Comparative Mathematical Radiotherapy of Some Dog and Human Cancers

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Methodology article

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Abstract

Background

Cancer is a serious disease in human and canine species and can be managed using surgical, chemotherapeutic, immunotherapeutic and radiotherapeutic interventions. But for radiotherapy, determination of radiotherapeutic doses for specific cancer treatment is a serious problem both in medical and veterinary oncology.

Results

In view of this, a number of formulas used in medical oncology has been adopted and applied for determination of effective radiotherapeutic doses especially for dogs. Findings revealed that the formulas could be used to estimate radiotherapeutic doses for a number of cancer diseases in dogs. More so, factors such as age, sex, type of cancer, location of cancer and biological effective dose should be considered. The most relevant formula is BED = nd [1 + (d)/(α/β)] where BED = biologically equivalent dose; d = dose per fraction; α/β = ratio for tumor (10) and n = number of fractions.

Conclusions

Metronomic radiotherapy which may be defined as repetitive exposure of cytotoxic radio-active rays of ≤ 2 Gy at regular and frequent intervals of 10-25 fractions of total 45 Gy may be safer for the treatment of malignancies in dog and human. But BED of 45 60 Gy has cancer control rate of 48 – 67%, and 50% probabilities of complications was caused by radiation rays of 54 Gy. Whereas a dose of ≥ 2Gy in 2 fractions may improve quality of life and reduce chronic pain associated with terminal malignancies.

Background

Cancer radiotherapy maybe the initial step or the last option in the treatment of benign or metastatic cancers. Therefore, biologically effective dose is a measure of time biological dose delivered by combination of dose per fraction and total dose to a specific tissue characterized by α/β [1]. Fasting caused a massive re-organization of liver chromatin that led to transcriptional response [2]. Tissue injury and radiation-induced cancers are the consequences of radiotherapy. Adjacent, near and distant tissue form the target tissue that receive high (≥ 45 Gy), intermediate (10-45Gy) and low (≤ 10 Gy) doses administered in ≥ 25 fractions [3]. However, dogs with sarcomas are models for studying biological responses to spatially fractionated radiotherapy [4]. But potential hyperthermia improved survival after radiation therapy [5]. This may be very much relevance to head and neck cancer therapy that requires 6R: repair, repopulation, reoxygenation, redistribution, remote cellular effects and radio-sensitivity [6]. Hence, precise delivery of escalated radiation doses to hypotic tumor cells is associated with better radiotherapeutic outcome [7]. Feed-forward alpha particle radiotherapy ablates androgen receptor-addicted prostate cancer in human [8]. Small doses of hyperfractionated radiation rays lower tissue toxicity by causing reoxygenation and killing hypotic tumor cells efficiently [9] despite. Immunotherapy

may be better for hypotic tumors [10]. All tumor models never reflect the full range of complex tumor and the patients [11]. In spite of all these, there is need to translate radiotherapeutic parameters of human to dog using some mathematical formulas currently applied in medical oncology.

Methods

Radiotherapeutic doses for transmissible veneral tumor (TVT), mast neoplasia, brain mass, nasal tumors, testicular seminoma and squamous cell carcinoma were calculated for optimal destruction of the cancer cells. Some vital radiotherapeutic parameters that could be used as indices of successful radiotherapy were also calculated. Biologically equivalent doses (BEDs) 2-Gy equivalent dose (EQD2) external beam radiation therapy (EBRT) and other radiotherapeutic parameters were used [12, 13]. Biologically equivalent dose (BED) of the x-ray emission is calculated as follows:

$$BED = nd\left[1 + \frac{d}{\alpha/\beta}\right]-$$

n = number of fraction; d= dose per fraction; α/β = ratio for tumors (α/β = 10). When proliferation during treatment is not incorporated, BED decreases by 1 Gy/day [14].

$$BED_{proliferation} = \sum_i BED_i - \frac{ln(2)}{\propto} x \frac{T_{treat} - T_k}{T_p}$$

Ttreat = Total treatment; T_k = Time of the proliferation on set; Tp = Effective doubling time during proliferation; α = linear parameter of LQ model; Tp = Time of proliferation following damage after treatment, Tk = available time for repopulation but no correction for repopulation if the time of treatment is shorter than Tk [14].

$$But\ BED_{EBRT} = nd\left[1 + \frac{d}{\propto/\beta}\right]$$

$$BED_{BT} = D\ \left\{1 + \frac{2D}{(\alpha/\beta)\mu T}\left[1 - \frac{1}{\mu T}(1 - e^{-\mu T})\right]\right\}$$

EBRT= External Beam Radiation Therapy; BT= Brachytherapy; D = Radiation dose; T = Duration of Brachytherapy; P = Parameter characterizing repair of sub lethal damage in the irradiated tissue; μ = ln (2)/ $T_{1/2,}$ where $T_{1/2}$ = half-life of sub lethal damage repair. EQD_2 = Effective Equivalent Dose of 2 Gy per fraction.

