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Scientific Article

Practical Clinical Implementation of the Special Physics Consultation Process in the Re-irradiation Environment

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Abstract

Purpose: The purpose of this work is to present a practical, structured process allowing for consistent, safe radiation therapy delivery in the re-treatment environment.

Methods and materials: A process for reirradiation is described with documentation in the form of a special physics consultation. Data acquisition associated with previous treatment is described from highest to lowest quality. Methods are presented for conversion to equieffective dose, as well as our departmental assumptions for tissue repair. The generation of organ-at-risk available physical dose for use in treatment planning is discussed. Results using our methods are compared with published values after conversion to biologically effective dose. Utilization of pulsed-low-dose-rate delivery is described, and data for reirradiation using these methods over the previous 5 years are presented.

Results: Between 2015 and 2019, the number of patients in our department requiring equieffective dose calculation has doubled. We have developed guidelines for estimation of sublethal damage repair as a function of time between treatment courses ranging from 0% for <6 months to 50% for >1 year. These guidelines were developed based on available spinal cord data because we found that 84% of organs at risk involved nerve-like tissues. The average percent repair used increased from 32% to 37% over this time period. When comparing the results obtained using our methods with published values, 99% of patients had a cumulative biologically effective dose below the limits established for acceptable myelopathy rates. Pulsed-low-dose-rate use over this period tripled with an average prescription dose of 49 Gy.

Conclusions: The methods described result in safe, effective treatment in the reirradiation setting. Further correlation with patient outcomes and side effects is warranted.

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Introduction

Since 1975, the cancer death rate in the United States has decreased by 21.9% with a 15% decrease from 2007 to 2017.[1,2] Although improvements in treatment are prolonging the lives of patients, the additional time may result in an increased risk of developing additional

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disease. Over the last 5 years, 27% of all patients undergoing external beam radiation therapy (RT) at our institution were treated with at least a second course of RT. The reasons for additional treatment include recurrence, metastasis, secondary malignancies, or new disease. Unfortunately, normal tissue structures may receive dose from multiple treatment courses and are at risk of exceeding tolerance. It is imperative that the established dose-volume limits for critical structures be maintained to avoid unwanted sequelae. The evaluation of structures receiving dose from >1 treatment course requires careful consideration with respect to total dose, factional dose, potential response (early or late), and potential repair between courses. Paradis et al presented a very thorough methodology as implemented by a large academic institution for using the special physics consultation to address issues associated with patients undergoing reirradiation.[3] Their emphasis on consistent structure is key to providing safe, effective treatments for these patients.

Herein, we present a practical, structured process allowing consistent, safe delivery of RT in the re-treatment environment that is applicable in departments of any size. In addition, we discuss the use of pulsed-low-dose-rate (PLDR) RT for re-treatment patients.

Methods and materials

The first and often only individual with knowledge of a patient's previous irradiation is the attending physician. It is incumbent on this physician to convey this information to the appropriate RT personnel to avoid potential unwanted issues due to excessive irradiation of organs at risk (OARs). In our department, this physician fills out a Special Physics Consultation Request form at the time of simulation and preferably at the time of simulation scheduling when the associated orders are placed. This form was designed so the physician simply checks off the reason(s) for the intended consultation, among which "Evaluation of Previous Treatment" is included. This request is forwarded by departmental billing personnel to the physicist in charge of this service.

Special physics consultation to evaluate previous treatment

Process: Before generation of current treatment plan

For patients previously treated at our institution, the physician indicates the patient name, medical record number, anatomic region, and date of previous treatment. The physician also indicates the intended current treatment region, total dose and fractionation, and potential OARs and acceptable dose limits if they differ from departmental standards. For patients treated at an outside institution, this information along with treatment record receipt status, inclusion of digital data, area, and dates of treatment are forwarded to the appropriate physicist by the physician or his or her designee.

