

Scientific Article

The Special Medical Physics Consult Process for Reirradiation Patients



Kelly C. Paradis PhD*, Charles Mayo PhD, Dawn Owen MD, Daniel E. Spratt MD, Jason Hearn MD, Benjamin Rosen PhD, Rojano Kashani PhD, Jean Moran PhD, Daniel S. Tatro CMD, Whitney Beeler MD, Karen Vineberg CMD, Dylan C. Smith MS, Martha M. Matuszak PhD

University of Michigan, Ann Arbor, Michigan

Received 20 February 2019; revised 12 April 2019; accepted 29 May 2019

Abstract

Purpose: To present a systematic approach to the reirradiation special medical physics consult (ReRT-SMPC) process.

Materials and Methods: An in-house reirradiation committee of physicians and physicists was formed to develop a streamlined and well-documented approach to ReRT-SMPCs. Dosimetric goals and considerations for tissue repair were generated by the committee with input from the literature, clinical trial guidelines, and physician experience. Procedural workflow was also defined.

Results: The total number of ReRT-SMPCs performed in our department in 2018 was 401, corresponding to 369 unique patients and 16% of the total number of patients receiving external beam radiation in our department that year. This constituted a large increase over the 183 ReRT-SMPCs performed in 2017. We have found that a standardized ReRT-SMPC workflow helps to safeguard patients, documents the clinical decision-making process for medical and legal purposes, and facilitates the peer-review process. The data being collected from each consult along with toxicity and outcomes data can be used to help inform future re-treatment guidelines.

Conclusions: As the number of patients returning for additional courses of radiation continues to increase, a uniform method for the ReRT-SMPC workflow and analysis is a powerful tool for ensuring patient safety, understanding and predicting treatment toxicity, and refining reirradiation dosimetric limits.

© 2019 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Sources of support: This work had no specific funding.

Disclosures: Dr Paradis reports grants from Varian Medical Systems, outside the submitted work; Dr Matuszak reports grants and personal fees from Varian Medical Systems, outside the submitted work; Dr Spratt reports personal fees from Janssen and personal fees from Blue Earth, outside the submitted work; Dr Kashani reports personal fees from

ViewRay Inc, outside the submitted work; Dr Moran reports research grant funding from Varian Medical Systems and Blue Cross Blue Shield of Michigan, outside the submitted work.

* Corresponding author.

E-mail address: kyoung@med.umich.edu (K.C. Paradis).

<https://doi.org/10.1016/j.adro.2019.05.007>

2452-1094/© 2019 The Author(s). Published by Elsevier Inc. on behalf of American Society for Radiation Oncology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

In 2016, about one-third of all 5-year cancer survivors in the United States had received radiation therapy, constituting more than 3 million patients.¹ This number is projected to grow to more than 4 million by the year 2030.¹ Survivors are at risk for recurrence of their original disease and in many cases have a notably higher risk than the general population of experiencing new primary cancers.²

As patients with cancer continue to live longer, the number of patients receiving multiple courses of radiation therapy is also growing. The number of reports on anecdotal, disease site—focused experiences are increasing.^{3–11} However as Niedler et al note in their review of the reirradiation literature, detailed data on cumulative doses and outcomes to form guidelines are lacking,¹² as are publications on the multidisciplinary management of radiation treatment planning for these patients.

Since 2017 at University of Michigan, we have taken a systematic, consensus-based approach to the management of patients returning for additional courses of radiation, including analysis of treatment overlap and cumulative radiation dose to relevant organs at risk (OARs). Our reirradiation special medical physics consult (ReRT-SMPC) is at the core of this approach. It provides a framework to evaluate risk while furnishing data that can be subsequently used to detail dosimetric associations with outcomes and inform future guidelines. Our objective in this publication is to describe our departmental strategy for ReRT-SMPCs. We also share 2 anonymized, patient-specific examples of ReRT-SMPCs performed in our department, along with our institutional dosimetric guidelines for re-treatment.