$$\therefore BED = Total\ Dose\ x\ RED$$

$$Then\ Total\ Dose = \frac{BED}{RE}$$

$$RED = \frac{1+d}{\propto/\beta}$$

$$EQD_2 = D \frac{BED}{1+2/\alpha/\beta}$$

$$EQD_2 = D \frac{d+\alpha/\beta}{2+\alpha/\beta}$$ Iso effective formula

But compensability index =

$$\left(1 - \frac{New\ tumor\ effect}{planned\ tumor\ effect}\right)^2 + \left(\frac{New\ Normal\ Tissue\ effect}{planned\ Normal\ Tissue\ effect} - 1\right)^2$$

The index runs aggressively from defensive to offensive, which may serve as a decision support system, based on existing and established recommendations [15].

$$\text{Amount of Radioactivity Required (GBQ)} = \frac{\text{[Desired Dose (Gy)] x [Mass of liver target (kg)]}}{50}$$

$$\text{Radio Therapeutic Dose (Gy)} = \frac{\text{50 [Injected Activity (GBq)] [1-F]}}{\text{Mass of liver Target (kg)}}$$

F = fraction of injected activity localizing in the liver as measured by Tc 99m scintigraphy. The upper limit of injected activity is F x A = 0.61GBq (16.5mCi) for hepatic arterial Y trium glass microspheres (therasphere) for unresectable hepatocellular caranoma [16].

The risk of radiotherapy can be calculated as follows:

$$Risk = B \times RED \times U$$

B = the organ specific cancer induction rate; RED = Risk Equivalent Dose; U= variable (age, sex)

$$OED = \frac{1}{Vt} \times V \times RED$$

OED = Organ Equivalent Dose; V_t = Volume of Treated Organ; V= Volume of Organ, RED = Risk Equivalent Dose

Malignancies secondary to radiotherapy can be assessed using the above formulas [17].

$$\text{Activity (GBq)} = \text{liver involvement activity 1sm x 1pm}$$

$$\text{Dose (GBq)} = (BSA^{-0.2}) = \left(\frac{Percent\ tumor\ involvment\ of\ liver}{100}\right)$$

BSA= is a proxy for liver volume (right- lobe 60%); Lobar dose (GBq) = ($BSA^{-0.2}$) = (% tumor involvement of treated /100) x (% of total liver).Modified partition model to solve for lung and normal liver dose limits using radius of tumors uptake to normal liver on MAA [18].

$$\frac{T}{N} = \frac{A\ tumor\ /\ Tumor}{A\ tumor\ /\ Tumor}$$

$$\text{D normal liver} = \frac{49.38A\ total}{m\ Nornal\ liver + \frac{T}{N} m\ Tumor}\ \text{x L}$$

$$\text{D lung} = \frac{49.38A\ total}{m\ Lung}\ \text{x L}$$

$$\text{But therasphere activity required (GBq)} = \frac{\text{Desired dose (Gy) x mass of liver (kg)}}{50\ \text{x}(1-\text{LSF})\ \text{x}\ (1-\text{R})}$$

$$\text{Total Dose (TD)} = \text{Half-life } (T\tfrac{1}{2}) \text{ x } 1.44$$

All the formulas (i – xx) could be used for calculation of radiotherapeutic parameters for dog and human.

Results

The biologically equivalent dose (BED), dose per fraction, time range of therapy, number of dose fractions, effective equivalent dose of 2 Gy per fraction, half-life of radiation rays for living tissue mean survival period of the affected patients for dogs and human are presented in Table 1 and 2 , respectively.

Discussion

The BED of 45 – 60 Gy reported, for dog and human cancers in the present study (Table 1 & 2) agrees with the report indicating that cancer control rate of 48-67% was achieved at 45 – 60 Gy. But 50% probability of causing serious complications was 54 Gy [19]. TVT was treated using 50 Gy in 3 fractions followed by 25Gy in 2 fractions over 4 days. Whereas chondrosarcoma was treated with 20 Gy [4]. Dose-response relationship of radiorays varies with mouse strain, tissue/organ and gender. Risk of radiotherapy to *Macaca mulatta* was not increased at 0.25 – 2.8 Gy. But the risk increased significantly from 1-45 Gy for stomach and pancreas, bladder as well as rectum (1-60 Gy) and kidney (1-15 Gy). Normal tissue tolerance to radiotherapy is a complex issue and multifunctional in nature, because 5% rate of radiotoxicity is unacceptable in some cases as 20% may be acceptable in other cases. Therefore, clinical Judgment of the physician should prevail [20]. The half-life of radiation rays is much higher in mast cell neoplasia (198 Gy), brain mass (104.2 Gy), nasal tumors (125 Gy), squamous cell carcinoma (138.9 Gy), soft tissue sarcoma (115.8 Gy) and canine soft tissue sarcoma (157.8 Gy), respectively, suggesting much higher risk of radiotoxicity that may rise from radiation therapy of the affected organs. The half-life of 90 Gy is 66 days. But the average half-life is equal to the half-life multiplied by 1.44 which equals the total dose received during treatment [21]. The relative risk of second malignant neoplasm is 0.7 - 1.8 [22]. Hemangiopericytoma is more responsible to rathiotherapy than fibrosarcoma. Dose per fraction of 2 – 20 Gy reported in the present study agrees with the report that the risk for organs is the dose above 2 Gy [23]. The use of fraction in excess of 3.5 Gy could induce osteosarcoma in dogs that