Upon review, the region(s) of potential overlap can be assessed. Previous treatment doses are converted to equivalent dose at 2 Gy per fraction (EQD2) using the following well known relationship:

$$EQD2 = D[(d + (\alpha/\beta)) / (2 + (\alpha/\beta))]$$

where D is total physical dose, d is fractional dose to the tissue region of interest, and α/β is the dose at which cell killing by the linear (α) and quadratic (β) components are equal on the dose response curve, based on the linear quadratic (LQ) model.[4] The usefulness of the EQD2 formulation is the fact that resultant doses are additive (on the same scale and therefore summable) and routinely used OAR dose limits at conventional fractionation are applicable. The endpoints for evaluation (ie, maximum dose, near maximum doses such as dose to 0.03cc, or volumetric limits) are discussed with the physician to conform to our routine, site-specific plan acceptance criteria.

The maximum or near-maximum dose to structures can be determined and converted to an EQD2. To account for potential sublethal damage repair over the time between treatment courses, a percentage repair factor is applied. Repair values are typically expressed for fraction sizes of 2 Gy; thus, repair is taken into account after conversion to EQD2. When applying repair to physical dose (D), it must be applied to the fractional dose (d) as well to ensure equivalency in the above equation. By subtracting the resultant EQD2 from the structure's dose limit for that volume (ie, maximum) and applying the physician's intended current course number of fractions, the equation can be solved for the available physical dose (D in this case). These calculations are easily performed with a simple spreadsheet. Of note, we frequently compare our spreadsheet results with manual calculations to prevent error propagation.

The available physical dose is forwarded to the physician for approval and use by the planner. Most treatment planning systems (TPS) display physical dose (not EQD2); thus, the dose from the previous course and the current course needs to be converted to EQD2 and summated. Although it is equally valid to convert the doses to biologically effective dose (BED), for convenience and consistency, we have used EQD2 in our practice. If the resultant summed EQD2 exceeds OAR tolerance, the current treatment plan must be reformulated to reduce the OAR dose, converted to EQD2, and summed with the course 1 value again. This process is repeated until an acceptable EQD2 value for each OAR is achieved. Having the available physical dose values for OAR limits makes planning much less iterative. Table 1 illustrates a portion of this process that is forwarded to the planner. Note that we have assumed the coincidence of the voxels containing the maximum or near-maximum

Table 1 Example of available physical dose derivation

Previous dose, Gy	EQD2, Gy	Repair, %	EQD2 with repair, Gy	Available EQD2, Gy	Available physical dose, Gy
27.50	31.63	50	15.81	34.19	**28.98**

Abbreviation: EQD2 = equivalent dose at 2 Gy per fraction.
Assume the patient had received 30 Gy in 10 fractions (27.5 Gy to the organ at risk) 21 months before the current course. The intended dose for the current course is 30 Gy in 10 fractions. The organ-at-risk limit is 50 Gy (maximum) and the α/β value used is 3 Gy. Note that the available physical dose is what is seen on the treatment planning system.

doses between the 2 plans, which may appear in different locations in reality.

Previous treatment data collection

Information pertaining to a patient's previous treatment at an outside institution comes in many forms and may be affected by the time between courses. A hierarchy of information sources from most to least preferable is given below.

Digital Imaging and Communications in Medicine data

Typically, data include the planning computed tomography (CT) scan, treatment plan, dose, and structure set in Digital Imaging and Communications in Medicine format. These data can be entered into the TPS and fused to the current planning CT. This allows for an estimate of dose summation between treatment courses with the least spatial uncertainty in the overlap region(s). At our institution, rigid registration is routinely performed based on bony anatomy for intracranial tumors or treatments near bony structures. The commercial software system (Velocity, Varian Medical Systems, Inc.) used at this center was validated for rigid registration per American Association of Physicists in Medicine Task Group report 132.[5]

Deformable registration is used with caution when appropriate, especially for regions with large motion or deformation effects. In both scenarios, uncertainties are discussed with the physician. Of note, the overlap region in an OAR should be delineated after image fusion. This allows for the contribution of both previous and current treatments to be assessed independently for final summation of EQD2 as fractional dose, and potential repair to this region will almost certainly differ between plans. It is of note that the summated EQD2 may be less than predicted in the preplanning example explanation above because this assumes a worse-case-scenario, and actual voxels containing the maximum or near-maximum doses between plans may not coincide. Information concerning the image guidance technique(s) used during the first course of treatment (eg, alignment to bony anatomy or soft tissue) may influence image fusion to the current data set. Depending on the anatomic site and potential structure motion, additional uncertainties can be approximated. The use of planning OAR volumes can add an additional level of conservatism where appropriate.