Materials and Methods

For the work described here, the radiation oncology information system was ARIA and the treatment planning system (TPS) was Eclipse v13.6 with the Eclipse Scripting Application Programming Interface (Varian Medical Systems, Palo Alto, CA).

Within our radiation oncology department, a committee of 3 physicians and 3 physicists was formed to develop a common approach to ReRT-SMPCs that was then adopted by the broader department. The group gathered input from multiple stakeholders, reviewed applicable literature and clinical trial guidelines, and consulted with clinicians at outside institutions. The committee developed dose limit recommendations, considerations for tissue repair, and workflows to create a solution that integrated with existing clinical software applications and our routine clinical practice. The committee met periodically to review and refine the ReRT-

SMPC policy, procedures, dosimetric objectives, and documents based on feedback from clinical use.

Workflow and documentation

Coordination of ReRT-SMPCs was carried out within our radiation oncology information system. A standardized workflow with 5 phases was established with corresponding sections in a standardized ReRT-SMPC electronic document that combined findings and recommendations from those phases. An overview of this workflow is described as follows.

Collection of relevant prior dose information

If the patient was treated at an outside institution, consent to acquire these records was obtained during consultation, and the records were requested by an advanced practice provider. When follow-up dosimetric information was needed (eg, DICOM files, additional renderings of dose distributions), a member of our dosimetry team reached out directly to the treatment planners at the outside institution to facilitate the request. We maintained a database of contact information to expedite future requests to the same department.

Physician documentation of prior dose and OARs

The physician specified the history of prior relevant radiation, including the site, date, dose, and fractionation scheme. For the anticipated treatment plan, the intended dose and number of fractions were specified. Reason(s) for the consult request were indicated (eg, assess treatment overlap, provide guidance on dosimetric limits for OARs, create a composite dose plan for analysis). Using a standardized table of OARs (described later), the physician indicated potential organs of concern for risk assessment.

Physicist preplanning assessment

Review of records, creation of image registrations, and composite dose (using historic treatment plans together with any available preliminary new treatment plans) were carried out to assess remaining dose that could be delivered without exceeding cumulative dose limits. Calculations were performed using biologically corrected dose (equivalent dose in 2-Gy fractions [EQD₂]), and remaining allowable dose for indicated OARs was specified in physical dose for the anticipated fractionation given by the physician. Physicists assessed OARs beyond those initially specified as needed. Recommended dose limits and comments were provided for reference for the dosimetrist. The physicist worked closely with the dosimetrist and physician team to develop a treatment plan, documenting the work performed, dosimetric trade-offs, and the decision-making process. This was often an iterative process.

Physicist postplanning evaluation

After completion of the final plan, the physicist again reviewed the cumulative doses with respect to OAR dose limits. Any organs not meeting limits were highlighted. The consult documents were signed by the physicist and subsequently approved by the physician.

Follow-up evaluation (as needed)

Peer review with additional physicists or physicians could be requested by any member of the team for any case, particularly when standard dosimetric limits were exceeded or in unusually complex cases. Each consult was also reviewed during a departmental weekly chart rounds. If a change to the plan was made during this phase (eg, volume change, adjustment fractionation), the consult was subsequently updated as needed.

Standardized practice consensus-based dose limits

A standardized table of parameters for calculating cumulative, biologically corrected dose from a set of previously delivered plans was defined for use in the ReRT-SMPC (Appendix E2; available online at <https://doi.org/10.1016/j.adro.2019.05.007>). For each identified OAR, a set of dose discount factors was assigned. These discounts were categorized by the time range from prior plan delivery to current treatment (eg, 0-3 months, 3-6 months). A biologically corrected dose-volume histogram (DVH) metric (eg, D0.1 cc[Gy]) and value for α/β were also selected. Cumulative biologically corrected dose limits reflecting physician consensus for “safe” treatment were defined. Where possible, parameters and dose-correction techniques were drawn from previously published literature.¹³⁻²⁰ However, in many cases, because of a dearth of published guidelines, our team relied on in-house experience and consultation with peers to create a complete list of dosimetric recommendations for retreatment. To inform future work (and when published guidance is not available), consistency in the way that ReRT-SMPCs are performed is a top priority.

