Development of in-house clinical guidelines for re-irradiation of spinal cord

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Background

- SLH pts with previous RT to cord – re-treat for bone mets/MSCC
- Eg., MSCC Trial: 17% pts had previous tx to same area of cord
- Wide range of schedules for initial tx
- Re-treat schedules: no set guidelines
- Re-treat to tolerance - EQD2 model used (50Gy/25#) *Interval and recovery not included*

- Purpose – to establish re-treatment guidelines for in-house use

Re-irradiation - warranted

- Pain relief bone mets - response rate 84% initial, 87% re-treat, 87.5% 2nd re-treat [Mithal et al 1994]

- MSCC - improvement of pain in majority; effect on ambulation - dependent on ambulatory status at pres [Schiff et al 1995]

Spinal Cord Tolerance

- BED – Biologically effective dose: Calculated using LQ model, α/β value of 2Gy, expressed in Gy_2 [Fowler 1989]

  $BED = nd\{1+d/(\alpha/\beta)\}$

  n = no of fractions
  d = dose per fraction

- BED of $100Gy_2$ accepted for spinal cord tolerance [Wong et al 1994; Rades et al 2005]
- Risk of RIM estimated at <0.5% for BED $100Gy_2$ (50Gy/25#) [Wong et al 1994]

Re-irradiation - influence of previous RT

- Re-treatment fractionation sensitivity not altered by previous RT for late reacting tissue [Stewart et al 1989;Ruifrok et al 1992]
- Size of initial injury does not influence % recovery – dependent only on time interval [Wong et al 1997]

Recovery of spinal cord

- Rodents: Recovery from 8 weeks onwards – 43% recovery by 20 weeks (Wong et al 1993); 45% recovery at 6mths [Ruifrok ACC, Kleiboer BJ, van der Kogel AJ 1992]
- Primates: Most conservative estimation 61% at 1yr [Ang et al 2001]
- Humans: estimated at 50% at 1yr, 60% at 2yrs, 65-70% >3yrs [Ang et al 2001]

Re-irradiation - risk of RIM

- Latency for development of RIM - single course mean = 18.5mths; re-irradiation mean = 11.4mths

  Risk of RIM associated with exceeding tolerance or mult fractions/day (single) *or* mean BED 148Gy_2 (re-treats)
  [Wong et al 1994]

Re-irradiation – Cumulative BED

- Cumulative BED 130Gy$_2$ to 135Gy$_2$: acceptable *if initial dose does not exceed 90Gy$_2$* [Nieder C, Milas L, Ang KK 2000]
- Cumulative BED 125Gy$_2$ to 205Gy$_2$: minimal risk for patients with reduced life expectancy [Grosu 2002]
- Cumulative BED ≤135Gy$_2$: minimal risk when interval <u>not shorter than 6mths</u> and each course ≤98Gy$_2$ [Nieder et al 2005]

Guidelines - BED calculations

- BED calculated for each schedule used in SLH for initial RT using α/β value of 2Gy (late responding tissue)
- Isoefficiency calculated for each schedule used in SLH for initial RT using α/β value of 10Gy (acute effects)

Guidelines - Interval ≤6mths

- Safe cumulative BED ≤ 100Gy2

In order to re-treat patients who received 17Gy/2# this limit must be exceeded

Guidelines - Interval ≥6mths

- Acceptable cumulative BED

  $\geq 100Gy_2 \leq 120Gy_2$

- Upper limit cumulative BED*

  $\geq 120Gy_2 \leq 130Gy_2$

*Note: for use only when initial treatment <90% of safe BED ie., $90Gy_2$

Guidelines - 17Gy/2#

- These patients have already reached the 90% safe BED ceiling.

- Re-treatment using *10Gy/4# or 12Gy/4#* will result in cumulative BED ≤120Gy$_2$, which is acceptable.

  Schedules exceeding this are not recommended.

Guidelines - 30Gy/10#

- Even with interval >6mths, re-treatment schedules resulting in cumulative BED $\leq 120 Gy_2$ are recommended.
- Upper limit BED to be applied with caution.

