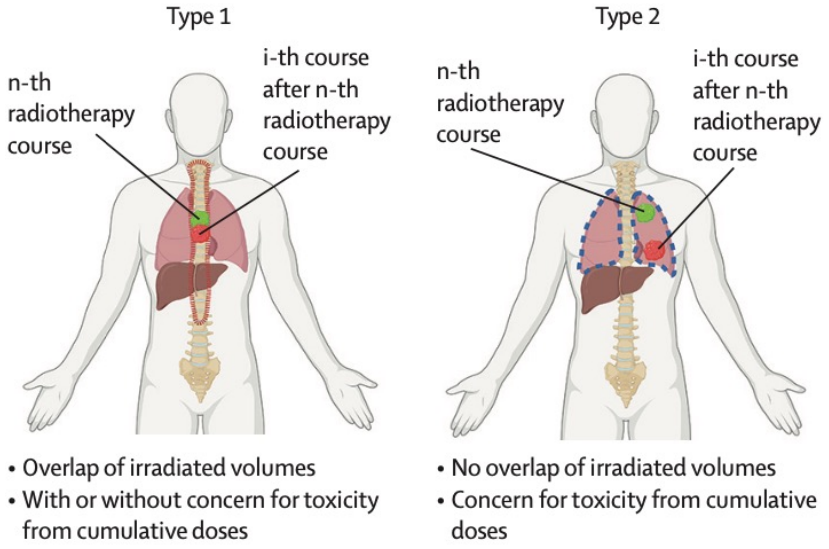
Relatore: Liliana Belgioia

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

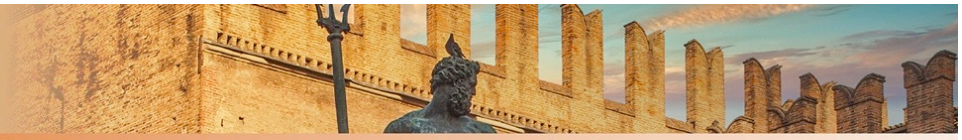
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
- Consulenza ad aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
- Partecipazione ad Advisory Board: NIENTE DA DICHIARARE
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario: NIENTE DA DICHIARARE
- Altro

Re-irradiation

«a new course of radiotherapy, either to a previously irradiated volume (irrespective of concerns of toxicity) or where the cumulative dose raises concerns of toxicity»



Consensus ESTRO –EORTC, Lancet Oncol 2022; 23: e469–78



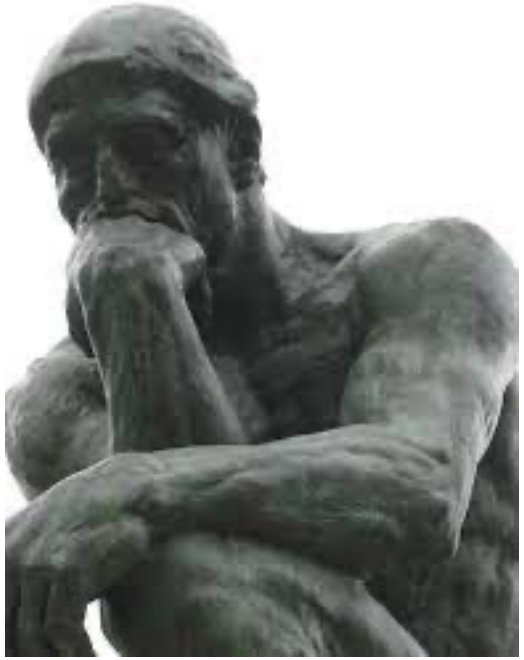
Reirradiation of previously treated areas: why?

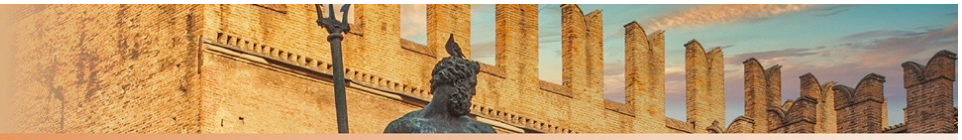
- New primary tumour
  - Cancer survivors are at increased risk of developing secondary malignancies
    - Patients still retain more risk (e.g. molecular predisposition)
    - Aetiological factor can continue (e.g. smoke)
    - Therapy itself

- Recurrence

Major technological advances have results in the ability to deliver larger biological doses to area of disease with improved sparing of OARs

IF IT DID NOT WORK THE FIRST TIME
WHY
WOULD IT WORK THE SECOND TIME?





Factors to consider for re-irradiation:

Patient factors	• PS • Severity of symptoms • Urgency of treatment • Prognosis
Tumours factors	• Histology • Natural history
Treatment factors	• Details of prevoious treatment – overall dose, dose per fraction, treatment technique • Time interval between the courses of radiotherapy • Duration and extent of symptoms control from previous course/s of radiotherapy • Toxicity from previous treatment • Additional treatment for the first tumour (e.g. chemotherapy, biologicals)
Other	• Type of OARs – serial vs parallel organ, to determine whether maximum dose or total volume needs to be taken into consideration at time of reirradiation • Extent of recovery of critical organs at risk

Armstrong S et al, Clinical Oncology 2020

Dose - Some concepts

- EQD_2: equivalent dose in 2 Gy fractions

Calculated using LQ model with α/β values
- 10 Gy for early reactions
- 3 Gy for late reactions

