Mathematical Proof that Simultaneous Irradiation is Not Optimal for Two Tumors

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Appendix - Proof of the proposition –

If we can show the non-optimality of simultaneous irradiation for two times, we can show the non-optimality for more than three times. In the following, we focus on any two of n times of irradiation. Select any i, j $(i \neq j)$ and fix the values other than $d_i^{(1)}, d_j^{(1)}, d_i^{(2)}, d_j^{(2)}$. Let $\boldsymbol{x} = \left(d_i^{(1)}, d_j^{(1)}, d_i^{(2)}, d_j^{(2)}\right)$.

It becomes a constrained maximization problem.

Constraints

$$g^{(1)}(\boldsymbol{x}) = \left(d_i^{(1)} + \frac{\alpha_1}{2\beta_1}\right)^2 + \left(d_j^{(1)} + \frac{\alpha_1}{2\beta_1}\right)^2 = r_1$$

$$g^{(2)}(\boldsymbol{x}) = \left(d_i^{(2)} + \frac{\alpha_1}{2\beta_1}\right)^2 + \left(d_j^{(2)} + \frac{\alpha_1}{2\beta_1}\right)^2 = r_2$$

Maximum objective function

$$f(\boldsymbol{x}) = \sum_{k=1}^{N} \exp\left(-\sum_{i=1}^{n}\left[\alpha_0\left(\delta_{10}^{(k)} d_i^{(1)} + \delta_{20}^{(k)} d_i^{(2)}\right) + \beta_0\left(\delta_{10}^{(k)} d_i^{(1)} + \delta_{20}^{(k)} d_i^{(2)}\right)^2\right]\right)$$

$$= \sum_{k=1}^{N} \exp\left(-2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left[\sum_{h=i,j} d_h^{(1)} d_h^{(2)} - A_k \sum_{h=i,j} d_h^{(1)} - B_k \sum_{h=i,j} d_h^{(2)} + C_k\right]\right)$$

$$= \sum_{k=1}^{N} \exp\left(-2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left[\left(d_i^{(1)} d_i^{(2)} + d_j^{(1)} d_j^{(2)}\right) - A_k\left(d_i^{(1)} + d_j^{(1)}\right)\right.\right.$$

$$\left.\left. - B_k\left(d_i^{(2)} + d_j^{(2)}\right) + C_k\right]\right)$$

The Lagrange function is

$$L(\boldsymbol{x}, \lambda_1, \lambda_2) = \sum_{k=1}^{N} \exp\left(-2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left[\sum_{h=i,j} d_h^{(1)} d_h^{(2)} - A_k \sum_{h=i,j} d_h^{(1)} - B_k \sum_{h=i,j} d_h^{(2)} + C_k\right]\right)$$

$$+ \lambda_1\left(\left(d_i^{(1)} + \frac{\alpha_1}{2\beta_1}\right)^2 + \left(d_j^{(1)} + \frac{\alpha_1}{2\beta_1}\right)^2\right) + \lambda_2\left(\left(d_i^{(2)} + \frac{\alpha_1}{2\beta_1}\right)^2 + \left(d_j^{(2)} + \frac{\alpha_1}{2\beta_1}\right)^2\right).$$

The vector $\boldsymbol{x} = \left(d_i^{(1)}, d_j^{(1)}, d_i^{(2)}, d_j^{(2)}\right)$ must satisfy the following two conditions in order to be a solution to the constrained maximization problem (1).

(1) FOC (first order condition: The first-order partial derivative of $L(\boldsymbol{x}, \lambda_1, \lambda_2)$ are zero.);

$$\frac{\partial L}{\partial d_i^{(1)}} = \frac{\partial L}{\partial d_j^{(1)}} = \frac{\partial L}{\partial d_i^{(2)}} = \frac{\partial L}{\partial d_j^{(2)}} = 0$$

