Feasibility Study of a Systematic Approach to Multi-Modality Treatment Planning

M. Kim[1], R. Levin[2] and A. Aravkin[2]

[1]University of Washington, Radiation Oncology, USA

[2]University of Washington, Applied Mathematics, USA

JULY 12–16 2020 VIRTUAL
JOINT AAPM | COMP MEETING
EASTERN TIME [GMT-4]

INTRODUCTION

There are emerging interests and developments of other radiation types than photons such as protons and carbon ions, owing to their unique biological and dosimetric characteristics that are distinctive from photons [1,2]. For example, protons have superior dosimetric effects owning to their Bragg peaks, and neutrons and carbon ions have superior biological effects (higher relative biological effect) compared to photons. It is unclear which modality is optimal for specific patients and current efforts to find an optimal modality or optimal combinations of multiple modalities are mostly empirical or anecdotal [3,4].

AIM

The purpose of this study is to develop and test the feasibility of a systematic optimization framework to treatment planning with multiple modalities to identify an optimal combination of the modalities and their fractionation regimens, which lead to the maximum feasible biologically effect (BE) to the tumor. Our approach allows a single modality as a potential solution and therefore, a correct optimal modality gets identified if a single modality leads to a larger tumor BE than multiple modalities combined.

METHOD

Consider a treatment planning problem with M modalities with u_m beamlet intensities and N_m fractions of each modality m. We utilize bi-level optimization, which consists of the upper level (Algorithm 1), where N_m is optimized using the optimal u_m found in the lower level for given N_m (Algorithm 2). For the maximum number of fractions, N_{max}, allowed, the upper level optimization can be written as

$$\min_{N_1,\dots,N_M} V(N_1,\dots,N_M)$$

subject to

$$1 \le \sum_{m=1}^{M} N_m \le N_{\max}, N_m \ge 0, m = 1,\dots,M,$$

$$1 \le \sum_{m=1}^{M} N_m \le N_{\max}, N_m \ge 0, m = 1,\dots,M,$$

where $V(N_1,\dots,N_M)$ is the value function of $\{N_m\}_{m=1}^M$ defined as $F(\{u_m^*(N_1,\dots,N_M)\}_{m=1}^M, N_1,\dots,N_M)$. Each optimal fluence map $\{u_m^*(N_1,\dots,N_M)\}_{m=1}^M$ is obtained by solving the following problem in the lower level:

$$\min_{u} \tilde{\alpha}^T (Tu) - f(Tu)$$

subject to

$$\tilde{\gamma^i}^T H^i u + \left(H^i u\right)^T D^i \left(H^i u\right) \le C^i_{\text{mean/max}}, \qquad \text{for all } i \in I_{\text{mean/max}},$$

where T and H are dose deposition matrices for the tumor and OAR of all modalities (stacked up together), $\tilde{\alpha}$, $(\gamma,\tilde{})$ and D are the radiobiological parameters in the LQ model (BE = αNd + βNd2, d is dose (=Tu for tumor, Hu for OAR), N is the number of fractions, α and β are linear and quadratic radiobiological coefficients) arranged appropriately, and C is the BE constraint for OAR.

This minimization is solved iteratively by updating auxiliary variables and u using non-convex relaxation to preserve the non-convex structure of the problem. The upper and lower level optimization is shown in Algorithm 1 and Algorithm 2 respectively.

Algorithm 1 $\{N_m\}$ Fractionation Schedule Optimization

Input: $u^{(0)}, N_1^{(0)}, \dots, N_M^{(0)}$
function ObjectiveFun($u, N1, \dots, N_M$)
  return $\sum_{i=1}^{M} N_i(\alpha_i{}^T T_i u_i - (T_i u_i)^T \text{diag}(\beta_i)(T_i u_i)) + n_{tx}\left(\sum_{j=1}^{M} N_j - 1\right)\ln 2/T_d$.
function ValueFun($N_1, \dots, N_M$) ▷ Define the value function to optimize
  $u_N^* \leftarrow$ LowerLevelSolver($u^{(0)}, N_1, \dots, N_M$)
  return ObjectiveFun($u_N^*, N1, \dots, N_M$)
$N_1^*, \dots, N_M^* \leftarrow$ TrustRegionConstr(ValueFun, $N_1^{(0)}, \dots, N_M^{(0)}$, $\sum_{j=1}^{M} N_j \le 25, \{N_j \ge 0\}_1^M$)
$u^* \leftarrow$ LowerLevelSolver($u^{(0)}, \lfloor N_1^* \rfloor, \dots, \lfloor N_M^* \rfloor$)
Output: $u^*, N_1^*, \dots, N_M^*$