- EQD_2: tolerance doses

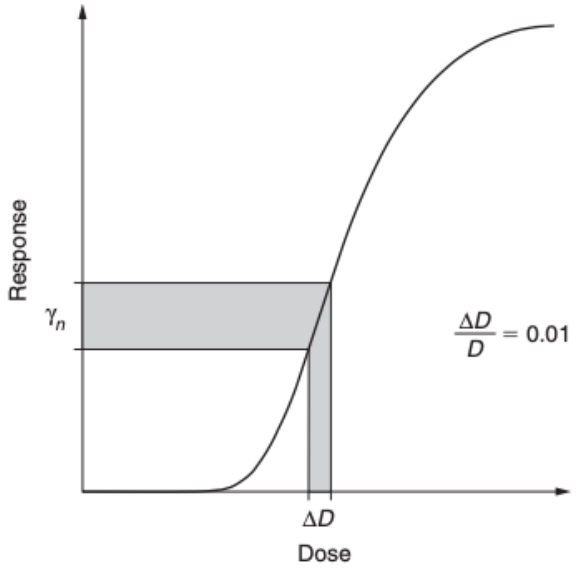
Threshold doses above which defined grades of toxicity are observed

- % EQD_2:

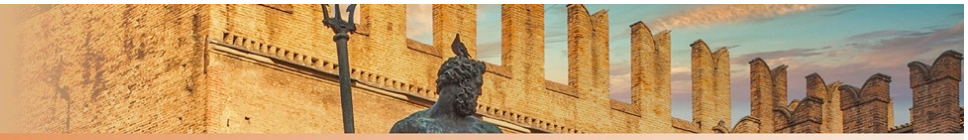
Intensity of the initial treatment or retreatment

Response rate refers to either a tumour control probability or a normal-tissue complication probability.
If the response rate is *R* after a dose *D*, the change in response rate, in percentage points, after an increment in dose, Δ*D*, is approximately:

$$\Delta R \approx \frac{\Delta D}{D} \times 100\% \times \gamma_n$$



where γ_n is the local value of the normalized dose–response gradient



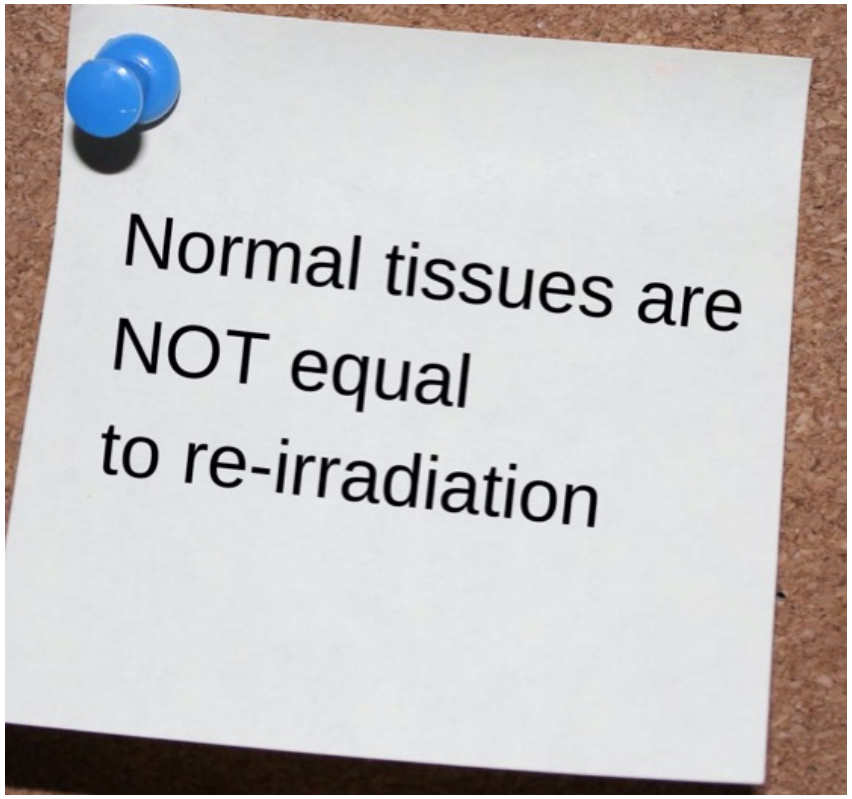
Eligibility: Restoration of tolerance?

If the radiation tolerance within a given volume or organ has already been exceeded during the first treatment

