Associazione Italiana Radioterapia Oncologica

Aspetti fisici e radiobiologici dell'ipofrazionamento

Stefano Pergolizzi

Treviso, 7 Giugno 2013

TABLE I. Comparison of typical characteristics of 3D/IMRT radiotherapy and SBRT.

Characteristic	3D/IMRT	SBRT
Dose/fraction	1.8–3 Gy	6–30 Gy
No. of fractions	10–30	1–5
Target definition	CTV/PTV (gross disease+clinical extension): Tumor may not have a sharp boundary.	GTV/CTV/ITV/PTV (well-defined tumors: GTV=CTV)
Margin	Centimeters	Millimeters
Physics/dosimetry monitoring	Indirect	Direct
Required setup accuracy	TG40, TG142	TG40, TG142
Primary imaging modalities used for treatment planning	CT	Multimodality: CT/MR/PET-CT
Redundancy in geometric verification	No	Yes
Maintenance of high spatial targeting accuracy for the entire treatment	Moderately enforced (moderate patient position control and monitoring)	Strictly enforced (sufficient immobilization and high frequency position monitoring through integrated image guidance)
Need for respiratory motion management	Moderate—Must be at least considered	Highest
Staff training	Highest	Highest+special SBRT training
Technology implementation	Highest	Highest
Radiobiological understanding	Moderately well understood	Poorly understood
Interaction with systemic therapies	Yes	Yes

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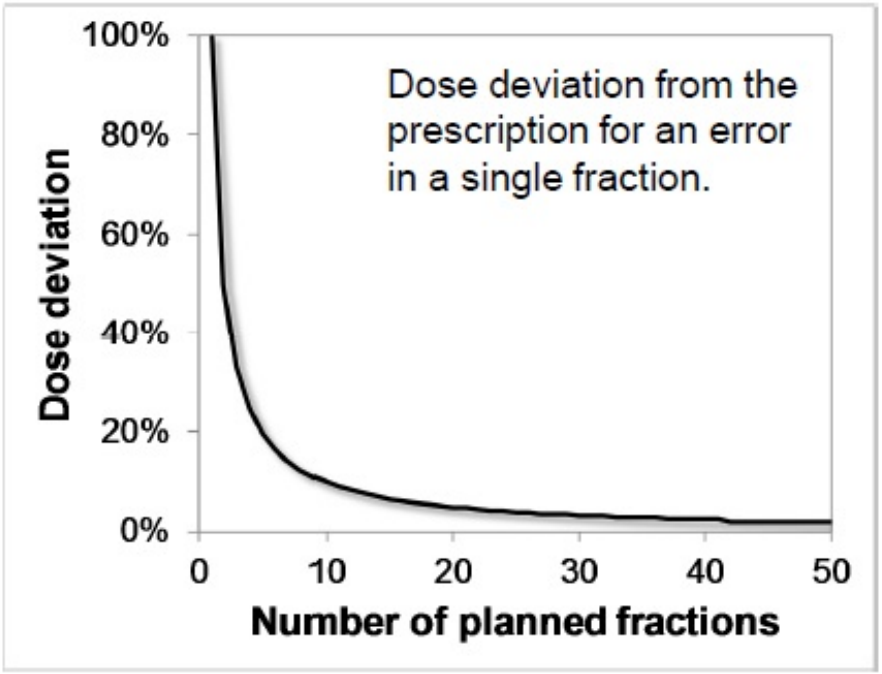
Problema


Dose deviation from the prescription for an error in a single fraction.
Dose deviation
100%
80%
60%
40%
20%
0%
0
10
20
30
40
50
Number of planned fractions