received 10 fractions ranging from 3.5 – 5 Gy in three weeks. The tumor was developed in 4-5 Gy radiation therapy [24]. Also, radiotherapy of bulky soft tissue sarcomas using 20 or 25 Gy caused grade 1 skin toxicity in 3 out of 6 dogs. But chondrosarcoma (21 cm) treated with radiation ray of 20 Gy was not evaluable [4].But median survival period of 2 years has been reported for radiotherapy of canine thyroid carcinoma of 10 cm in diameter using 6.5 – 8 Gy fractions [25]. A fractional dose of 2 Gy at week 1, 3 and 4 yielded optimal relief [26] and brain glioma was tolerant to re-irradiation with median survival of 26 months [27].The intraoperative radiotherapy associated with tumor in dogs was 20-35 Gy [28]. However palliative radiotherapy which controls pains from the incurable tumor, and improves quality of life could be used [29]. Hence, palliative dose of 2 fractions for osteosarcoma; 800 cGy (lcGy = 1rad) followed by 800 cGy after 24 h making a total of 1600 cGy was used. A median survival period of 2.7 yr was reported for dogs with mast cell tumors treated with radiation therapy. But leukotrichia resulted from palliative radiotherapy of osteosarcoma 3 months after treatment [29]

This improvement might have originated from anti-metastatic immune activities by NK cells harvested from dogs treated with a dose of 9 Gy once weekly for 4 treatments. Out of the treated 10 dogs, 5 remained metastasis-free at 6 months, whereas there was regression of suspected pulmonary nodule detected at the time of diagnosis [30]. The choice of cancer therapeutic modalities is based on tumor type, histologic grade, and stage that may include surgery, radiotherapy, chemotherapy, immunotherapy, adjuvant and neo-adjuvant therapies [31]. But effective ablative radiotherapy of a local tumor requires $CD8^{+}$T cells which is a dynamic strategy for cancer treatment [32]. Single radiotherapy may be more effective against bulky tumors than fractionated radiotherapy. SRT takes 4 – 6 months to shrink after which surgery may be considered. But pet owners have reduced risk of non-Hodgkin's lymphoma as compared to non-owners [33]. Hence pet ownership may decrease the incidence of cancer in humans [34].

Neoplasm was the most common terminal disease in 73 out of 82 canine breeds and the most common cause of death in dogs greater than 1 yr of age with an incidence greater than 3 times that of traumatic injury [35]. Unluckily, not all cancers respond well to radiation therapy including soft tissue sarcoma [36]. Prostate tumors of dogs, most commonly, adenocarcinomas are models of prostate neoplasia in humans [37]. Prostate carcinoma in dog treated with intraoperative orthovoltage resulted in median survival time of 114 days [38]. But intensity-modulated and image-guided radiation therapy on genitourinary carcinomas showed clinical benefit in 9 out of 10 dogs with median survival time of 654 days and dogs with prostate carcinoma had survival time of 317 days [39]. Ameloblastoma and keratinizing ameloblastoma observed in 3-13 years-old dogs were treated with radiation rays and one survived for 4.8 months with no-evidence of tumor regrowth. But regrowth was observed in 3 dogs at 6, 21, 34 months after completion of radiotherapy [40]. Stereotactic body radiation therapy (SBRT) for heart-base tumors in dogs resulted in median survival day of 408 – 751 days [41]. Canine soft tissue dose per fraction daily, resulted in median survival of 1,851 days, but median time to local recurrence was 540 days as compared to other tumors (2, 270 days). Hence radiotherapy could be used as an adjuvant therapy for incompletely excized soft-tissue sarcomas with long-term median survival in the affected patients [42]. One gray is equal to 100 rads (Dabielzig and Thrall, 1982). Exposure to weekly radiation of 8 Gy with carboplatin