When electronic DICOM records for prior treatments were available to use in constructing composite dose plans, the DVH metric used was a near-maximum dose (eg, D0.1 cc[Gy] or D0.03 cc[Gy]). We used the near-maximum dose so as not to skew results by a single dose point. If DICOM records were not available, maximum point dose in the area of overlap evaluable from the available paper records was estimated. This value may be found or estimated in several ways depending on the details provided in the obtained treatment records. For example, it may be determined from a table listing maximum doses, estimated from a

DVH, or estimated from images of isodose lines on patient anatomy.

Composite dose

If DICOM files for prior treatments were available, they were rigidly registered to the image set for the current treatment. Structures representing the largest recognized clinical risk for overlap resulting in high cumulative doses were prioritized in image registrations. Deformable image registration (DIR) options from multiple vendors were investigated for potential use with ReRT-SMPCs. These algorithms were not used in the work described here owing to uncertainty in their accuracy in areas of extreme deformation and positional changes. The utility of each image registration was specified by the physicist. American Association of Physicists in Medicine Task Group #132 describes the image registration process and quantitative and qualitative uncertainty assessment.²¹ There were some cases with anatomic deformations large enough that the composite dose plan would have been inaccurate. In these cases, the composite dose plan was not used for evaluation. The utility of the composite plan was determined by the physicist in consultation with the rest of the treatment team. The level of deformation that can be tolerated may depend strongly on the dose distribution and is more detrimental in areas of high dose gradients than in areas of uniform dose.

We note that the image registration strategy may need to be tailored to the TPS. In Eclipse v13.6, only a single image registration is allowed between data sets that are used in a composite dose plan. Therefore, if not all regions of interest could be registered simultaneously (eg, because of deformation), multiple registrations had to be created in series, overwriting the previous registrations as needed to visualize composite dose in different regions.

If DICOM files for prior treatments were not available but paper records contained sufficient details of the treatment plan construction and dose distribution, then replica plans (ie, “fake” plans representing the prior dose) were sometimes created using the imaging data set for the current plan to represent the prior dose. This was done using as much information as could be derived from the records, such as field size and shape, gantry parameters, beam energy, total dose, dose per fraction, and isocenter location. This process was performed only when deemed beneficial for the analysis.

A composite dose plan including all evaluable plans was constructed in our TPS with no discount factor for prior dose. In addition, sets of composite plans were created corresponding to the set of discount factors used for all OARs evaluated in the ReRT-SMPC. For example, if 2 OARs did not have matching discounts for the same time range, then a composite plan would be created for

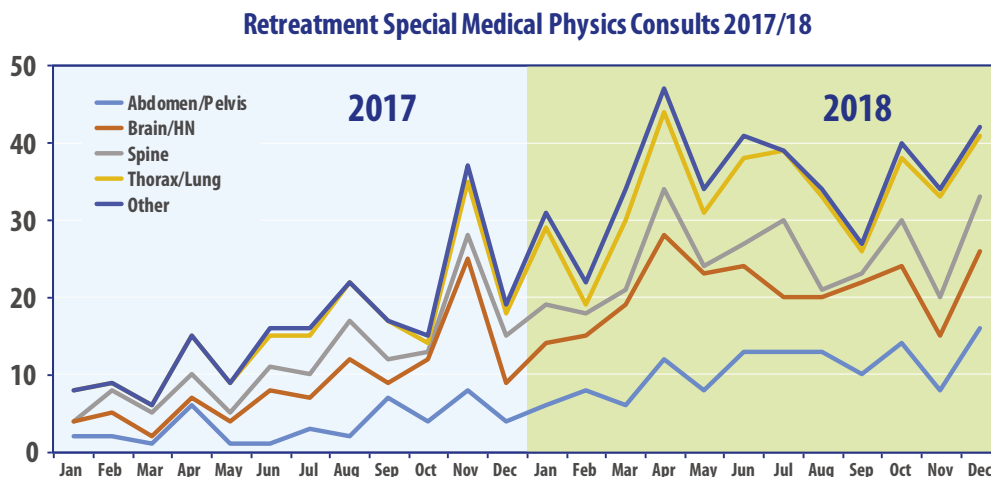


Figure 1 Stacked line graph of the number of reirradiation special medical physics consults performed monthly over a 2-year period from 2017 to 2018. Results broken out by body region.

each OAR's discount factor (see examples in [Appendix E2](#); available online at <https://doi.org/10.1016/j.adro.2019.05.007>).