Printed data

These data typically include multiplane isodose distributions, dose-volume histograms, and treatment planning/delivery data including beam directions and field sizes. For complex delivery, such as intensity modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), the appropriate data are extracted from these dose distributions or dose-volume histograms and applied as a worse-case-scenario. For 3-dimensional conformal RT plans, it is often possible to reconstruct the plan on the current planning CT scan and regenerate dose distributions using local TPS-defined machines of the same energy. This can be an alternative for centers without advanced image fusion and dose summation software. This will result in decreased uncertainty associated with image fusion but may introduce uncertainties due to changes in body habitus.

Referring physician notes

If digital or printed data are not available, information may be extracted from the referring physician's end-of-treatment notes. This will almost certainly be limited to total dose and fractionation, region treated, and possibly treatment technique. Physician notes are unlikely to include OAR doses. In this scenario, the physician and physicist can estimate the dose believed to have been received from previous treatment(s). If the OAR was within the full-dose region, an estimate of dose heterogeneity or hot spot can be made based on treatment technique used.

Information from the patient

Sometimes no digital or printed data are available; however, patients will indicate that they were treated for a particular disease at a particular time. The total dose or fractionation will likely not be known accurately, and the physician and physicist may use the standard of care for the time when the patient was treated to estimate dose heterogeneity.

Process: After generation of current treatment plan

During treatment plan generation, the planner uses the available physical dose document for OAR dose limits. Using IMRT/VMAT techniques is often useful to meet

these criteria. Upon approval, the physicist generates a complete special physics consultation to evaluate previous treatment (SPC_{PrevTx}) document, including available physical dose information and assumptions made with respect to α/β ratio and percentage repair for OARs. Summation of the physical dose to the endpoint of interest and EQD2 with/without repair are recorded and provided to the physician for approval.

Pulsed low-dose-rate radiation therapy

When a low effective or apparent dose rate is achieved, repair of sublethal damage is possible, resulting in the dose-rate effect. This effect is most evident between 0.01 and 1 Gy/min,[6] Additionally, many human cell lines exhibit increased radiosensitivity to doses <0.3 to 0.5 Gy, known as low-dose hyperradiosensitivity.[7-9] Richards et al combined these effects during reirradiation by delivering 0.2 Gy pulses separated by 3-minute intervals to take advantage of low-dose hyperradiosensitivity in tumor cells and sublethal repair in normal tissues.[10] PLDR or pulsed-reduced-dose-rate RT is an external beam technique where a fractional dose is delivered in smaller increments, arrived at by dividing each fraction into smaller subfractions (pulses) given over discrete time intervals. We use the PLDR delivery technique in the re-treatment setting and have adapted it to IMRT/VMAT delivery.[11] Of note, regardless of the intended total dose prescribed, a fractional dose of 1.8 to 2 Gy is used at this institution. This fractional dose was used to acquire our clinical experience and limits overall daily delivery time to approximately 30 minutes.

Results

Figure 1 illustrates that the number of re-treatment patients requiring equieffective dose calculation as a function of year has doubled since 2015. This figure also illustrates the number of re-treatment patients for whom PLDR was used. This number has increased by a factor of 3 since 2015 with a mean PLDR total dose of 49 Gy being prescribed in excess of the patient's initial treatment course(s).