every 21 days for 4 times resulted in mean survival time (390 days) for stage I, stage II (1, 286 days), stage III (159 days) and stage IV (90 days) respectively. Hence radiotherapy is a viable palliative treatment of canine oral melanoma [43]. But acute radiation side-effects are completely healed 4-week post radiation treatment in nontonsillar squamous cell carcinoma [44]. A total dose of radiation (48 Gy) of 12 fractions given 4 Gy per fraction thrice weekly led to continuous decrease in tumor size after completion of treatment [45]. Late toxicity is a major concern for patients treated with adjuvant radiotherapy [46]. But single radiotherapeutic dose of 24 Gy not 3 x 9 Gy fractions coupled early tumor ischaemia and or reperfusion to human cancer ablation [47]. Diffusion-weighted and positron emission tomography (PET)/magnetic resonance imaging (MRI) may reveal radiotherapy induced changes and complications [48]. Primary or adjunctive radiotherapy has become a mainstay for intracranial neoplasia and more beneficial than surgery in case of meningiomas [49]. Median survival time of radiation treatment is 33 – 49 weeks [50]. Radiotherapeutic dose of 2 – 5 fractions are referred to as stereotactic radiosurgery compared to 16 – 20 fractions for standard radiation protocols [51]. Since salinomycin can kill cancer stem cells and therapy resistant cancer cells [52], it may be used in combination with radiotherapy in treatment of very resistant cancers. Radiotherapy enhances natural killer cell and cytotoxicity in canine sarcoma [53]. Canine models of malignant cancers such as osteosarcomas are more advantageous and reliable than current murine models [54]. Combination of doxorubicin, cisplatin vinblastine or cyclophosphamide with radiotherapy of tonsillar squamous carcinoma of dog yielded a favourable higher rate of therapeutic response and significantly longer survival times [54]. But radiotherapy is a viable alternative for the palliative treatment of canine oral melanoma [43], in spite of the fact that hypoxia has negative influence on determining response to conventional therapy [56], suggesting that substantial differences in intrinsic radio-sensitivity exist in canine cancers [57]. Fluorodeoxyglucose (FDG)/PET is an effective imaging technique for lymph mode staging of locally advanced cervical carcinoma with negative computed tomography (CT) findings, despite PET-CT could customize and guide brachytherapy planning [58]. However, choline PET/CT is complementary to imaging modalities with the advantage of restaging prostate cancer in a single step [59]. But FDG-PET is mainly used for diagnosis, staging, early response prediction and re-staging of different gastrointestinal tumors [60] and allow more thorough staging avoiding unnecessary radiotherapy [61]. FDG-PET is also recommended in case of cervical metastases from an unknown primary tumor [62]. Whereas the intensity modulated radiotherapy (IMRT) combined with treatment plan based on imaging is individualized, the phenomenon called customized radiation therapy or dose painting [63]. Hence individual adaptation based on functional PET imaging is highly promising [64]. Respiratory gated (RD) 4D-PET/CT improved diagnostic performance of PET/CT and defines better, the target volume for radiation therapy [65]. Quantitative analysis with PET-imaging protocols could help in tumor diagnosis [66]. But segmentation of PET-images could delineate target cancer cells during radiation therapy [67]. Accurate positioning and immobilization is very vital for effective radiotherapy [68], which is a function of nuclear medicine [69]. This requires potential radiopharmaceuticals that include tracers, monitoring proliferation, aminoacid metabolism, hypoxia, lipid metabolism and receptor expression [70]. Really personalized approach of radiation target volume delineation requires many parameters [71], suggesting that the use of PET requires awareness among radiotherapists and oncologists [72]. Intensity modulated radiotherapy (IMRT)

of 0.3-3.5 Gy and 3D tangetial beams of 0.4-4.3 Gy have been suggested for heart and lung. The median dose to the lung of IMRT was 4.9-5 Gy and 5.6 Gy for the 3D tangetial beams, respectively. Hence, IMRT technique for early breast cancer allows more homologous dose distribution in target volume, but reducing the dose to critical organ.

Conclusion

Formulas used for calculation of radiotherapeutic parameters in humans are also applicable to dog. But parameters such as sex, age, tumor type, staging and radiotherapeutic dose must be considered. Therapeutic dose (2 Gy) of 10-25 fractions of total 45 Gy may be safer and improve the quality of life of affected dog and human.

Abbreviations

BED = biologically equivalent dose; TD = total dose; EQD_2 = Effective equivalent dose of 2 Gy per fraction; T(1/2) = Half-life of radiation rays in living tissues; MSP = Mean Survival Period; α/β = ratio for tumors - = No available information

Declarations

Author's contributions

SAS designed, carried out the study, analyzed data, wrote and proof read the manuscript.

Competing interest

No financial competing interest.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

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Tables

Due to technical limitations, Tables 1-2 available in the Supplementary Files section below.

Supplementary Files

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- Table21.docx