(2) SOC (second order condition: Conditions on the bordered Hessian matrix consisting of second-order partial derivatives of $L(\boldsymbol{x}, \lambda_1, \lambda_2)$)

$$|H_3| \leq 0 \text{ and } |H_4| \geq 0,$$

where

$$H_4 = \begin{bmatrix} 0 & 0 & \frac{\partial g^{(1)}}{\partial d_i^{(1)}} & \frac{\partial g^{(1)}}{\partial d_j^{(1)}} & \frac{\partial g^{(1)}}{\partial d_i^{(2)}} & \frac{\partial g^{(1)}}{\partial d_j^{(2)}} \\ 0 & 0 & \frac{\partial g^{(2)}}{\partial d_i^{(1)}} & \frac{\partial g^{(2)}}{\partial d_j^{(1)}} & \frac{\partial g^{(2)}}{\partial d_i^{(2)}} & \frac{\partial g^{(2)}}{\partial d_j^{(2)}} \\ \frac{\partial g^{(1)}}{\partial d_i^{(1)}} & \frac{\partial g^{(2)}}{\partial d_i^{(1)}} & \frac{\partial^2 L}{\partial {d_i^{(1)}}^2} & \frac{\partial^2 L}{\partial d_j^{(1)} \partial d_i^{(1)}} & \frac{\partial^2 L}{\partial d_i^{(2)} \partial d_i^{(1)}} & \frac{\partial^2 L}{\partial d_j^{(2)} \partial d_i^{(1)}} \\ \frac{\partial g^{(1)}}{\partial d_j^{(1)}} & \frac{\partial g^{(2)}}{\partial d_j^{(1)}} & \frac{\partial^2 L}{\partial d_i^{(1)} \partial d_j^{(1)}} & \frac{\partial^2 L}{\partial {d_j^{(1)}}^2} & \frac{\partial^2 L}{\partial d_i^{(2)} \partial d_j^{(1)}} & \frac{\partial^2 L}{\partial d_j^{(2)} \partial d_j^{(1)}} \\ \frac{\partial g^{(1)}}{\partial d_i^{(2)}} & \frac{\partial g^{(1)}}{\partial d_i^{(2)}} & \frac{\partial^2 L}{\partial d_i^{(1)} \partial d_i^{(2)}} & \frac{\partial^2 L}{\partial d_j^{(1)} \partial d_i^{(2)}} & \frac{\partial^2 L}{\partial {d_i^{(2)}}^2} & \frac{\partial^2 L}{\partial d_j^{(2)} \partial d_i^{(2)}} \\ \frac{\partial g^{(1)}}{\partial d_j^{(2)}} & \frac{\partial g^{(1)}}{\partial d_j^{(2)}} & \frac{\partial^2 L}{\partial d_i^{(1)} \partial d_j^{(2)}} & \frac{\partial^2 L}{\partial d_j^{(1)} \partial d_j^{(2)}} & \frac{\partial^2 L}{\partial d_i^{(2)} \partial d_j^{(2)}} & \frac{\partial^2 L}{\partial {d_j^{(2)}}^2} \end{bmatrix},$$

$$H_3 = \begin{bmatrix} 0 & 0 & \frac{\partial g^{(1)}}{\partial d_i^{(1)}} & \frac{\partial g^{(1)}}{\partial d_j^{(1)}} & \frac{\partial g^{(1)}}{\partial d_i^{(2)}} \\ 0 & 0 & \frac{\partial g^{(2)}}{\partial d_i^{(1)}} & \frac{\partial g^{(2)}}{\partial d_j^{(1)}} & \frac{\partial g^{(2)}}{\partial d_i^{(2)}} \\ \frac{\partial g^{(1)}}{\partial d_i^{(1)}} & \frac{\partial g^{(2)}}{\partial d_i^{(1)}} & \frac{\partial^2 L}{\partial d_i^{(1)} \partial d_i^{(1)}} & \frac{\partial^2 L}{\partial d_j^{(1)} \partial d_i^{(1)}} & \frac{\partial^2 L}{\partial d_i^{(2)} \partial d_i^{(1)}} \\ \frac{\partial g^{(1)}}{\partial d_j^{(1)}} & \frac{\partial g^{(2)}}{\partial d_j^{(1)}} & \frac{\partial^2 L}{\partial d_i^{(1)} \partial d_j^{(1)}} & \frac{\partial^2 L}{\partial d_j^{(1)} \partial d_j^{(1)}} & \frac{\partial^2 L}{\partial d_i^{(2)} \partial d_j^{(1)}} \\ \frac{\partial g^{(1)}}{\partial d_i^{(2)}} & \frac{\partial g^{(1)}}{\partial d_i^{(2)}} & \frac{\partial^2 L}{\partial d_i^{(1)} \partial d_i^{(2)}} & \frac{\partial^2 L}{\partial d_j^{(1)} \partial d_i^{(2)}} & \frac{\partial^2 L}{\partial d_i^{(2)} \partial d_i^{(2)}} \end{bmatrix}.$$

