Radiobiological Aspects

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Radiobiological Aspects
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• How does single fraction IORT work?
• Why is 50 Kv x-rays, radiobiologically more effective
• What is the ‘Sphere of Influence’
• Is 20Gy single fraction dose tumoricidal?
Secondary Electrons
Radiobiological Aspects

Radiation Damage

Indirect Action

Direct Action

Disease cell
Rate of DNA damage > rate of repair

Healthy cell
Rate of DNA damage = rate of repair

Double-strand DNA damage

Single-strand DNA damage

Pathology

nuclear DNA un repaired
mitochondrial DNA un repaired

Damage

cancer

up to 500,000 DNA modification events per cell per day
The Linear Quadratic Model

\[ SF = \exp(- (\alpha D + \beta D^2)) \]

\[ \text{BED} = D[1 + d/(\alpha/\beta)] \]

The BED represents the dose that is calculated to be required to reach a certain level of effect when the total dose, \( D \), is given in very small fractions.

The classical BED expression is not applicable when comparing fractionation schemes obtained with different radiation qualities:

high LET IORT vs low LET standard Radiotherapy
Radiation Quality

With high LET radiation the particles give rise to well-defined tracks of ionization which cause extensive damage along the path.

With low LET radiation the interactions that are produced are relatively far apart from each other, therefore, they will be spread throughout the cell, making for a more uniform dose distribution throughout the cell.
Bullet Train .vs Car
(a) High LET radiation

- Clustered DNA damage
- Radiation:
  - ~a few nm

(b) Low LET radiation

- Ionization
- Excitation
- Isolated lesions

DNA molecule
Relative Biological Effectiveness (RBE)

$$RBE = \frac{X - \text{rays dose to produce a given effect}}{\text{test radiation dose needed to produce the same biological effect}}$$

Factors that determine RBE
- Radiation quality (LET)
- Radiation dose
- Number of dose fractions
- Dose rate
- Biologic system or endpoint

Why is radiation with an LET of 100 keV/\mu m optimal?

- At this density of ionization, average separation density between ionizing events roughly coincides with diameter of DNA double helix, i.e., 2nm (20A)
- Radiation of this density has the greatest probability of causing a double-strand break by the passage of a single charged particle.
High LET vs Low LET

As the LET increases the cell survival Curve changes: the slope of the cell survival curve increases (becomes steeper) and $D_0$ becomes smaller.

- The same dose kills more cells if delivered as high LET radiation
- 5 Gy with INTRABEAM are more effective than 5 Gy with Linac
The Intraoperative Device
low energy X-rays: 30-50 kV

A Novel Mobile Device for Intraoperative Radiotherapy (IORT)
U. Kraus-Tiefenbacher Onkologie 2003; 26:596-5998
IORT device temporarily inserted into lumpectomy cavity

Zone of Radiation
Risk of Local Recurrence (RLR) and Sphere of Equivalence

Sphere of equivalence in relation to excised tumour plus 10 mm margin. The relative dose and probability of recurrence are given on the y-axis as function of arbitrary distances on the x-axis. For IORT, the probability of recurrence increases as the absorbed dose decreases with depth in the tumour bed. The recurrence is constant for the external beam uniform dose irradiation.

20 Gy single dose at the applicator surface  →  Equivalent Dose $\text{EQD}2 = 67.8-73.0$ Gy
Exceeding 50 Gy given in a standard course of external radiotherapy
Patients who had previous whole brain radiation therapy can safely have 20Gy single fraction using Gamma Knife radiosurgery to areas of relapse if lesion is around 2 cm. Hence IORT delivered as a boost with EBRT or alone as adjuvant PBI should be safe and tumoricidal in the immediate vicinity of the tumor cavity.
SINGLE DOSE RADIOSURGICAL TREATMENT OF RECURRENT PREVIOUSLY IRRADIATED PRIMARY BRAIN TUMORS AND BRAIN METASTASES: FINAL REPORT OF RTOG PROTOCOL 90-05

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Purpose: To determine the maximum tolerated dose of single fraction radiosurgery in patients with recurrent previously irradiated primary brain tumors and brain metastases.