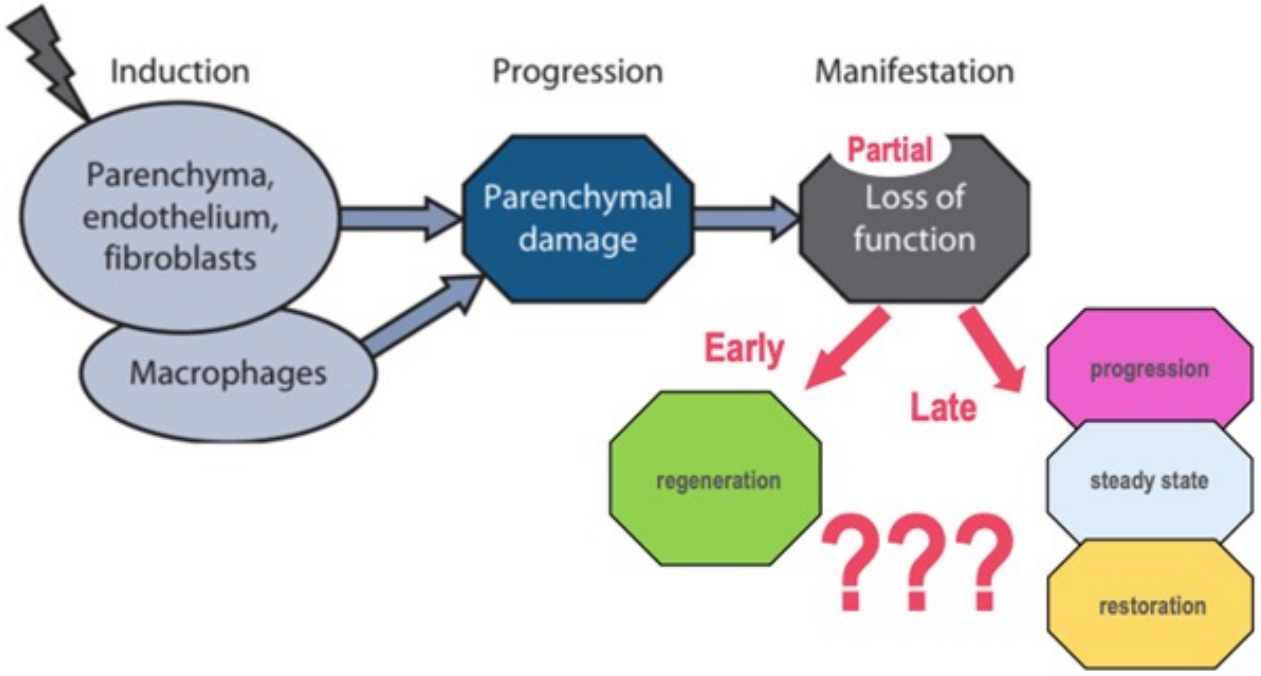
And function is lost (or loss is to be expected)

- If initial radiation treatment was in subtolerance dose range
- With the induction of only subclinical or minimal damage
- And with possible long-term recovery or potential residual damage after longer periods

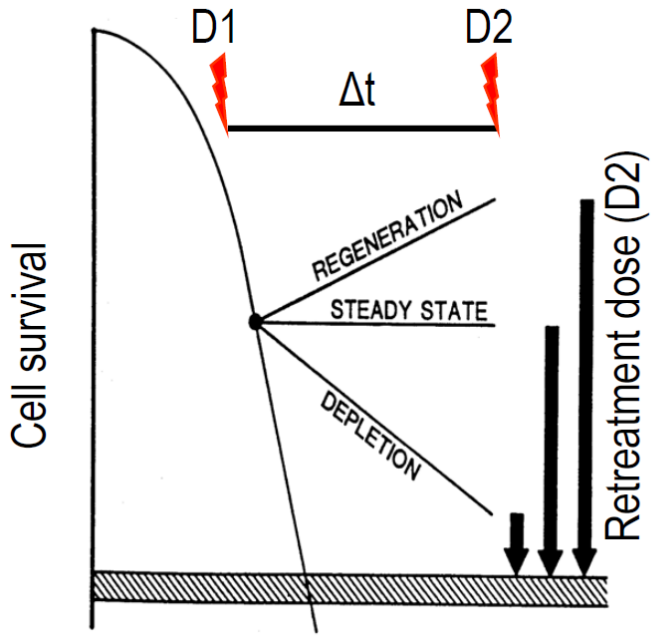
- Patients with a likely QoL/time to progression benefit of the anticancer effect of reRT
- Patients who are likely to have bearable late toxicity