LA RADIOTERAPIA PALLIATIVA CON TECNICHE SPECIALI DELLA MALATTIA METASTATICA
TREVISO
7 giugno 2013

Due scenari

A. Bersagli “fissi”

Encefalo

Colonna

Altri

B. Bersagli “in movimento”

Polmone

Fegato

Altri

Immobilizzazione

↓

Acquisizione immagini

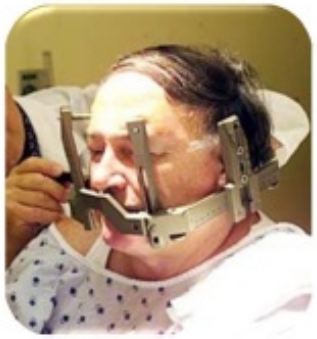
↓

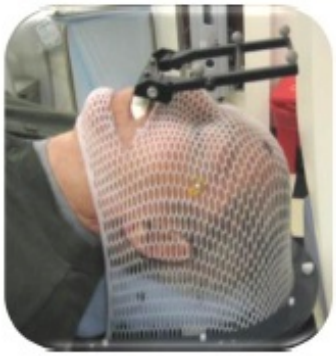
Pianificazione

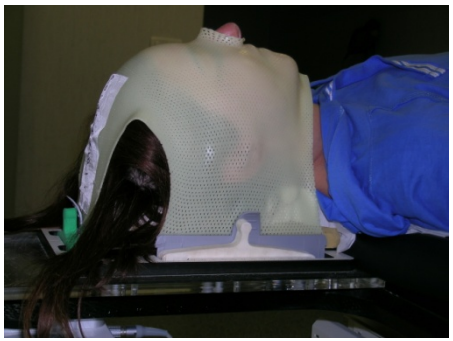
↓

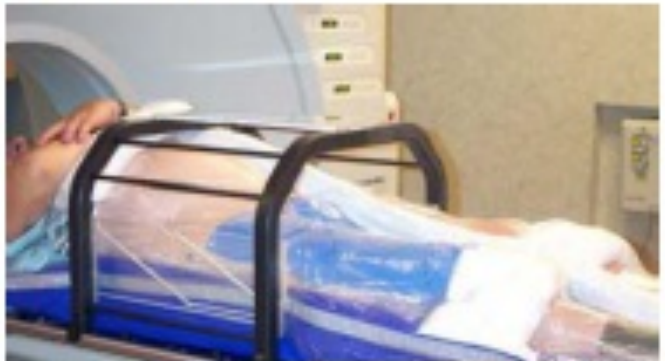
Trattamento

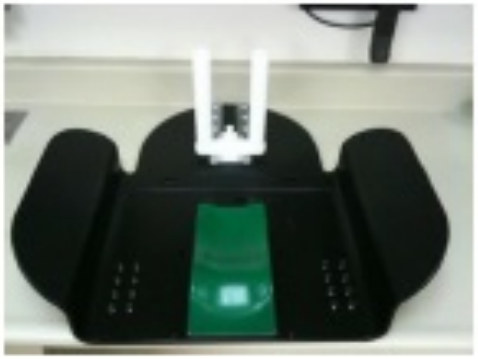
Framed → **Frame-less**

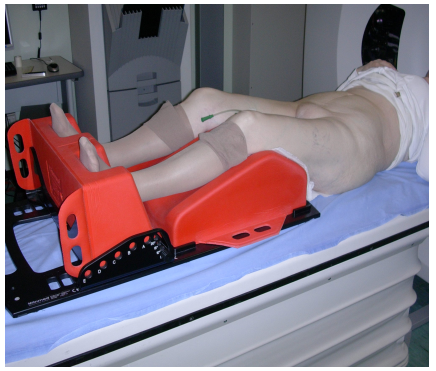








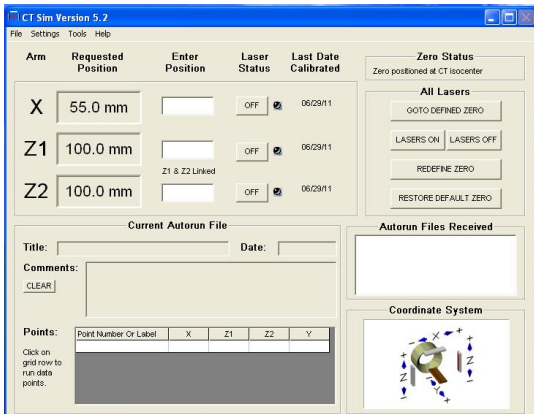




Laser Sagittale

Laser Laterale sinistro

Laser Laterale destro



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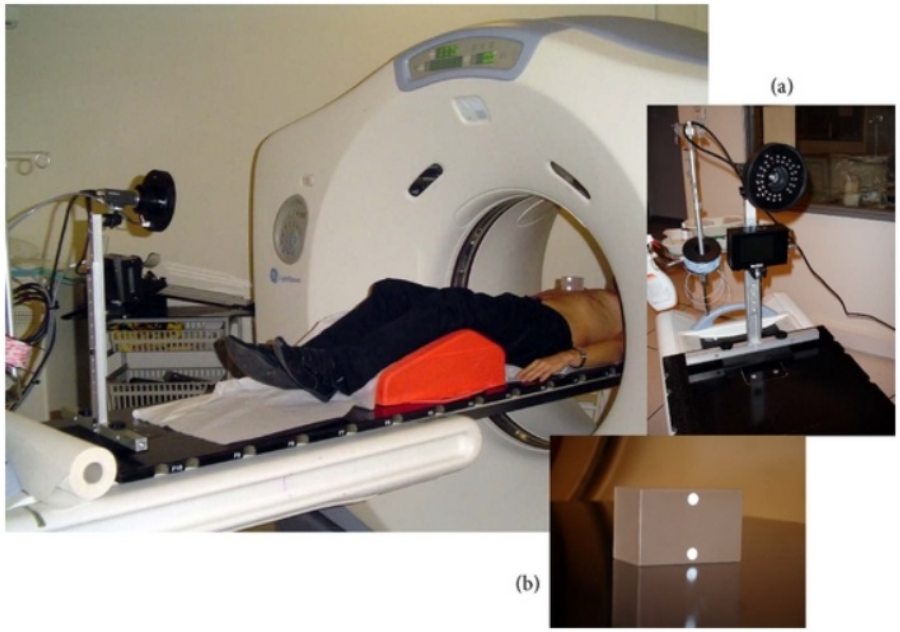

Hindawi Publishing Corporation
ISRN Pulmonology
Volume 2013, Article ID 519602, 13 pages
http://dx.doi.org/10.1155/2013/519602