Table 2 illustrates our rules for application of percentage repair for OARs during the evaluation of EQD2 reflective of time between courses. These rules are for guidance purposes as percentage repair is discussed with the physician on a case-by-case basis. In general, we follow the repair rules given; however, there are times when a physician may choose to add additional levels of conservatism, typically by choosing 25% repair when the time between courses would indicate 50%. A number of factors affect the choice of therapy in the reirradiation setting. The relative aggressiveness of the dose or size of the volume to be treated must be balanced against the potential for harm from the therapy. If a patient has additional nonsymptomatic, metastatic cancer that is not being treated, then a less aggressive path should be taken. Similarly, if a patient has comorbidities that constitute a

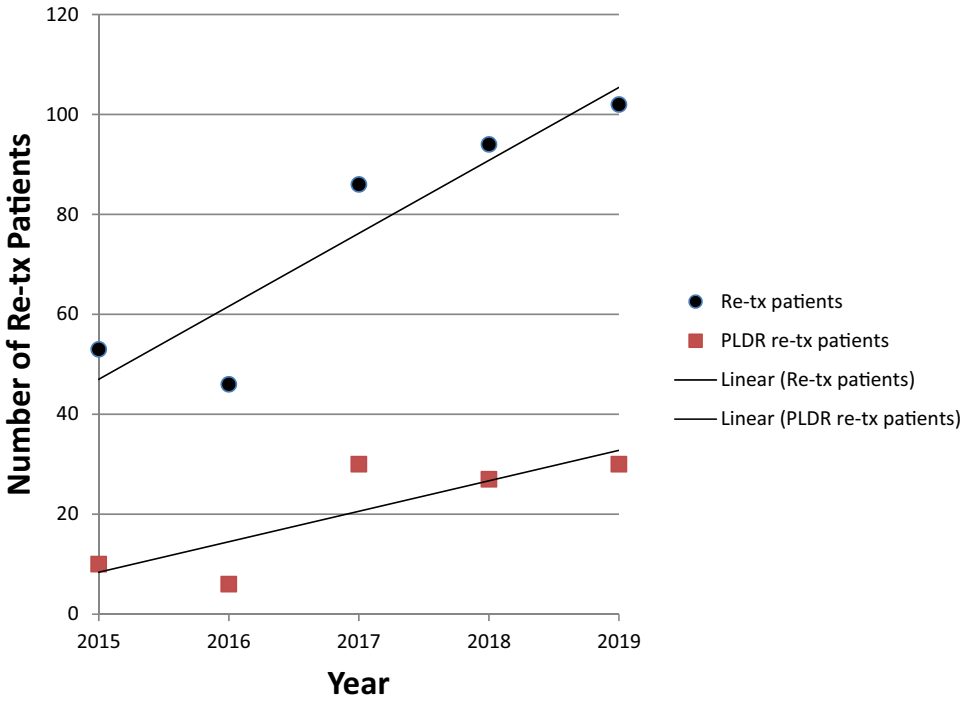

Figure 1 Re-treatment patients per year requiring evaluation of equivalent dose at 2 Gy per fraction and pulsed-low-dose-rate delivery.

Table 2 Percentage repair applied to calculations of equivalent dose at 2 Gy per fraction

	<6 mo	6 mo to 1 y	>1 y
Repair, %	0	25	50

significant competing risk of death, there is less incentive to expose the patient to substantial risk of toxicity from the radiation. However, if the treated region represents the only site of disease (local or distant), the goal of durable control may be worth a higher risk of toxicity. This balance always includes the local anatomy and radiation tolerance of surrounding structures, as well as the dose administered in the initial versus re-treatment setting.

These repair data were derived primarily from spinal cord reirradiation recommendations in the QUANTEC study: "For reirradiation of the full cord cross-section at 2Gy per day after prior conventionally fractionated treatment, cord tolerance appears to increase at least 25% 6 months after the initial course of RT based on animal and human studies."[12] This value for increase in cord tolerance, or repair, has been extrapolated to other structures due to the limited repair data availability. For structures that exhibit little or no repair or even progressive damage after irradiation, such as the bladder, kidneys, and heart, a repair factor should not be considered.[13-17]

Figure 2 illustrates the average time between treatment courses for patients over this period, as well as the average percentage repair assumed during calculation of EQD2. If the summated EQD2 does not exceed our clinical tolerance value, percentage repair is not applied regardless of the time between courses. This process results in a worst-case scenario with respect to the available physical dose initially conveyed to the planner and hopefully leads to increased conformity and critical structure sparing. For these cases, a statement such as "Note, no correction for time between the previous and current treatment regimes has been made" is added to the SPC_{PrevTx}. Of note, for the correlation with outcomes, repair needs to be applied and doses calculated according to the rules in Table 2.