Algorithm 2 Fluence Map Optimization with Fixed Parameters and Fractions

Input: $u^{(0)}, \eta_0, \eta_1, \dots, \eta_{\tilde{n}}, N_1, \dots, N_M$
function LowerLevelFixedParams($u^{(0)}, \eta_0, \eta_1, \dots, \eta_{\tilde{n}}, N_1, \dots, N_M, I_{\text{mean}}, \tilde{I}_{\max}$)
  Initialize: $k = 0$
  $\tilde{\alpha} := \begin{bmatrix} N_1\alpha_1 \\ N_2\alpha_2 \\ \vdots \\ N_M\alpha_M \end{bmatrix}, D := \begin{bmatrix} N_1\text{diag}(\beta_1) & & & \\ & N_2\text{diag}(\beta_2) & & \\ & & \ddots & \\ & & & N_M\text{diag}(\beta_M) \end{bmatrix}$
  for $i = 1, \dots, \tilde{n}$ **do**
    $\tilde{\gamma}^i := \begin{bmatrix} N_1\gamma_1^i \\ N_2\gamma_2^i \\ \vdots \\ N_M\gamma_M^i \end{bmatrix}, D^i := \begin{bmatrix} N_1\text{diag}(\delta_1^i) & & & \\ & N_2\text{diag}(\delta_2^i) & & \\ & & \ddots & \\ & & & N_M\text{diag}(\delta_M^i) \end{bmatrix}$
  while not converged do
    $k \leftarrow k + 1$
    $w_0^{(k)} \leftarrow \text{prox}_{-\eta_0 f}(Tu - \eta_0\tilde{\alpha})$
    for $i \in I_{\text{mean}}$ **do**
      $\Omega_i = \{w_i : (\tilde{\gamma}^i)^T w_i + w_i^T D^i w_i \le C^i_{\text{mean}}\}$
      $w_i^{(k)} \leftarrow \text{proj}_{\Omega_i}(H^i u)$
    for $i \in \tilde{I}_{\max}$ **do**
      $\Omega_i = \{w_i : (\tilde{\gamma}^i)^T w_i + w_i^T D^i w_i \le C^i_{\max}\}$
      $w_i^{(k)} \leftarrow \text{proj}_{\Omega_i}(H^i u)$
    $u^{(k)} \leftarrow \arg\min_{u \ge 0} \tilde{\alpha}^T w_0^{(k)} - f(w_0^{(k)}) + \frac{1}{2\eta_0}\|w_0^{(k)} - Tu\|^2 + \sum_{i=1}^{\tilde{n}} \frac{1}{2\eta_i}\|w_i^{(k)} - H^i u\|^2$
  $u^* \leftarrow u^{(k)}$
  return u^*
Output: u^*

We applied the framework to the simple 2D head-and-neck phantom shown in Figure 1 with two different modalities M1 and M2 assuming that M1 represents 6 MV photons. For M2, we investigated the results with a dose deposition matrix of 250 MeV protons and various α/β ratios of the tumor and OAR to capture the effect of different biological characteristics of M2. We also varied the ratio r , which is defined as $\alpha_{OAR}/\alpha_{tumor}$, to 0.8 – 1.2 for M2 to capture the different biological effect of M2 between the tumor and OAR. This means that when r<1, M2 is more effective in damaging tumor than OAR. Similarly, when r>1, M2 is more effective in damaging OAR than tumor. We varied tumor doubling time Td. The total number of fractions was constrained to be less than 25.

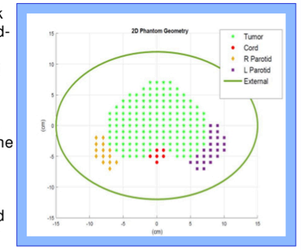

Figure1 Phantom geometry

RESULTS

The convergence of the upper level algorithm for the fractionation optimization is shown in Figure 2. The color of the dots represents a different initial guess, e.g., green dots have the initial guess of (N1, N2) = (1, 24). Each dot represents an iteration. Blue initial guess (N1=24, N2=1) leads to the optimal solution in this case.

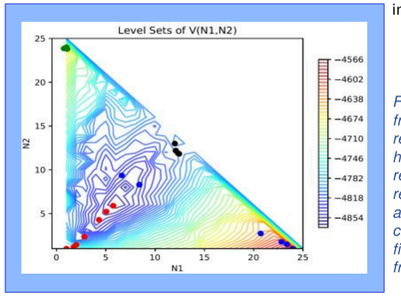

Figure 2 Convergence of the upper level fractionation optimization. The level sets represent true objective function values obtained heuristically for two modalities. Each dot represents an iteration and different color represents different initial guess used in the algorithm. Initial guess starts at the corner and converges to an optimal value in the middle. The final solution is the minimum of the 4 solutions from 4 different initial solutions.