Normal tissues are
NOT equal
to re-irradiation

Pathogenesis of normal tissue radiation effects



Retreatment tolerance depends on the level of cell kill and regeneration



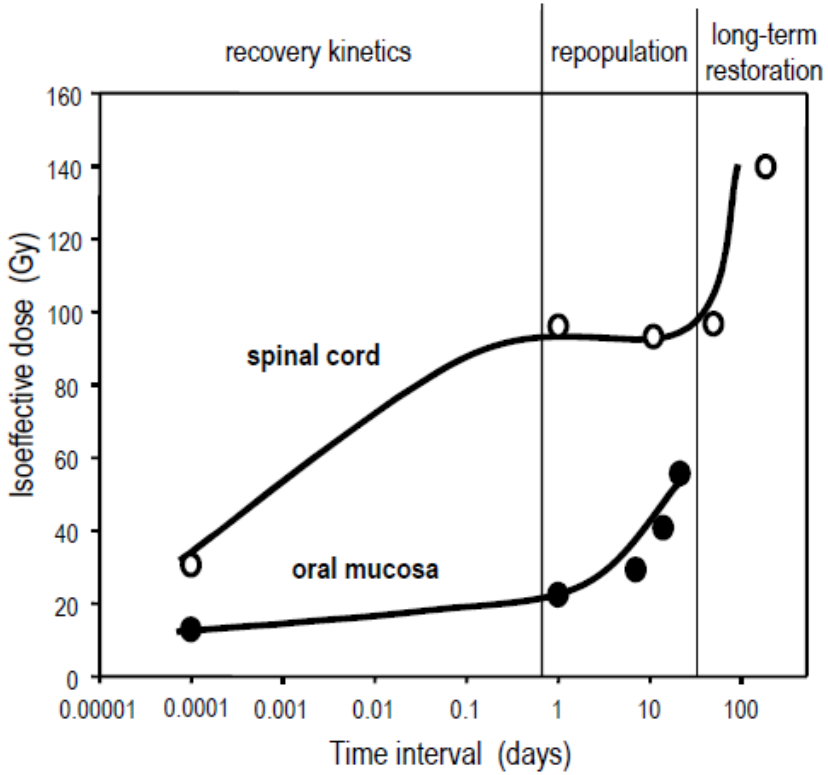
Normal tissue damage recovery

Another R……

Radiosensitivity
Recovery
Redistribution
Repopulation
Reoxygenation

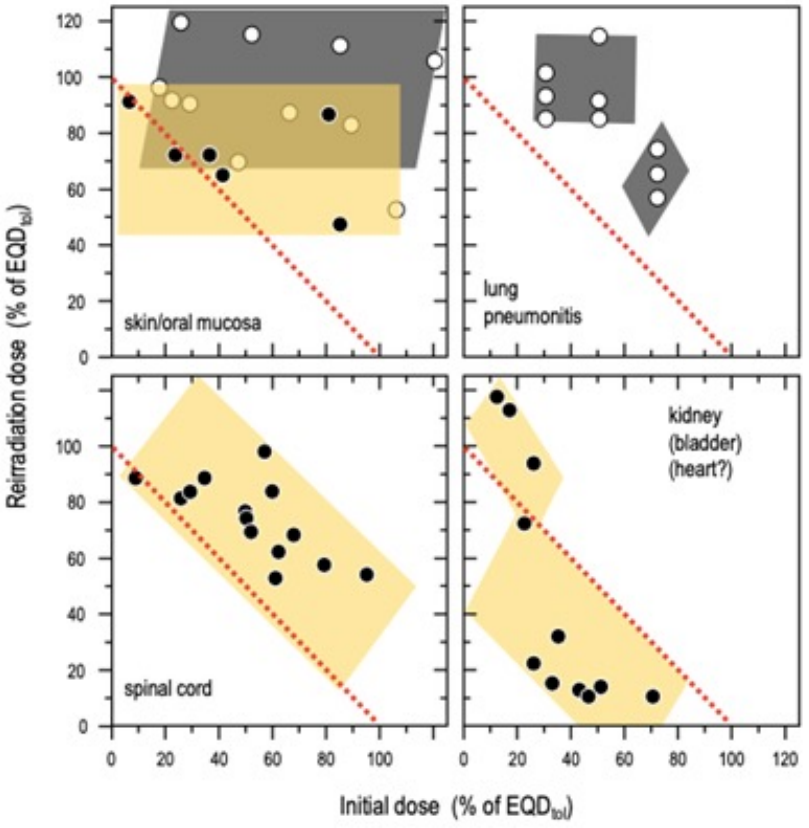
RESTORATION (long term recovery)

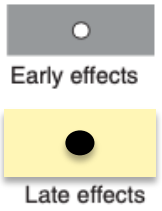
Changes in normal tissue tolerance with time



Long-term recovery from radiation injury in some tissues (not all!)

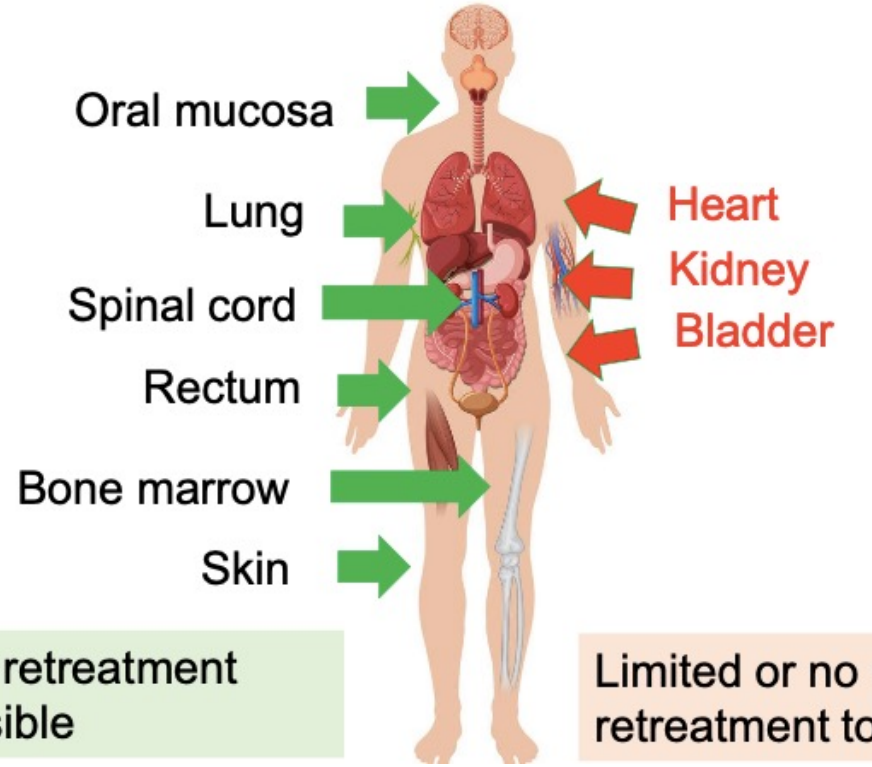
Several normal tissues can tolerate considerable retreatment with radiation