Calculate the partial derivatives.

$$\begin{aligned} \frac{\partial L}{\partial d_i^{(1)}} = \sum_{k=1}^{N} 2\delta_{10}^{(k)} \delta_{20}^{(k)} \beta_0 \Big(A_k \\ - d_i^{(2)} \Big) \exp\left(-2\delta_{10}^{(k)} \delta_{20}^{(k)} \beta_0 \left[\sum_{h=i,j} d_h^{(1)} d_h^{(2)} - A_k \sum_{h=i,j} d_h^{(1)} - B_k \sum_{h=i,j} d_h^{(2)} + C_k \right] \right) \\ + 2\lambda_1 \left(d_i^{(1)} + \frac{\alpha_1}{2\beta_1} \right) \end{aligned}$$

$$\frac{\partial L}{\partial d_i^{(2)}} = \sum_{k=1}^{N} 2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left(B_k - d_i^{(1)}\right)\exp\left(-2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left[\sum_{h=i,j} d_h^{(1)}d_h^{(2)} - A_k\sum_{h=i,j} d_h^{(1)}\right.\right.$$

$$\left.\left. -\ B_k\sum_{h=i,j} d_h^{(2)} + C_k\right]\right) + 2\lambda_2\left(d_i^{(2)} + \frac{\alpha_1}{2\beta_1}\right),$$

and so on.

Here, it is assumed that "simultaneous irradiation", i.e., $d_i^{(1)} = d_j^{(1)}, d_i^{(2)} = d_j^{(2)}$ satisfies the constraints (1) , (2) and takes the maximum value of $f(\boldsymbol{x})$. From (1),(2),

$$d_i^{(1)} = d_j^{(1)} = \sqrt{\frac{r_1}{2}} - \frac{\alpha_1}{2\beta_1} =: d^{(1)},$$

$$d_i^{(2)} = d_j^{(2)} = \sqrt{\frac{r_2}{2}} - \frac{\alpha_1}{2\beta_1} =: d^{(2)}.$$

From FOC i.e. $\frac{\partial L}{\partial d_i^{(1)}} = \frac{\partial L}{\partial d_i^{(2)}} = \frac{\partial L}{\partial d_j^{(1)}} = \frac{\partial L}{\partial d_j^{(2)}} = 0$, we get

$$\lambda_1 = \frac{\sum_{k=1}^{N} 2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left(\sqrt{\frac{r_2}{2}} - \frac{\alpha_1}{2\beta_1} - A_k\right)E_k}{\sqrt{2r_1}},$$

$$\lambda_2 = \frac{\sum_{k=1}^{N} 2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left(\sqrt{\frac{r_1}{2}} - \frac{\alpha_1}{2\beta_1} - B_k\right)E_k}{\sqrt{2r_2}}$$

and $|H_3|, |H_4|$ are

$$|H_3| = 64\lambda_1\left(d^{(1)} + \frac{\alpha_1}{2\beta_1}\right)^2\left(d^{(2)} + \frac{\alpha_1}{2\beta_1}\right)^2,$$

$$|H_4| = 16r_1r_2\left(4\lambda_1\lambda_2 - \left(\sum_{k=1}^{N}\left(2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\right)E_k\right)^2\right),$$

where $E_k := \exp\left(-4\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\left[d^{(1)}d^{(2)} - A_kd^{(1)} - B_kd^{(2)} + C_k/2\right]\right)$.

By assumption, $|H_3| \leq 0, |H_4| \geq 0$. In other words, $\lambda_1 \leq 0$ and $4\lambda_1\lambda_2 - \left(\sum_{k=1}^{N}\left(2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0\right)E_k\right)^2 \geq 0$. $\lambda_2 \leq 0$ is also easily derived.