Hindawi

Review Article

Respiratory Gating for Radiotherapy: Main Technical Aspects and Clinical Benefits

Philippe Giraud[1] and Annie Houle[2]

Figure 1: The VARIAN RPM system. An infrared camera (a) illuminates a marker on which are attached two reflectors (b). The marker is placed on the patient's abdomen.

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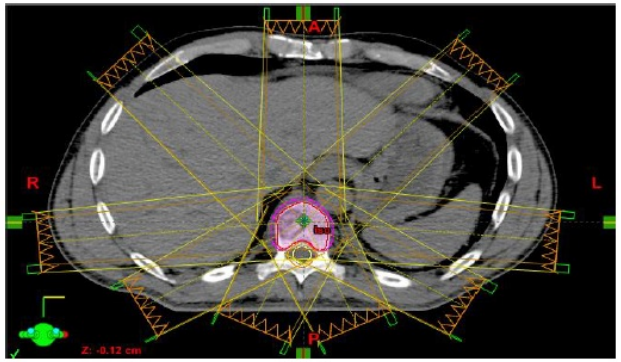
Treatment Planning

Rapida caduta di dose fuori dal target

Rispetto organi a rischio

Treatment Planning



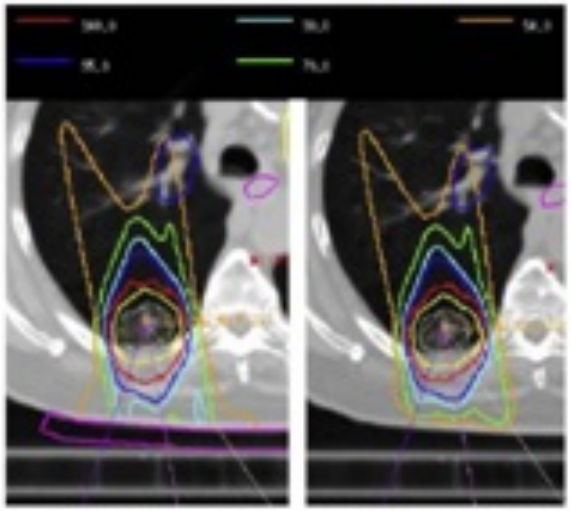
-Uso di campi multipli “concentrici”

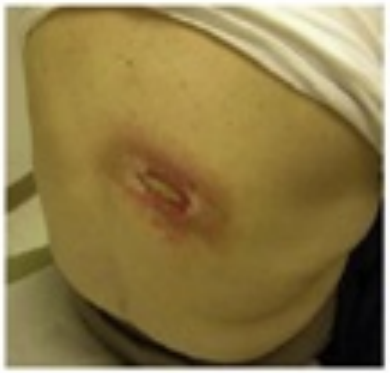
-Numero adeguato di fasci mantenendo entrance dose <30% dose cumulativa

-Evitare sovrapposizione fasci

Multiple Beams

5 – 11 static beam OR 1 – 3 arcs





B Hoppe et al, IJROBP, 2008

Treatment Planning

-Energia fotonica 6MV.