Experimental studies

Location – reirradiation tolerance



Restoration of retreatment tolerance possible

Limited or no restoration of retreatment tolerance possible

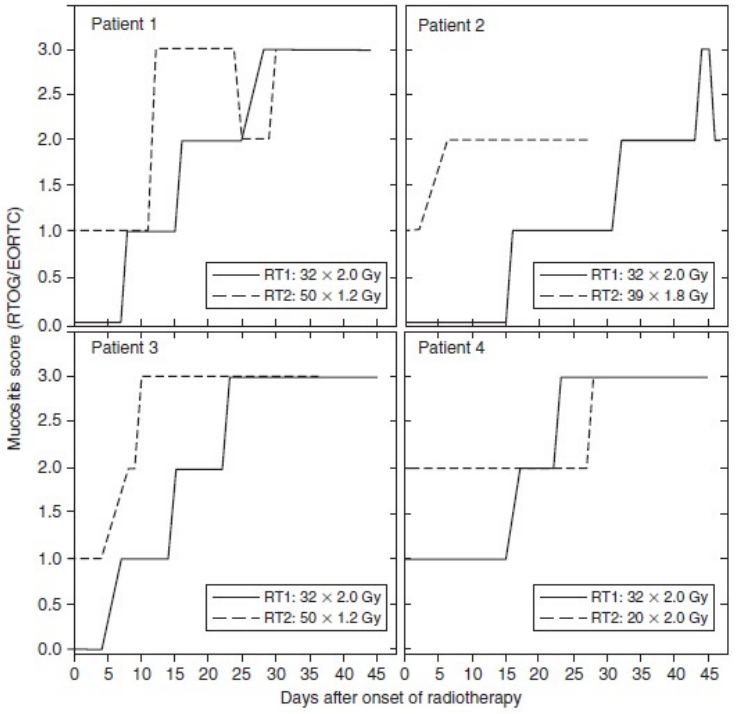
Clinical Data: Caution

- Extremely heterogeneous populations
- Curative and palliative intent in the same series
- Change in staging and radiotherapy technique
- Change in normal tissue scoring

Experimental animal system have been essential to understand the radiobiology of retreatment tolerance

Oral and oesophageal mucosa

Clinical scores of oral mucositis according to Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) for four patients during their first course of radiotherapy
(solid lines) and during re-irradiation (dashed lines).



Oral and oesophageal mucosa

Patients subject to reirradiation in the head and neck region after longer time interval of 2-3 years may present with mucosal erythema or even focal lesions, already before the start of the second radiotherapy course.

More severe mucosal reactions (confluent: G3) are frequently observed at earlier timr points after reirradiation than in the first radiation series

Brain

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S20–S27, 2010
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0360-3016/10/$–see front matter

doi:10.1016/j.ijrobp.2009.02.091

QUANTEC: ORGAN SPECIFIC PAPER **Central Nervous System: Brain**

RADIATION DOSE–VOLUME EFFECTS IN THE BRAIN

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We have reviewed the published data regarding radiotherapy (RT)-induced brain injury. Radiation necrosis appears a median of 1–2 years after RT; however, cognitive decline develops over many years. The incidence and severity is dose and volume dependent and can also be increased by chemotherapy, age, diabetes, and spatial factors. For fractionated RT with a fraction size of <2.5 Gy, an incidence of radiation necrosis of 5% and 10% is predicted to occur at a biologically effective dose of 120 Gy (range, 100–140) and 150 Gy (range, 140–170), respectively. For twice-daily fractionation, a steep increase in toxicity appears to occur when the biologically effective dose is >80 Gy. For large fraction sizes (≥2.5 Gy), the incidence and severity of toxicity is unpredictable. For single fraction radiosurgery, a clear correlation has been demonstrated between the target size and the risk of adverse events. Substantial variation among different centers' reported outcomes have prevented us from making toxicity–risk predictions. Cognitive dysfunction in children is largely seen for whole brain doses of ≥18 Gy. No substantial evidence has shown that RT induces irreversible cognitive decline in adults within 4 years of RT. © 2010 Elsevier Inc.

For conventional fractionation, risk of symptomatic RN :

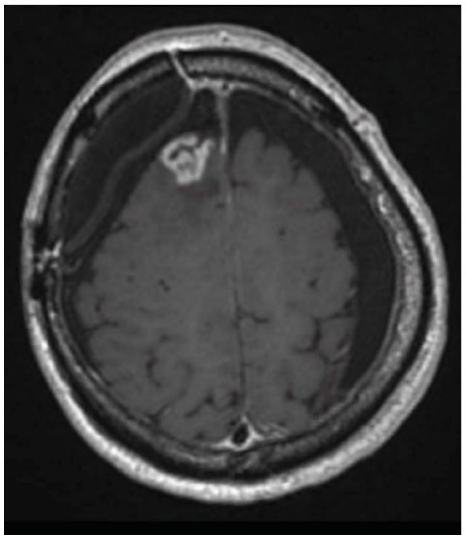
- 5% at BED of 72 Gy (range, 60–84 Gy)
- 10% BED of 90 Gy (range,84–102 Gy)