To evaluate the efficacy of the proposed multi-modality optimization framework compared to current practice, we introduce the following evaluation criteria.

pObj_conv = BE using optimal (N1,N2)/BE using conventional 25 fractions * 100
pObj_single = BE using optimal (N1,N2)/BE using optimal N1 * 100

pObj_conv is the percentage improvement in BE of the tumor in the plan using the multi-modality optimization framework relative to that in the conventional plan using M1 only with the standard fractionation (N1 = 25 fractions assumed in this study). pObj_single is the percentage improvement in BE relative to the plan with M1 only and the optimized fractionation schedule rather than 25 fractions fixed. Note that we can compare the tumor BE increase only since OAR BE was constrained to be at the tolerance for all plans used in this study.

The tumor BE increase was 7.8-22.9 % compared to a single modality (M1) with 25 fractions fixed, and 5.7-7.9% compared to a single modality with optimal fractionation. The range in the BE increase depends on the tumor doubling time and radiobiological parameters used (alpha2 and r). The results are shown in Table 1 below. When r<1 (M2 damages tumor more than it damages OAR), the optimal solution includes more fractions from M2 compared to r=1, which also agrees with the clinical intuition.

Td (days)	Dual modality optimal (N1, N2)	Single modality optimal (N1)	pObj_single (%)	pObj_conv (%)
2	(2, 2)	2	105.7	122.9
5	(6, 6)	6	106.8	110.1
10	(13, 12)	13	107.9	108.2
50	(12, 12)	25	107.8	107.8
100	(12, 12)	25	107.8	107.8

Table 1 Optimal BE improvement with various tumor doubling time (Td) : parameters are fixed at α2 = 0.35/Gy and r=1.0.

r	Dual modality optimal (N1, N2)	Single modality optimal (N1)	pObj_single (%)	pObj_conv (%)
0.8	(7, 11)	6	104.7	107.9
1.0	(3, 4)	3	103.2	105.7
1.2	(3, 3)	3	102.0	104.7

Table 2 Optimal BE improvement with various r : parameters are fixed at Td = 5 days and α2 = 0.35/Gy

CONCLUSIONS

We successfully set up a framework to optimize treatment plans involving multiple modalities and developed the efficient, bi-level optimization algorithms to solve the resulting non-convex, mixed integer problem [5]. The results of our numerical simulations on a simplified 2D phantom, where the clinical intuition can be readily drawn, validate our approach in the clinical setting showing the promise of our mathematical framework for further clinical investigation. We note that the results shown in this study are not directly relevant to the clinical setting as we applied the theoretical values to the input parameters in the phantom rather than clinically relevant parameter values and patient datasets.

Our hope is that the systematic approach we took opens the door to new opportunities to consider multiple radiation types to best optimize an individual patient plan. Our method can also be used to optimize the brachytherapy and external beam radiotherapy, which is left for future work along with further clinical investigation of multiple modality optimization in radiation treatment planning.

ACKNOWLEDGEMENTS

This work was funded in part by NSF Grant # 156043, and by the Washington Research Foundation Data Science Professorship

REFERENCES

1. Vogel, J., Lin, L., Litzky, L. A., Berman, A. T., and Simone, C. B. (2017).Predicted rate of secondary malignancies following adjuvant proton versus photon radiation therapy for thymoma. International Journal of Radiation Oncology Biology Physics,99(2):427–433.
2. Britten, R. A., Peters, L. J., and Murray, D. (2001). Biological factors influencing the RBE of neutrons: implications for their past, present and future use in radiotherapy. Radiation Research, 156(2):125–131.
3. Zhou, J., Yang, B., Wang, X., and Jing, Z. (2018). Comparison of thee effectiveness of radiotherapy with photons and particles for chordoma after surgery: A meta-analysis. World Neurosurgery, 117:46–53
4. Haefner, M. F., Verma, V., Bougatf, N., et al. (2018). Dosimetric com-parison of advanced radiotherapy approaches using photon techniques and particle therapy in the postoperative management of thymoma. Acta Oncologica.
5. R Levin, A. Aravkin, M Kim. A proof of principle: Multi-Modality Radiotherapy Optimization arXiv:1911.05182v2 [math.OC]

CONTACT INFORMATION

Minsun Kim: mk688@uw.edu