Application

- **<u>One previous schedule</u>:** Determine interval since RT and select an appropriate re-treatment schedule from the interval-dependent options

  - **<u>Two or more previous schedules</u>:** Determine interval since *<u>most recent</u>* RT; calculate the BED given to date; select an appropriate re-treatment schedule in line with the interval-dependent cumulative BED limit

    - May also assist with schedule selection for initial RT - isoefficiency/options remaining

Guidelines & Reference Table

SLH – IN-HOUSE GUIDELINES FOR RE-TREATMENT OF SPINAL CORD

NB: Cumulative BED limits include current schedule.

Cumulative BED Š CONSERVATIVE LIMIT (100Gy_2)

- The maximum cumulative BED, which may be prescribed without risk of RIM is 100Gy_2. For example, patients who initially received a BED ² 40Gy_2 may be safely re-treated with a further BED ² 60Gy_2 to the same area of spinal cord.

- This cumulative BED limit is conservative and does not take into account any spinal cord repair that may have occurred in the interval since initial treatment.

Cumulative BED Š UPPER LIMIT (130Gy_2)

- In some cases, it may be necessary to exceed a cumulative BED of 100Gy_2 in order to re-treat, regardless of interval. For example, patients who initially received 17Gy/2# will automatically exceed the conservative BED limit if the same area is re-treated.

- Re-treatment within the cumulative BED range of 100Gy_2 to 120Gy_2 is considered acceptable, while evidence exists in the literature to suggest that a cumulative BED of 130Gy_2 to 135Gy_2 may be reached without adverse effect, *if* the initial dose given did not exceed 90% of the safe BED i.e., 90 Gy_2.

GUIDELINES

1. **RE-TREATMENT where the INTERVAL SINCE INITIAL RT ² 6 MONTHS:**
   Wherever possible, apply the conservative cumulative BED limit of 100Gy_2. It is not possible to apply this limit if patients initially received 17Gy/2# - see guideline 3.

2. **RE-TREATMENT where the INTERVAL SINCE INITIAL RT ³ 6 MONTHS:**
   Re-treatment within the BED range of 100Gy_2 to 120Gy_2 is acceptable. The upper cumulative BED limit of 130Gy_2 may be applied, at the discretion of the prescriber.
   EXCEPTION: see guidelines 3 & 4.

3. **RE-TREATMENT for all patients INITIALLY TREATED WITH 17Gy/2#:**
   These patients have already reached the 90% of initial safe BED ceiling. Re-treatment using 10Gy/4# or 12Gy/4# will give a cumulative BED of ² 120Gy_2 which is acceptable. *Schedules exceeding this are not recommended for this subgroup of patients.*

4 **RE-TREATMENT for all patients INITIALLY TREATED WITH 30Gy/10#:**
   Schedules approaching the upper BED limit of 130Gy_2 should be used *with caution* for this subgroup of patients. Even with an interval ³ 6 months, a schedule resulting in a cumulative BED of ² 120Gy_2 is recommended.

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SLH – SPINAL CORD RE-TREATMENT REFERENCE TABLE: (See overleaf for guidelines & instructions for use of table)