Biologically corrected DVH metrics

If DICOM files for prior plans were available, a custom software application, DVH Analysis (*University of Michigan*), was used to extract relevant dosimetric information. This previously commissioned program used the Eclipse Scripting Application Programming Interface to access the physical dose distribution for each plan and calculated a corresponding biologically corrected dose distribution by calculating EQD₂ on a voxel level for the treatment plan. For composite plans, the biologically corrected dose grids for each plan were summed by the script using the data set registrations. The application allowed users to specify physical and biologically corrected DVH metrics, which were then calculated for all selected treatment plans and composite plans.

If DICOM files needed to create composite plans were not available, then manual point calculations were performed using maximum doses as described previously.

Results

Our standardized ReRT-SMPC document with suggested dosimetric limits, discount factors, and α/β ratios was implemented in April 2017 (consults performed before this date used a “free-form” document). The latest version of this ReRT-SMPC form can be found in [Appendix E2](#) (available online at <https://doi.org/10.1016/j.adro.2019.05.007>). In 2018, University of Michigan performed 401 ReRT-SMPCs (corresponding to 369 unique patients, or 16% of the patients receiving external

beam radiation in our department that year), which represented a substantial increase over the 183 that were performed in 2017. The numbers cited here include cases in which the previous radiation was deemed either relevant or potentially relevant enough to warrant additional analysis and tailoring of the new dose distribution to account for the previously delivered radiation. The number of consults per month broken down by body region is shown in [Figure 1](#). The surge in the number of consults reflects the general trend of an increasing number of patients returning for additional courses of radiation and the growing confidence in our ReRT-SMPC workflow by the requesting physicians.

A core group of 3 physicists performed the majority of ReRT-SMPCs in 2017. With the increase in number of consults, an additional 4 physicists were added to the ReRT-SMPC team over the course of 2018. On average, a single ReRT-SMPC took a physicist approximately 90 minutes with a minimum of 20 minutes up to a maximum of approximately 10 hours (estimated based on time studies done by 2 physicists and surveys of the physics team performing these evaluations). The number of previously treated plans, difficulty of image registration, number of relevant OARs, and availability of prior dosimetric data all contributed to the length of time the consult took to complete. Although not explicitly measured in this study, effort from our dosimetry team was also increased for the ReRT-SMPC process. This included tasks such as working with outside institutions to obtain DICOM files, creating or reviewing image registrations, creating additional planning optimization structures, and iteratively working in consultation with the physicist to generate a treatment plan meeting the retreatment dosimetric goals.

Two detailed, patient-specific examples of ReRT-SMPCs can be found in [Appendix E1](#) (available online at <https://doi.org/10.1016/j.adro.2019.05.007>).

Discussion

Biological and physical dose

To compare doses across multiple plans, conversion to biological effective dose or equivalent dose (eg, EQD₂) is necessary. Biological effective dose has been in use for the last 30 years and is based on the linear-quadratic model of cell survival.²² This conversion is required even when plans of identical fractionation schemes are added because the fractionation scheme specifically describes the dose to target tissues and not to the relevant OARs. These OARs may receive a substantially different total dose and dose per fraction compared with the target volumes. When viewing composite dose, users should recognize that their planning system may support only the visualization of physical dose and not the corresponding biological dose.