Methods and Materials: Adults with cerebral or cerebellar solitary non-brainstem tumors ≤ 40 mm in maximum diameter were eligible. Initial radiosurgical doses were 18 Gy for tumors ≤ 20 mm, 15 Gy for those 21–30 mm, and 12 Gy for those 31–40 mm in maximum diameter. Dose was prescribed to the 50–90% isodose line. Doses were escalated in 3 Gy increments providing the incidence of irreversible grade 3 (severe) or any grade 4 (life threatening) or grade 5 (fatal) Radiation Therapy Oncology Group (RTOG) central nervous system (CNS) toxicity (unacceptable CNS toxicity) was < 20% within 3 months of radiosurgery. Chronic CNS toxicity was also assessed.

Results: Between 1990–1994, 156 analyzable patients were entered, 36% of whom had recurrent primary brain tumors (median prior dose 60 Gy) and 64% recurrent brain metastases (median prior dose 30 Gy). The maximum tolerated doses were 24 Gy, 18 Gy, and 15 Gy for tumors ≤ 20 mm, 21–30 mm, and 31–40 mm in maximum diameter, respectively. However, for tumors < 20 mm, investigators’ reluctance to escalate to 27 Gy, rather than excessive toxicity, determined the maximum tolerated dose. In a multivariate analysis, maximum tumor diameter was one variable associated with a significantly increased risk of grade 3, 4, or 5 neurotoxicity. Tumors 21–40 mm were 7.3 to 16 times more likely to develop grade 3–5 neurotoxicity compared to tumors < 20 mm. Other variables significantly associated with grade 3–5 neurotoxicity were tumor dose and Karnofsky Performance Status. The actuarial incidence of radionecrosis was 5%, 8%, 9%, and 11% at 6, 12, 18, and 24 months following radiosurgery, respectively. Forty-eight percent of patients developed tumor progression within the radiosurgical target volume. A multivariate analysis revealed two variables that were significantly associated with an increased risk of local progression, i.e., progression in the radiosurgical target volume. Patients with primary brain tumors (versus brain metastases) had a 2.85 greater risk of local progression. Those treated on a linear accelerator (versus the Gamma Knife) had a 2.84 greater risk of local progression. Of note, 61% of Gamma Knife treated patients had recurrent primary brain tumors compared to 30% of patients treated with a linear accelerator.

Conclusions: The maximum tolerated doses of single fraction radiosurgery were defined for this population of patients as 24 Gy, 18 Gy, and 15 Gy for tumors ≤ 20 mm, 21–30 mm, and 31–40 mm in maximum diameter. Unacceptable CNS toxicity was more likely in patients with larger tumors, whereas local tumor control was most dependent on the type of recurrent tumor and the treatment unit. © 2000 Elsevier Science Inc.
In many European countries for decades, elderly patients with small skin cancers (BCC & SCC) get treated with 50 to 100 KV x-rays, to a dose of 20Gy in a single fraction. Hence 20Gy is a tumoricidal dose as well a safe dose, in the immediate vicinity of the tumor cavity and overlying skin.
Original Article

Single Fraction Radiotherapy for Small Superficial Carcinoma of the Skin

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ABSTRACT:
Aims: To define the optimal dose and maximum tumour size of basal and squamous cell carcinoma of skin that can be treated by single fraction radiotherapy.
Materials and methods: A review was undertaken of 1005 lesions of basal/squamous cell carcinoma of the skin involving 806 patients treated at a single centre with 10 years of follow-up. Doses of 18, 20 and 22.5 Gy were used. The recurrence and necrosis free survival rates for different anatomical sites and radiation doses were calculated.
Results: The overall disease-free and necrosis-free rates at 5 years were 90% and 84%, respectively. The crude 10-year recurrence rate was 4% (95% CI 3.4–5.4%), with late skin necrosis at 6% (95% CI 4.8–7.2%). There was no difference in tumour recurrence rates between 20 and 22.5 Gy (P = 0.3), but there was a significantly higher skin necrosis rate at the treated site in the patients who had received 22.5 Gy (P = 0.003). Most skin necrosis healed spontaneously, with only 16% requiring surgical intervention. Tumours involving the inner canthus had a significantly higher recurrence rate than those involving other areas of the head and neck.
Conclusions: Single fraction radiotherapy is an acceptable treatment for small superficial BCC and SCC of the head and neck region in patients who have difficulty attending multiple hospital visits as long as the field size required for treatment is no larger than 3 cm in diameter. The optimal applied dose for such a lesion on a flat surface is 20 Gy. Chan, S. et al. (2007). Clinical Oncology 19, 256–259

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