PREVIOUS RT SCHEDULE	BIOLOGICALLY EFFECTIVE DOSE (BED) $\alpha/\beta = 2$*	ISOEFFICIENCY $\alpha/\beta = 10$**	INTERVAL ≤ 6 MTHS	INTERVAL ≥ 6 MTHS	
			SAFE CUMULATIVE BED (*inc curr tx*) ≤100Gy_2	*ACCEPTABLE* CUMULATIVE BED (*inc curr tx*) ≥100Gy_2 ≤120Gy_2	*UPR LIMIT* CUMULATIVE BED (*inc curr tx*) ≥120Gy_2 ≤130Gy_2
			(1) RE-TREAT OPTIONS Select from below according to PREVIOUS RT SCHEDULE	**(2) RE-TREAT OPTIONS** Select from (1) *or* from additional options below	**(3) RE-TREAT OPTIONS** As for (2) *or* select from upper limit options below
6Gy/1#	**24Gy_2**	**9.6Gy_{10}**	6/1, 8/1, **10/1**, 10/4 12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, 20/4, **20/5**, 20/10, 25/10, 30/10	17/2	-
8Gy/1#	**40Gy_2**	**14.4Gy_{10}**	6/1, 8/1, **10/1**, 10/4,12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, **20/5**, 20/10, 25/10	20/4, 30/10	17/2
10Gy/1#	**60Gy_2**	**20.0Gy_{10}**	6/1, 8/1, 10/4, 12/3, 12/4, 15/6, 16/8, 20/10	10/1,12/2, 15/3, 16/4, 20/5, 25/10	20/4
10Gy/4#	**22.5 Gy_2**	**12.5Gy_{10}**	6/1, 8/1, **10/1**, 10/4, 12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, 20/4, **20/5**, 20/10, 25/10, 30/10	17/2	-
12Gy/2#	**48Gy_2**	**19.2Gy_{10}**	6/1, 8/1, 10/4, 12/2, 12/3, 12/4, 15/6, 16/4, 16/8, 20/10	10/1, 15/3, 20/4, 20/5, 25/10	30/10
12Gy/3#	**36Gy_2**	**16.8Gy_{10}**	6/1, 8/1, **10/1**, 10/4, 12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, **20/5**, 20/10, 25/10	20/4, 30/10	17/2
12Gy/4#	**30Gy_2**	**15.6Gy_{10}**	6/1, 8/1, **10/1**, 10/4, 12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, 20/4, **20/5**, 20/10, 25/10	17/2, 30/10	-
15Gy/3#	**52.50Gy_2**	**22.5Gy_{10}**	6/1, 8/1, 10/4, 12/3, 12/4, 15/6, 16/8, 20/10	10/1, 12/2, 15/3, 16/4, 20/5, 25/10	20/4, 30/10
15Gy/6#	**33.75Gy_2**	**18.75Gy_{10}**	6/1, 8/1, **10/1**, 10/4, 12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, **20/5**, 20/10, 25/10	20/4, 30/10	17/2
16Gy/4#	**48Gy_2**	**22.4Gy_{10}**	6/1, 8/1, 10/4, 12/2, 12/3, 12/4, 15/6, 16/4, 16/8, 20/10	10/1, 15/3, 20/4, 20/5, 25/10	30/10
16Gy/8#	**32Gy_2**	**19.2Gy_{10}**	6/1, 8/1, **10/1**, 10/4, 12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, **20/5**, 20/10, 25/10	20/4, 30/10	17/2
17Gy/2#	**89.25Gy_2**	**31.45Gy_{10}**	**NO OPTIONS**	10/4, 12/4	**LIMIT NOT RECOMMENDED**
20Gy/4#	**70Gy_2**	**30.0Gy_{10}**	10/4, 12/4	6/1, 8/1, 12/2, 12/3, 15/6, 16/4, 16/8, 20/10	10/1, 15/3, 20/5, 25/10
20Gy/5#	**60Gy_2**	**28.0Gy_{10}**	6/1, 8/1, 10/4, 12/3, 12/4, 15/6, 16/8, 20/10	10/1, 12/2, 15/3, 16/4, 20/5, 25/10	20/4
20Gy/10#	**40Gy_2**	**24.0Gy_{10}**	6/1, 8/1, **10/1**, 10/4, 12/2, 12/3, 12/4, 15/3, 15/6, 16/4, 16/8, **20/5**, 20/10, 25/10	20/4, 30/10	17/2
25Gy/10#	**56.25Gy_2**	**31.25Gy_{10}**	6/1, 8/1, 10/4, 12/3, 12/4, 15/6, 16/8, 20/10	10/1, 12/2, 15/3, 16/4, 20/5, 25/10	20/4
30Gy/10#	**75Gy_2**	**39.0Gy_{10}**	10/4	6/1 8/1, 12/3, 12/4, 15/6, 16/8 20/10	**CAUTION:** 12/2, 15/3, 16/4

BED = $nd\{1 + (d/\alpha/\beta)\}$ Where n = no of fractions; d=dose/fraction *α/β for spinal cord = 2 Gy (ratio for late effects) **α/β = 10 Gy (ratio for acute effects)

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Thank you for your attention

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