Although there is some concern that the linear-quadratic model fails to accurately predict cell kill at higher doses per fraction,^{23,24} it remains one of the most frequently used and accepted forms of dose summation.²⁵ The calculated biological dose may be sensitive to the chosen α/β ratio, and using a single value for a biological dose limit does not always realize practical results when adding together multiple hypofractionated plans or a combination of multiple different fractionations. Similarly, we note that our institutional dose limits for re-treatment break down in some contexts with high dose per fraction, where certain reirradiation constraints may be exceeded by the prior course alone, even though the plan had met the original constraints appropriate for that dose and fractionation. In such cases, composite dosimetric objectives were modified as appropriate on a case-by-case basis. Additionally, cumulative physical dose was reported alongside biologically corrected dose with an interpretation of the utility of the quantitative results.

Quantitative DVH metrics

We primarily rely on near-maximum point dose limits as opposed to volumetric or mean dose limits when performing dose calculations for ReRT-SMPCs. Evaluation of biological mean dose involves the conversion of each voxel within the structure to biological dose before calculating the mean. This is problematic in that doses very different from 2 Gy per fraction may skew the mean, making the result difficult to interpret. The same problem exists to an even greater extent for volumetric dose limits. Additionally, conversion of composite DVHs to biological dose relies on accurate voxel-to-voxel image registration between data sets and rarely makes sense for organs that will experience considerable day-to-day deformation. Finally, regarding DVH metrics derived from patient contours on composite plans, care should be

taken to evaluate any changes in the shape and positioning of those OARs between imaging data sets.

Considerations for patients treated at an outside institution

For patients previously treated at an outside institution, the ideal workflow involves the collection of both DICOM planning records and printed pdf records. The dose imported into the treatment planning system should be compared against the printed records to ensure that the import was performed correctly and that the documented dose indicated by the outside institution matches the plan. Contours in outside records should be evaluated according to institutional standards to ensure that any reported dose metrics or DVHs are accurate.

When DICOM files of previous treatments are not available, pdf records can be used for analysis. Results in these cases are frequently more conservative, relying on maximum point doses and assuming overlap of dose unless spatial separation between the plans is clear. As described earlier, in some cases creating a replica of the previously delivered plan can help with visualizing potential overlap.

Benefits of this workflow

The ReRT-SMPC process requires considerable institutional resources. As a department, we believe this is time well spent because it helps to ensure patient safety, generates clear documentation of the clinical decision-making process for medical and legal purposes, and simplifies the peer-review process. A standardized approach enables the thoughtful and measured delivery of multiple courses of reirradiation, which is becoming increasingly common within our hospital system. A separate analysis of toxicity is ongoing based on clinical experience to date. This will aid in refining future reirradiation treatment strategies and dosimetric limits.

Weaknesses and potential improvements of this workflow

The effectiveness of the ReRT-SMPC is heavily dependent on accurate, thorough clinical input from the physician before the consult. Preliminary review of patient toxicities indicates that some grade 3 and higher toxicities occurred when the OAR was not “checked” for review on the consult form, which was in turn not caught by the physicist performing the consult. Additionally, some toxicities have occurred in organs that are not included on our standardized ReRT-SMPC form. It is often difficult to know up front which OARs will need evaluation in a given case. Judicious selection of OARs must strike a balance between being complete without

creating unnecessary work and increasing the time required for the consult. This may be an iterative process with input from the physicist after the consult begins.

For some OARs, the cumulative biological dose limit and discount factors are not based on published results but rather on institutional consensus. Our team views the consistency of our current process as an improvement over a previous workflow in which dose limits and discounts were chosen on a per-patient and per-physician basis. We now use consistent metrics across all patients unless alternative values are specifically requested. In these cases, we perform additional peer review to help ensure patient safety.

We currently do not regularly use DIR when performing ReRT-SMPCs. The use of only rigid registration has the potential to introduce considerable uncertainty and inaccuracy in composite dose metrics and may even render analysis of dose to some OARs impossible. During consultations, we are careful to highlight any uncertainties that occur because of the rigid registration process. DIR has the potential to be helpful in many situations, such as extreme patient deformation, tissue loss, positional changes, and calculation of composite dose in regions of high dose gradient. Accurate DIR would also allow the calculation of volume-based metrics, which would be more appropriate for parallel organs than the currently employed point-based metrics. However, we caution that the accuracy of DIR should be evaluated on a case-by-case basis, and any dose information extracted from composite plans using DIR should be accompanied by an uncertainty estimation. We are currently evaluating commercial systems for DIR and may use this method in the future.