From $\lambda_1 \leq 0$ and $\lambda_2 \leq 0$,

$$\sum_{k=1}^{N}\delta_{10}^{(k)}\delta_{20}^{(k)}\left(d^{(2)}-A_k\right)E_k=\sum_{k=1}^{N}\delta_{10}^{(k)}\delta_{20}^{(k)}\left(\sqrt{\frac{r_2}{2}}-\frac{\alpha_1}{2\beta_1}-A_k\right)E_k\le 0,$$

$$\sum_{k=1}^{N}\delta_{10}^{(k)}\delta_{20}^{(k)}\left(d^{(1)}-B_k\right)E_k=\sum_{k=1}^{N}\delta_{10}^{(k)}\delta_{20}^{(k)}\left(\sqrt{\frac{r_1}{2}}-\frac{\alpha_1}{2\beta_1}-B_k\right)E_k\le 0.$$

Because $r_1=\left(d_i^{(1)}+\frac{\alpha_1}{2\beta_1}\right)^2+\left(d_j^{(1)}+\frac{\alpha_1}{2\beta_1}\right)^2>2\left(\frac{\alpha_1}{2\beta_1}\right)^2$, $r_2=\left(d_i^{(2)}+\frac{\alpha_1}{2\beta_1}\right)^2+\left(d_j^{(2)}+\frac{\alpha_1}{2\beta_1}\right)^2>2\left(\frac{\alpha_1}{2\beta_1}\right)^2$, $\sqrt{\frac{r_1}{2}}>\frac{\alpha_1}{2\beta_1}, \sqrt{\frac{r_2}{2}}>\frac{\alpha_1}{2\beta_1}$ holds. We can get

$$4\lambda_1\lambda_2-\left(\sum_{k=1}^{N}2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0E_k\right)^2$$

$$=\frac{8{\beta_0}^2}{\sqrt{r_1r_2}}\left(\sum_{l=1}^{N}\sum_{k=1}^{N}\delta_{10}^{(k)}\delta_{20}^{(k)}\delta_{10}^{(l)}\delta_{20}^{(l)}E_kE_l\left(\sqrt{\frac{r_2}{2}}\sqrt{\frac{r_1}{2}}-\left(\frac{\alpha_1}{2\beta_1}+A_k\right)\sqrt{\frac{r_1}{2}}\right.\right.$$

$$\left.\left.-\left(\frac{\alpha_1}{2\beta_1}+B_l\right)\sqrt{\frac{r_2}{2}}+\left(\frac{\alpha_1}{2\beta_1}+A_k\right)\left(\frac{\alpha_1}{2\beta_1}+B_l\right)\right)\right)-\left(\sum_{k=1}^{N}2\delta_{10}^{(k)}\delta_{20}^{(k)}\beta_0E_k\right)^2$$

$$<\frac{8{\beta_0}^2}{\sqrt{r_1r_2}}\sum_{l=1}^{N}\sum_{k=1}^{N}\delta_{10}^{(k)}\delta_{20}^{(k)}\delta_{10}^{(l)}\delta_{20}^{(l)}E_kE_l\left(-\left(\frac{\alpha_1}{2\beta_1}+A_k\right)\frac{\alpha_1}{2\beta_1}-\left(\frac{\alpha_1}{2\beta_1}+B_l\right)\frac{\alpha_1}{2\beta_1}\right.$$

$$\left.+\left(\frac{\alpha_1}{2\beta_1}+A_k\right)\left(\frac{\alpha_1}{2\beta_1}+B_l\right)\right)$$

$$=\frac{2{\beta_0}^2}{\sqrt{r_1r_2}}\sum_{l=1}^{N}\sum_{k=1}^{N}\delta_{10}^{(k)}\delta_{20}^{(l)}E_kE_l\left(-\delta_{10}^{(k)}\frac{\alpha_1}{\beta_1}+\frac{\alpha_0}{\beta_0}-\delta_{20}^{(l)}\frac{\alpha_1}{\beta_1}\right)\frac{\alpha_0}{\beta_0}$$

$$<\frac{2\alpha_0}{\sqrt{r_1r_2}}\sum_{l=1}^{N}\delta_{20}^{(l)}E_l\left(\sqrt{2r_1}\lambda_1-\sum_{k=1}^{N}\delta_{10}^{(k)}\beta_0\left(\delta_{20}^{(l)}\frac{\alpha_1}{\beta_1}\right)E_k\right)<0.$$

This contradicts $|H_4|\ge 0$. Therefore, simultaneous irradiation does not maximize the mean survival probability of OAR.

Q.E.D.

Reference for Appendix

(1) Mas-Colell A, Whinston M, Green J. Microeconomic theory: Oxford University Press; 1995.