Brain

- Cumulative dose is the most important factor associated with RN

- A meta-analysis of brain re-RT (interval between courses, 3–55 months) found no cases of necrosis when the total radiation dose was <100 Gy (normalized to 2 Gy/fraction; α/βratio: 2)

- There was no correlation between the time interval between the radiation courses and the incidence of radionecrosis



Mayer et al, Int. J. Radiation Oncology Biol. Phys. (2008);

Brain – SRT/SRS

- the reported risk was about 0–3% after conventional fractionation at cumulative EQD2 < 101Gy
- 7–13% after hypofractionated SRT at cumulative EQD2 of 102–130 Gy
- up to 24.4% after SRS using a cumulative EQD2 of about 124–150 Gy

- No data are available on other end points, such as neurocognitive impairment

Minniti *et al. Radiat Oncol (2021)*

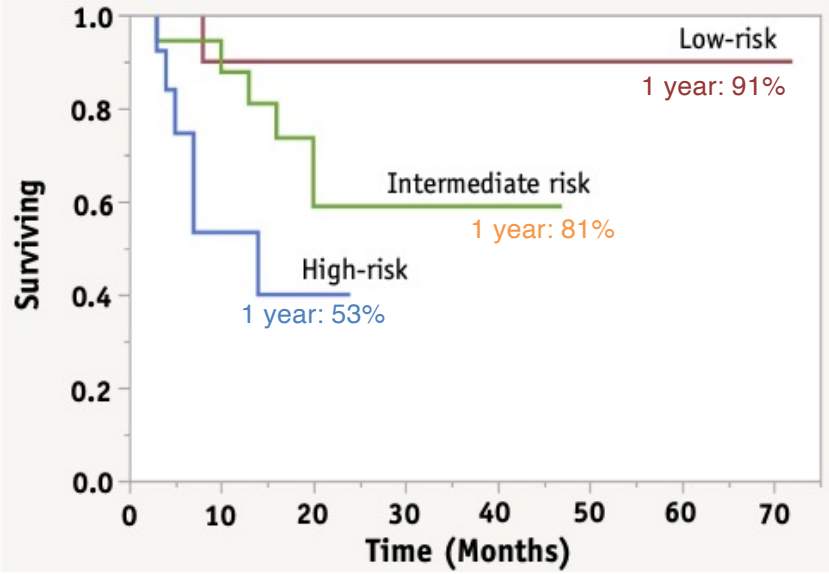
Brachial Plexus

43 pts (8 SBRT – 37 IMRT)

- Median re-RT dose: 66 Gy (EQD2)
- Median time 1 RT and re-RT: 24 months
- Median time to symptoms: 7 (2-16 months) after re-RT

Time interval between radiation courses and Dmax

- Low-risk: >2 years and Dmax <95 Gy
- Intermediate-risk: <2 years and Dmax >95 Gy; or >2 years and Dmax >95 Gy
- High-risk: <2 years and Dmax >95 Gy



Freedom from brachial plexus related neuropathy

Chen A et al, Int J Radiation Oncol Biol Phys, 2017

Spinal cord

- Spinal cord is the major dose-limiting organ in RT
- Radiation induced myelopathy is the most common catastrophic side effect of RT involving spinal cord
- The risk-benefit ratio is the most important point to be considered during re-RT
- Clinical data are very sparse in terms of toxicity and tolerance of spinal cord re-irradiation.

Spinal cord

Table 5. Risk groups for development of radiation myelopathy (number of patients with myelopathy/number of patients in the group)*

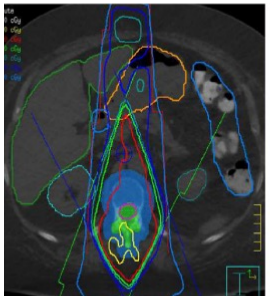
Group	Points	Myelopathy 2005 (1)	**Myelopathy updated**	% Myelopathy 2005 (1)	**% Myelopathy updated**
Low risk	≤3	0/24	**1/30**	0	**3**
Intermediate risk	4–6	2/6	**2/8**	33	**25**
High risk	>6	9/10	**9/10**	90	**90**

Risk factor	Characteristic	Points
Time interval	<6 months	4.5
	≥6 months	0
EQD2 for first or second course	≥51 Gy	4.5
EQD2 for both courses	<51 Gy	0
Cumulative EQD2, both courses	60.1–65 Gy	1
	65.1–70 Gy	2
	70.1–75 Gy	3
	75.1–80 Gy	4
	80.1–85 Gy	5
	85.1–90 Gy	6

The risk of myelopathy appears small after <135.5 Gy_2 when the interval is not shorter than 6 months and the dose of each course is <98 Gy_2

Nieder et al, 2005 – Nieder et al, 2006

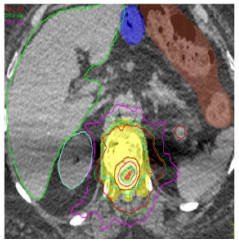
Spinal cord



- Recovery from initial damage is well established
- In general, a higher retreatment dose can be given following lower initial doses and longer intervals between treatments.
- From the sparse clinical and primate data, it appears that at least 50% recovery from 45Gy would be obtained 2 years after treatment