Partnership with vendors

Treatment planning system vendors have an opportunity to improve their commercial products to facilitate the previously described workflows, especially in light of the growing need for reirradiation analysis. Currently, the previous treatment records that we may receive for patients span a wide range of quality, from hand-drawn fields to a few screenshots in an e-mail to complete DICOM-RT records and pdf printouts. The export of radiation treatment records from commercial planning systems should be standardized and streamlined such that users may easily export requested data in an accurate and consistent manner. Correspondingly, the import of these records into the requesting institution's database should also be streamlined and standardized.

Additionally, commercial planning systems should support the display of biological dose and enable dose metric analysis and inverse optimization using these dose distributions. The work described here requires our

in-house script DVH Analysis and is not possible with our treatment planning system alone. Other institutions have also implemented in-house solutions; eg, McVicar et al developed an in-house Matlab tool that creates a biologically corrected base plan dose distribution for optimization of new plans for reirradiation patients.²⁶

Partnership with the radiation oncology community

Radiation oncology department team members should be prepared to both send and receive treatment records as needed to ensure the safe treatment of patients with previous irradiation history. The value of ReRT-SMPCs is considerably higher when complete DICOM files are available. We also would like to highlight the importance of initiatives such as Integrating the Healthcare Enterprise - Radiation Oncology, an American Association of Physicists in Medicine/American Society for Radiation Oncology–sponsored initiative that aims to maximize interoperability between radiation oncology systems.

Finally, patients can play a vital role in these efforts. They should be counseled in the importance of receiving treatment at the same institution when possible and helping to ensure their health care providers have up-to-date treatment history if they have changed institutions.

Future work

We are currently in the process of analyzing total delivered physical and EQD₂ doses for these patients and combining these data with patient outcomes. This will then facilitate the review of our current dose limits and discounts.

Conclusions

In this work, we have presented our institutional workflow for patients receiving reirradiation. Nearly 600 ReRT-SMPCs have been performed using this consistent workflow. A standardized method of analysis is a powerful tool for ensuring patient safety, understanding and predicting treatment toxicity, and refining reirradiation dosimetric limits.

Acknowledgments

The authors gratefully acknowledge the large team of physicists and physicians at the University of Michigan who have provided input into the reirradiation special medical physics consult process, workflow, and policies

and continue to work on consults daily. We thank Steven Kronenberg for providing figure design for this manuscript.

Supplementary data

Supplementary material for this article can be found at <https://doi.org/10.1016/j.adro.2019.05.007>.