Figure 3 illustrates the frequency the listed OARs were of interest over the 5-year period. Approximately 84% of cases during this period involved nerve-type tissues (ie, spinal cord, brachial plexus, brain stem, cauda equina, sacral plexus, optic nerves, optic chiasm), which helps support the use of the listed repair rates.

Discussion

The increase in patients receiving a second course of RT (Fig 1) may be attributed to multiple factors. With advanced therapies, patients may live longer than in the past. The implementation of advanced treatment techniques, such as IMRT, VMAT, stereotactic body RT, and PLDR, along with the structured evaluation methods described, may give the physician added confidence in offering additional RT in a safe, reproducible manner. This confidence may explain the decreasing average time between courses demonstrated in Figure 2. A second or third course of RT in a potential overlap region may not have been offered in the past. In addition, percentage repair applied to previously delivered doses is increasing toward our maximum value of 50%.

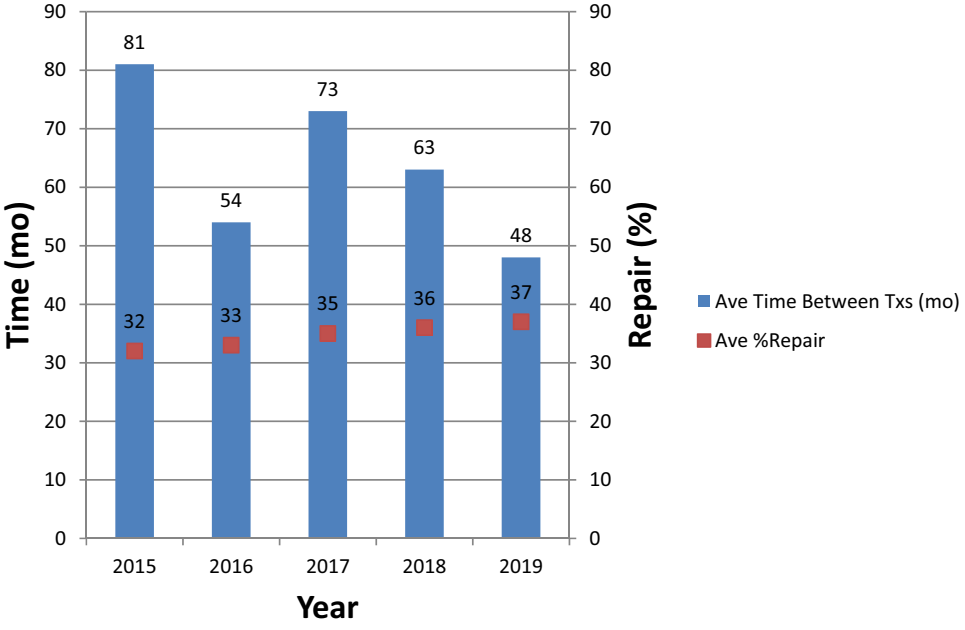

Figure 2 Average time between treatment courses and average percentage repair assumed per calendar year.