REIRRADIATION HUMAN SPINAL CORD TOLERANCE FOR STEREOTACTIC BODY RADIOTHERAPY

Arjun Sahgal, M.D.,* Lijun Ma, Ph.D.,† Vivian Weinberg, Ph.D.,‡ Iris C. Gibbs, M.D.,§ Sam Chao, M.D.,¶ Ung-Kyu Chang, M.D.,‖ Maria Werner-Wasik, M.D.,** Liliyanna Angelov, M.D.,¶ Eric L. Chang, M.D.,†† Moon-Jun Sohn, M.D.,‡‡ Scott G. Soltys, M.D.,§ Daniel Létourneau, Ph.D.,§§ Sam Ryu, M.D.,¶¶ Peter C. Gerszten, M.D.,‖‖ Jack Fowler, Ph.D.,*** C. Shun Wong,††† and David A. Larson.†



For safe practice after conventional radiotherapy of an nBED of 30–50 Gy2/2, we currently recommend

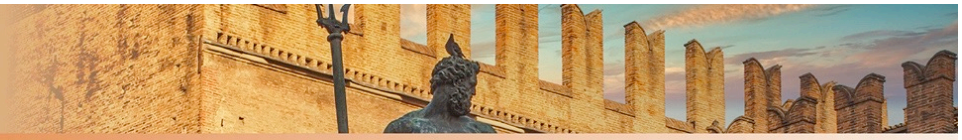
- a cumulative thecal sac EQD2 Dmax < 70 Gy2/2
- a SBRT thecal sac retreatment dose to the Pmax not exceeding 25 Gy2/2
- a thecal sac SBRT Pmax nBED/total Pmax nBED ratio not exceeding 0.5
- a minimum time interval to reirradiation of at least 5 months

Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 1, pp. 107–116, 2012

Radiation myelopathy following SBRT for spine metastases

Study	n	Prior cEBRT spinal cord Dmax		Duration from cEBRT to SBRT, months	SBRT reir-radiation pre-scribed dose, Gy/ fraction	SBRT spinal cord Dmax		Cumulative spinal cord Dmax $EQD2_2$, Gy	Duration from SBRT to RM, months
		Gy/ fraction	$EQD2_2$, Gy			Gy/ fraction	$EQD2_2$, Gy		
Sahgal[#], 2012 [26]	5	40/22	38.2	81	20/2	20.3/2	61.7	99.8	6
		25.2/28	18.3	70	21/2	20.9/2	65.1	83.3	5
		21.2/5	33.1	11	14/1	12.3/1	44.0	77.0	3
		51.9/28	50.0	18	33/3	32.6/3	104.9	154.9	18
		43.2/15	52.7	12	16/1	14.7/1	61.3	114.1	12
Ito, 2021 [27]	4	31.1/10	39.7	43	24/2	12.2/2	24.7	64.4	5
		32[$]/16	32.0	84	24/2	12.2/2	24.7	56.8	21
		4*/1 + 36.1/14	47.3	33	24/2	12.2/2	24.7	72.0	37
		4*/1 + 36.3/14	47.3	65	24/2	12.2/2	24.7	72.4	5

Ong et al, Journal of Neuro-Oncology (2022) 159:23–31



HyTEC Organ-Specific Paper: Spinal Cord

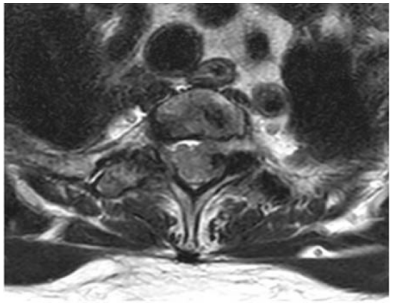
Spinal Cord Dose Tolerance to Stereotactic Body Radiation Therapy

Prior cEBRT		Recommended spinal cord# Dmax in 1–5 fractions, Gy				
Dose, Gy/ fractions	$EQD2_2$, Gy	1 fraction	2 fractions	3 fractions	4 fractions	5 fractions
0/0	0	12.4–14	17–19.3	20.3–23.1	23–26.2	25.3–28.8
20/5	30	9	12.2	14.5	16.2	18
30/10	37.5	9	12.2	14.5	16.2	18
40/20	40	N/A	12.2	14.5	16.2	18
45/25	43	N/A	12.2	14.5	16.2	18
50/25	50	N/A	11	12.5	14	15.5

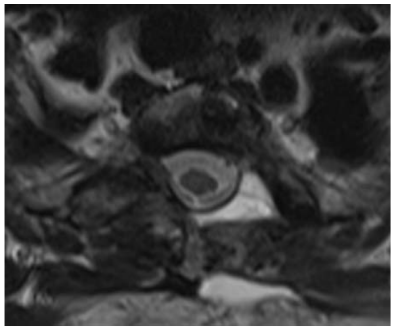
Sahgal A et al, Int J Radiat Oncol Biol Phys. 2021 May 1;110(1):124-136

Spinal Cord Reirradiation: Balancing Benefit Against Risks

- 58 yy
- BC Lum A, 20 years previously -> RT right chest wall + regional N (45Gy/25fx)
- 5 yy later bone mets (D1) -> RT C7-D3 (39.6 Gy in 1.8 Gy fractions)
- Tamoxifen for 10 yy + cyclophophamide, methotrexate, 5-FU > 10 yy ago and bisphosphonates until 3 years ago (stopped after jaw necrosis)
- thoracic spinal cord decompression (slight preoperative numbness in both arms caused by thoracic spine cord compression), including a left hemilaminectomy of the thoracic vertebrae 1 to 3 and remaining tumor at the left and right nerve roots Th1/2 and Th 2/3.
- DFS > 15 years since initial diagnosis of the metastasis

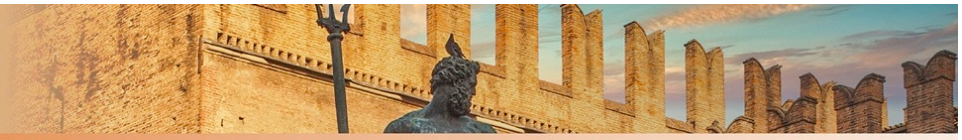


Preoperative T2-weighted axial magnetic resonance imaging.