References

- Bryant AK, Banegas MP, Martinez ME, Mell LK, Murphy JD. Trends in radiation therapy among cancer survivors in the United States, 2000-2030. *Cancer Epidemiol Biomarkers Prev.* 2017;26:963-970.
- American Cancer Society. *Cancer Treatment & Survivorship Facts & Figures, 2016-2017*. Atlanta, GA: American Cancer Society; 2016.
- Vyfhuis MA, Rice S, Remick J, et al. Reirradiation for locoregionally recurrent non-small cell lung cancer. *J Thorac Dis.* 2018;10:S2522-S2536.
- von der Grün J, Köhn J, Loutfi-Krauss B, Blanck O, Rödel C, Balermmpas P. Second infield re-irradiation with a resulting cumulative equivalent dose (EQD2_{max}) of >180 Gy for patients with recurrent head and neck cancer. *Head Neck.* 2019;41:E48-E54.
- Navarria P, Minniti G, Clerici E, et al. Re-irradiation for recurrent glioma: Outcome evaluation, toxicity and prognostic factors assessment. A multicenter study of the Radiation Oncology Italian Association (AIRO). *J Neurooncol.* 2019;142:59-67.
- Kong F, Zhou J, Du C, et al. Long-term survival and late complications of intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma. *BMC Cancer.* 2018;18:1139.
- Rulach R, Hanna GG, Franks K, McAleese J, Harrow S. Re-irradiation for locally recurrent lung cancer: Evidence, risks and benefits. *Clin Oncol.* 2018;30:101-109.
- Nieder C, Langendijk JA, Guckenberger M, Grosu AL. Preserving the legacy of reirradiation: A narrative review of historical publications. *Adv Radiat Oncol.* 2017;2:176-182.
- Milano MT, Mihai A, Kong FS. Review of thoracic reirradiation with stereotactic body radiation therapy: A focus on toxicity risks. *Pract Radiat Oncol.* 2018;8:251-265.
- McDuff SGR, Remillard KA, Zheng H, et al. Liver reirradiation for patients with hepatocellular carcinoma and liver metastasis. *Pract Radiat Oncol.* 2018;8:414-421.
- Balermmpas P, Stera S, Müller von der Grün J, et al. Repeated in-field radiosurgery for locally recurrent brain metastases: Feasibility, results and survival in a heavily treated patient cohort. *PLoS One.* 2018;13:e0198692.
- Nieder C, Langendijk JA, Guckenberger M, Grosu AL. Second re-irradiation: A narrative review of the available clinical data. *Acta Oncol.* 2017;57:305-310.
- Fowler JF. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. *Acta Oncol.* 2004;44:265-276.
- Fowler JF, Tome WA, Fenwick JD, Mehta MP. A challenge to traditional radiation oncology. *Int J Radiat Oncol Biol Phys.* 2004;60:1241-1256.
- Chapet O, Kong FM, Lee JS, Hayman JA, Ten Haken RK. Normal tissue complication probability modeling for acute esophagitis in patients treated with conformal radiation therapy for non-small cell lung cancer. *Radiother Oncol.* 2005;77:176-181.
- Chapet O, Thomas E, Kessler ML, Fraass BA, Ten Haken RK. Esophagus sparing with IMRT in lung tumor irradiation: An EUD-based optimization technique. *Int J Radiat Oncol Biol Phys.* 2005;63:179-187.
- Feng M, Normolle D, Pan CC, et al. Dosimetric analysis of radiation-induced gastric bleeding. *Int J Radiat Oncol Biol Phys.* 2012;84:e1-e6.
- Chen C, Uytterlinde W, Sonke JJ, de Bois J, van den Heuvel M, Belderbos JS. Severe late esophagus toxicity in NSCLC patients treated with IMRT and concurrent chemotherapy. *Radiother Oncol.* 2013;108:337-341.
- Lee SH, Lee KC, Choi J, et al. Clinical applicability of biologically effective dose calculation for spinal cord in fractionated spine stereotactic body radiation therapy. *Radiol Oncol.* 2015;49:185-191.
- Dipasquale G, Zilli T, Fiorino C, Rouzaud M, Miralbell R. Salvage reirradiation for local failure of prostate cancer after curative radiation therapy: Association of rectal toxicity with dose distribution and normal-tissue complication probability models. *Adv Radiat Oncol.* 2018;3:673-681.
- Brock KK, Mutic S, McNutt TR, Li H, Kessler ML. Use of image registration and fusion algorithms and techniques in radiotherapy: Report of the AAPM radiation therapy committee task group No. 132. *Med Phys.* 2017;44:e43-e76.
- Fowler JF. A review: The linear quadratic formula and progress in fractionated radiotherapy. *Br J Radiol.* 1989;62:679-694.
- Garau MM. Radiobiology of stereotactic body radiation therapy (SBRT). *Rep Pract Oncol Radiother.* 2017;22:86-95.
- McMahon SJ. The linear quadratic model: Usage, interpretation and challenges. *Phys Med Biol.* 2018;64:01TR01.
- Brenner DJ. Point: The linear-quadratic model is an appropriate methodology for determining iso-effective doses at large doses per fraction. *Semin Radiat Oncol.* 2008;18:234-239.
- McVicar N, Thomas S, Liu M, Carolan H, Bergman A. Re-irradiation volumetric modulated arc therapy optimization based on cumulative biologically effective dose objectives. *J Appl Clin Med Phys.* 2018;19:341-345.