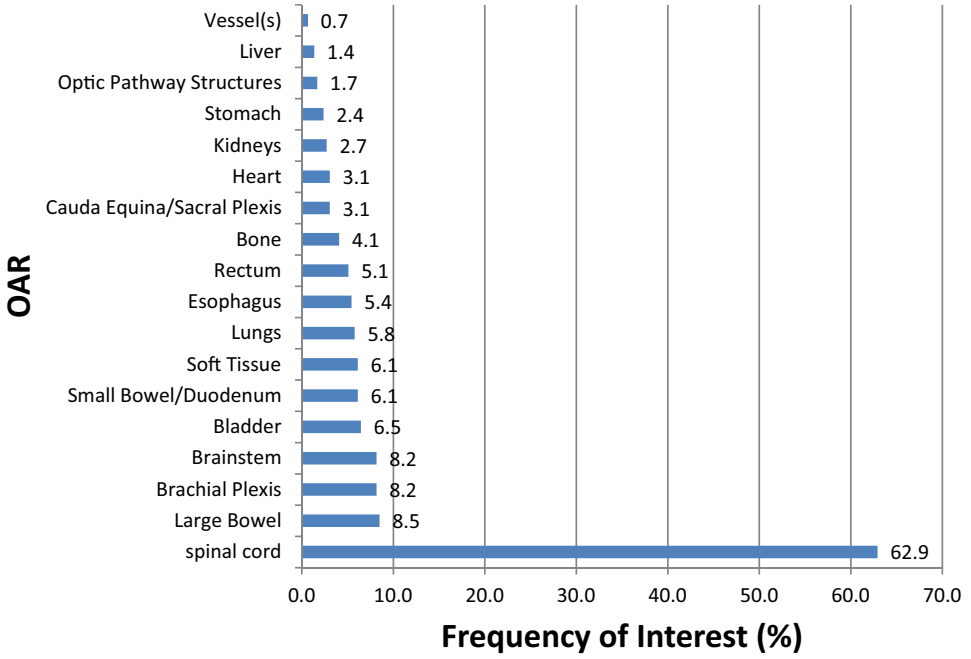

Figure 3 Frequency an organ at risk was of interest for re-treatment patients for calendar years between 2015 and 2019. Note that multiple organs at risk may be involved in the same patient.

The use of the LQ model for fraction sizes of 1 Gy to approximately 6 Gy is generally thought to be safe. However, for fraction sizes >6 Gy, caution is advised because the expected outcome may differ from that associated with the calculation. Fortunately, for modern delivery techniques, such as IMRT/VMAT, even where fractional doses to the target may far exceed this limit, dose to the OARs typically falls within the acceptable range. When this is not the case, limitations of EQD2 are presented to the physician and a note such as "The EQD2 method is based on the LQ model. This model exhibits increased deviation of predicted versus actual results at fractional doses above approximately 6 Gy/fraction" is included in the SPC_{PrevTx}.

The choice of α/β used in the EQD2 calculation depends on whether the OAR is early or late responding. If the OAR expresses damage within a period of days to weeks after irradiation, the α/β range is 7 to 20 Gy. If damage is expressed within months to years, α/β will generally range from 0.5 to 6 Gy.[18] Because the spinal cord is thought to be late responding, we use an α/β value of 3.0 Gy for the EQD2 calculation. If OAR-specific values of α/β are available for the damage of interest, this value is chosen. When not available, the late responding value of 3.0 Gy is our relatively conservative default for late effects. These values are discussed with the radiation oncologist on a case-by-case basis with potential morbidity due to reirradiation and the impact on the patient's quality of life weighed against potential benefits.[19]

Clinical information on OAR repair is sparse. Much of what is used is extrapolated from available data. In 2005 to 2006, Nieder et al presented data on 78 patients with spinal cord doses converted to BED using an α/β of 2 Gy. They found that as long as the interval between courses was >6 months and the BED of each course was ≤98 Gy, no patients developed myelopathy for BED <120 Gy. Additionally, the risk of myelopathy is small for BED ≤135.5 Gy, and they advocate for use of spinal cord BED in the range of 130 to 150 Gy in situations in which tumor control would be compromised by limiting dose further.[20,21] Figure 4 illustrates spinal cord doses over our 5-year period, recalculated as BED using an α/β of 2 Gy. Approximately 87%, 96%, and 99% of cases fall below the 120 Gy, 135.5 Gy, and 150 Gy cumulative BED cutoffs, respectively. Of note, all these patients were treated with plans generated using our departmental process of EQD2 calculation, α/β of 3 Gy, and repair limited to 50%, demonstrating the utility of our methods.

In 2018, Lee et al reported on the use of PLDR in the reirradiation setting and found it to be effective and well tolerated.[22] As demonstrated in the figures, we use this technique frequently for cases in which we cannot meet OAR tolerance using the methods described, when an additional level of caution is needed, or when the gross tumor volume overlaps an OAR (eg, recurrent esophageal cancer).

