TFY4315 Biophysics of Ionizing Radiation
Exam 2020: Suggested Solutions

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Question 1: Theory photons

Max 15 points (3 per each of a-e)

(a) Tumor control probability (TCP)/normal tissue complication probability modeling (NTCP) curves are a convenient way to assess the therapeutic ratio of a treatment as it relates to the prescribed dose. The probability of either tumor control or tissue complication is typically sigmoidal. The therapeutic ratio can be estimated by the widest vertical separation of the TCP and NTCP curves. The ideal treatment plan (i.e., a high therapeutic ratio) demonstrates a high likelihood (e.g., ¿90%) of tumor control while maintaining TCP as low as possible.

(b) The goal of biologic response modifiers is to improve the TCP while maintaining the same NTCP, thus increasing the therapeutic index.

(c) The example in A is the worst case scenario, in which normal tissue toxicity is nearly certain at doses that would provide meaningful tumor control. Such is sometimes the case in situations where reirradiation is being considered. Examples B and C show suboptimal scenarios in which NTCP is still highly likely if trying to achieve curative doses. Of the depicted curves, example D demonstrates the highest therapeutic ratio.

(d)
- Accelerated: Same total dose as conventional, half of the overall time, two or more fractions per day
  - To reduce repopulation in rapidly proliferating tumors
  - Typically in head/neck cancer
- Hyperfractionated: less than 2 Gy per fraction and increased total number of fractions
  - To further separate early and late effects
  - To reduce late effects and improve tumor control
  - To obtain the same (or slightly increased) early effects

  - Typically in head/neck cancer
- Hypofractionated: Total number of fractions is reduced, fraction size more than 2 Gy
  - For tumors with low a/b (e.g. prostate)
  - Palliative
  - Proton therapy

(e)
- CHART: Continuous Hyperfractionated Accelerated Radiation Therapy
  - 36 fractions over 12 days (three fractions per day with 6 hour interval) to a total dose of 50.4 ? 54 Gy
  - Tumor control maintained because of the extreme acceleration of treatment time (despite low total dose)
  - Is the only accelerated treatment that has resulted in less late effects (probably because of small dose per fraction)
- ARCON: Accelerated hyperfractionated radiation therapy while breathing carbogen and with the addition of nicotinamide
  - Accelerated treatment to avoid tumor cell proliferation
  - Hyperfractionated treatment to minimize late effects
  - Carbogen breathing to overcome chronic hypoxia
  - Nictonamide to overcome acute hypoxia

Janssens et al. Journal of Clinical Oncology, 2012: From April 2001 to February 2008, 345 patients were accrued. The local tumor control at 5 years was 78% for AR versus 79% for ARCON (P = .80). The 5-year regional control was significantly better with ARCON (93%) compared with AR (86%, P = .04) and was specifically observed in patients with hypoxic tumors and not in patients with well-oxygenated tumors (100% vs 55%, respectively; P = .01). Additional points if newer/other studies are mentioned.

Question 2: Theory protons

Max 15 points (a: 3, b: 4, c: 4, d: 4)

(a) Protons are charged particles that delivers the dose as an intense burst of ionization (the Bragg peak), having mostly low LET but high LET in the Bragg peak.

Advantages:

- Superior physical dose distribution
- Sparsely ionizing, except for a very short region at the end of the particles range, just before they stop

- Precisely confine the high dose region to the tumor volume
- Minimize the dose to surrounding normal tissue
- Radiobiological properties (RBE and OER) similar to photon radiation
- For the same tumor dose, protons will deliver a lower dose to a smaller volume of normal tissue than high energy photons
- Proton therapy is a favorable treatment modality especially for tumors located near radiation sensitive critical organs

Estimated 2023 in Norway.

(b) Some reasons:

- Expensive
- Uncertainty if one hits the target precisely
- RBE is unclear
- Photon-based therapy came from the oncology discipline, whereas proton therapy came from the particle physicists. Have other traditions many places.

(c) Traditionally, the ability to deliver large doses of ionizing radiation to a tumor has been limited by radiation-induced toxicity to normal surrounding tissues. This was the initial rationale for the development of conventionally fractionated radiation therapy, where large volumes of healthy tissue received radiation and were allowed the time to repair the radiation damage. However, advances in radiation delivery techniques and image guidance have allowed for more ablative doses of radiation to be delivered in a very accurate, conformal, and safe manner with shortened fractionation schemes. Hypofractionated regimens with photons have already transformed how certain tumor types are treated with radiation therapy. Additionally, hypofractionation is able to deliver a complete course of ablative radiation therapy over a shorter period of time compared to conventional fractionation regimens making treatment more convenient to the patient and potentially more cost-effective. Recently, there has been an increased interest in proton therapy because of the potential further improvement in dose distributions achievable due to their unique physical characteristics.