Postperative T2-weighted axial magnetic resonance imaging.

Int J Radiation Oncol Biol Phys, Vol. 109, No. 2, pp. 312–313, 2021



1. Radiate Once More:

- 41.4 Gy in 23 fractions, 1.8 Gy/fx with no concomitant radiosensitizer (Sum after 3 courses: EQD2 79.5 Gy)
- Treatment volume: D1-D3

2. Postoperative SBRT then observe:

- 24 Gy in 2 fractions or 35 Gy in 5 fractions, a total thecal sac maximum point EQD2 of 70 Gy2/2.
- Treatment volumes: entire extent of the pre- and postop disease + the adjacent anatomic segment

3. Cautious SBRT:

- The most adopted schedule is 24 Gy in 2 fx,
- PTV= GTV+2mm, posteriorly, PTV=GTV approach should be considered to reduce the dose to the spinal cord,

Pelvic SBRT re-irradiation

Conservativ approach

Less conservativ approach

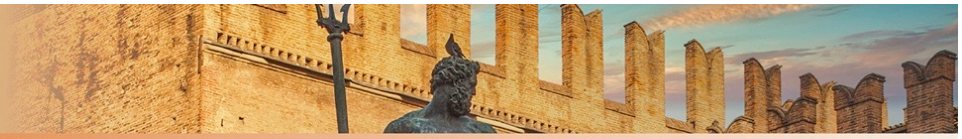
OAR		Abusaris [14]	Smith [17]	Paradis* [16]	AAPM* [15]		
Conservative approach, based on use of a traditional constraint in a cumulative manner (may prevent delivery of meaningful re-irradiation dose in some circumstances)							
Bladder	Constraint (no recovery;	-	–	85 Gy	80 Gy		AAPM constraints used
							mandatory constraints for use after at least 12 month interval in statements above)
Colon/Colon_Sigmoid/ Rectum	(includes additional recovery where appropriate) Cumulative constraint (includes additional recovery where appropriate)	110 Gy	110 Gy	91.5 Gy	91.4 Gy	102.2 Gy	101 Gy

35. The degree of recovery of Bladder after radiotherapy is uncertain but if 12 months or more have elapsed it is reasonable to assume some recovery and the Bladder may receive up to a maximum cumulative EQD2 of 110 Gy_3 to 0.5 cc

38. Optimally, the CaudaEquina/SacralPlex should receive no more than a cumulative dose of 67 Gy_2 EQD2 to 0.1 cc (assuming no recovery)

ary of published nstraints: n cumulative EQD2 to 0.5 cc OAR is shown based on first treatment of 45 Gy in 25 fractions 2 Gy3) ut allowance for

Slevin F et al, Radiotherapy and Oncology (2021)



Second re-irradiation: Efficacy, dose and toxicity in patients who received three courses of radiotherapy with overlapping fields

Huda Abusaris *, Pascal R.M. Storchi, Rene P. Brandwijk, Joost J. Nuyttens

		No. of patients	%
Primary tumor	Rectum	13	57
	Breast	3	13
	Lung	2	9
	Cervix	2	9
	Sarcoma	2	9
	Anal	1	4
Re-irradiation region	Pelvis	14	61
	Thoracic wall	6	26
	Intra-thoracic	2	9
	Head	1	4

For re-irradiation of the organs at risk, the maximum dose was set as 50% more than the normal constraint if the interval was at least of 12 months.

No patients with grade 4 acute and late toxicity

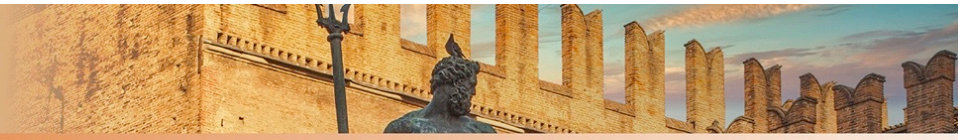
Taking into account the time between the radiation courses, the constraints of:

- 100 Gy3 for rectum
- 90 Gy3 for bowel
- 110 Gy3 for bladder

are safe and can be used as guidelines in the decision for re-irradiation

Delivery: technique

- Reports of safe SBRT reirradiation are increasing across several sites
- Protons is a notably safe re-irradiation modality for effective salvage of recurrent disease



Clinical Oncology 32 (2020) 688–703

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Complex Clinical Decision-Making Process of Re-Irradiation

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Recovery and Tolerance of the Organs at Risk during Re-irradiation

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Conclusions

- Re- irradiation is an option for selected patients with recurrent or second primary tumours
- Therapeutic window is narrow
- If tolerance has already been exceeded: no re-irradiation possible without loss of function
- Sometimes relevant or fatal side effects
- Population based dose constraints replaced by personalized information based on predictive models