Conservative practices

Maximum or near-maximum dose is routinely used for nonvolumetric dose-limiting values. Repair percentage,

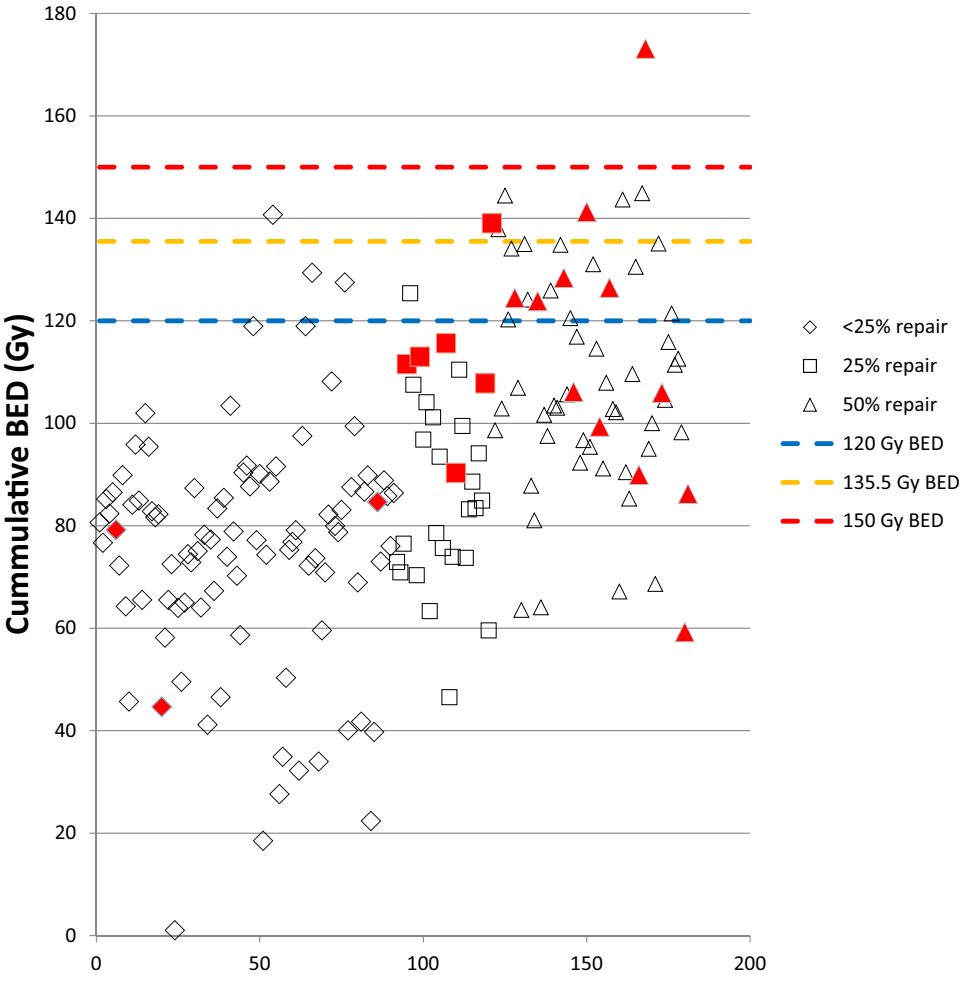

Figure 4 Spinal cord cumulative biologically effective dose with α/β of 2 Gy. Solid markers indicate the use of pulsed-low-dose-rate delivery.

regardless of the length of time between courses, is typically limited to 50%.

Conclusions

We have presented our institutional practice for RT in the reirradiation setting. We believe they result in safe and effective treatments, and the methods described are implementable for routine use. Further improvements will come with the correlation of resultant doses with patient outcome and side effect data. However, collection of these data can be arduous because patient-reported outcomes may lack the metrics needed to further modify our current understanding of dose versus toxicity, and functional and/or diagnostic tests may not be standard of care during routine follow-up and present economic issues. We should encourage our vendor colleagues to develop software, perhaps employing artificial intelligence, to search patient electronic medical records and correlate appropriate data with toxicity as well as patient-reported outcomes to gain additional knowledge and allow for the safe delivery of radiation in the re-treatment environment.

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