(d) Example topics from the article from A. Luhr (which was literature for the exam): Proton beam irradiation has not yet reached its full potential. A major underlying reason is the lack of detailed radiobiological knowledge particularly on the clinical distribution of radiobiological effectiveness and also on effects of combination with systemic chemo- or immunotherapies. Patient stratification based on biomarker expression is still missing to identify patients with highest probability to benefit from proton radiotherapy. Overall, among the most important research avenues for improvement of proton radiotherapy based on radiobiological knowledge are:

- Systematic preclinical experiments on RBE distribution as function of dose and LET in normal tissues of animals and/ or relevant three dimensional in vitro models using late toxicity endpoints or surrogate parameters of late toxicity. Systematic preclinical evaluation of radiobiological (e.g. DNA repair, signal transduction, anti-vascular effects) and functional effects of chemotherapy or targeted drug combinations with protons versus photons including the development of biomarkers to predict tumor response.
- Development of biomarkers predicting late toxicity in patients. These can include tissue based markers but also imaging methods serving as surrogate markers. In the latter, voxel-based accuracy need to be improved. Image information need to be correlated with local dose and LET distributions. Image signatures, i.e. radiomics, may be a further strategy to predict treatment effects. Generally, biomarker development requires the collection of biomaterial, high-quality diagnostic images, and radiation treatment plans of all patients treated in prospective clinical trials.
- Translation of accumulating preclinical radiobiological knowledge into clinical proton radiotherapy treatment planning and stratification of patients for treatment in clinical trials.
- Reverse translation studies on RBE using large data bases integrating clinical outcome data, radiation treatment plans, initial and follow-up imaging studies, and (potential) biomarkers.
- Development of new clinical trial designs and involving patients and payers in how to make trials more attractive to stakeholders.
- Create large high-quality data repositories with detailed dosimetric and outcomes data for hypothesis-generating studies.

Question 3: Calculations

Max 30 points (a: 4, b: 4, c: 4, d: 4, e: 4, f: 5, g: 5)

(a) This can be calculated using the linear-quadratic formula that allows comparison of two different fractionation schedules and the resulting relative biological effective dose (BED).

$$BED = nd[1 + d\frac{\alpha}{\beta}]$$

where n is number of fractions and d is dose per fraction.

Three different combinations of input values were given. The answer should therefore be 50.4 Gy, 67.5 Gy or 72 Gy.

(b) The formula for a single-hit survival curve is

$$S = e^{-\alpha D}$$

Because the SF_2 (the surviving fraction following a dose of 2 Gy) is 0.37, it follows that

$$0.37 = e^{-\alpha D}$$

or

$$\alpha D = 1 = \alpha(2Gy)$$

Hence,

$$\alpha = 0.5Gy^{-1}$$

(c) 20 colonies/2000 cells plated = 0.01 absolute surviving fraction (1% survival). This value must be corrected for the plating efficiency of unirradiated cells, which was 40 colonies/200 cells plated = 0.2 (20% survival). Thus, the normalized percent survival is 0.01/0.2 = 0.05% = 5%.

Some had different input values; the answer should then become 7.2% or 4.4%.

(d) Since the survival curve for high LET carbon ions is exponential, the surviving fraction following 5 irradiations with a dose that results in a surviving fraction of 0.4 would be $(0.4)^5 = 0.01$.

Some had different input values; the answer should then become 0.027 or 0.082.

(e) The $\frac{\alpha}{\beta}$ ratio for this tissue can be determined by setting

$$n_1 d_1[1 + d_1\frac{\alpha}{\beta}] = n_2 d_2[1 + d_2\frac{\alpha}{\beta}]$$

where n_1 and n_2 are the number of fractions and d_1 and d_2 are the doses per fraction used for the first and second protocols, respectively. Thus,

$$25 \cdot 1.8Gy \cdot (1 + 1.8Gy/\frac{\alpha}{\beta}) = 17 \cdot 2.5Gy \cdot (1 + 2.5Gy/\frac{\alpha}{\beta}) =$$
$$45Gy + 81Gy^2/\frac{\alpha}{\beta} = 42.5Gy + 106.25Gy^2/\frac{\alpha}{\beta}$$

hence

$$25.25Gy^2/2.5Gy = 10.1Gy$$

(f) In order to achieve a 37% tumor control probability, the total dose delivered must reduce the number of surviving clonogenic cells to 1. This is based on the equation $P = e^{-M \cdot SF}$, where P is the probability of tumor cure (37% or 0.37 in this case), M is the initial number of tumor clonogens (10^6), and SF is the surviving fraction resulting from the irradiation protocol. Thus, for 10^6 clonogenic cells, a total dose that reduces the surviving fraction to 10^{-6} (i.e., 1 surviving clonogen) must be used to achieve a 37% control rate. Since the survival curve is exponential with a D_{10} of 5.75 Gy ($D_{10} = D_0 \cdot ln10 = 2.5 \cdot 2.3 = 5.75Gy$) it would be necessary to use a dose of 34.5 Gy.

(g) Three cell divisions would result in an 8-fold increase in the number of cells. Therefore, the dose would need to be increased by a dose D, where $e^{D/D_0} = 8$. Hence, $D = 2.5 \cdot ln8 = 5.2Gy$ of additional dose would be needed to achieve the same level of tumor control. It is also worth remembering that 3.3 times the number of cell doubling corresponds to one log_{10} of cell kill.

Question 4-23: Multiple choice

Correct answers given on request