-Prescrizione dose ad isodosi “basse” (es. 80%) -> No margine per penombra

-Dosi di tolleranza degli organi a rischio diverse rispetto frazionamento standard

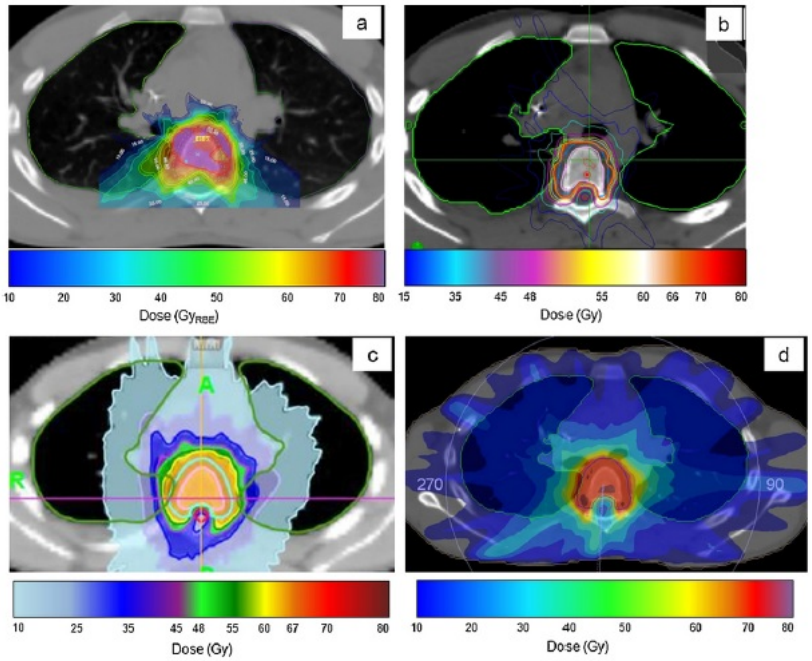
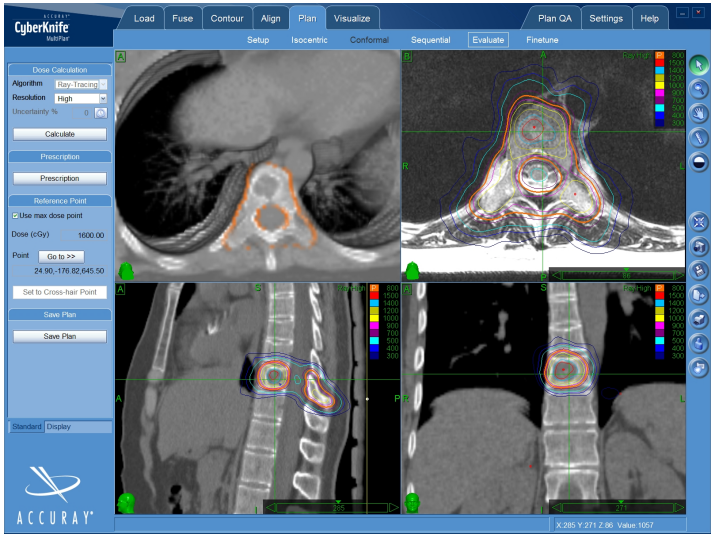


Fig. 1. Distribution de dose axiale à l'isocentre pour le palier 70,4 Gy$_{(\text{dose biologique effective})}$ dans le scénario 1. a : protonthérapie ; b : radiothérapie stéréotaxique robotisée ; c : tomothérapie ; d : arcthérapie. La radiothérapie conformationnelle tridimensionnelle a été comparée avec les techniques innovantes telles que : modulation d'intensité statique, tomothérapie hélicoïdale, arcthérapie volumétrique modulée, radiothérapie stéréotaxique robotisée et protonthérapie avec diffusion passive.
Axial dose distribution for a prescribed dose of 70.4 Gy$_{(RBE)}$ in the isocentric slice in case 1. a: passive scattering protontherapy; b: stereotactic body robotic radiotherapy; c: helical tomotherapy; d: volumetric modulated arc therapy.



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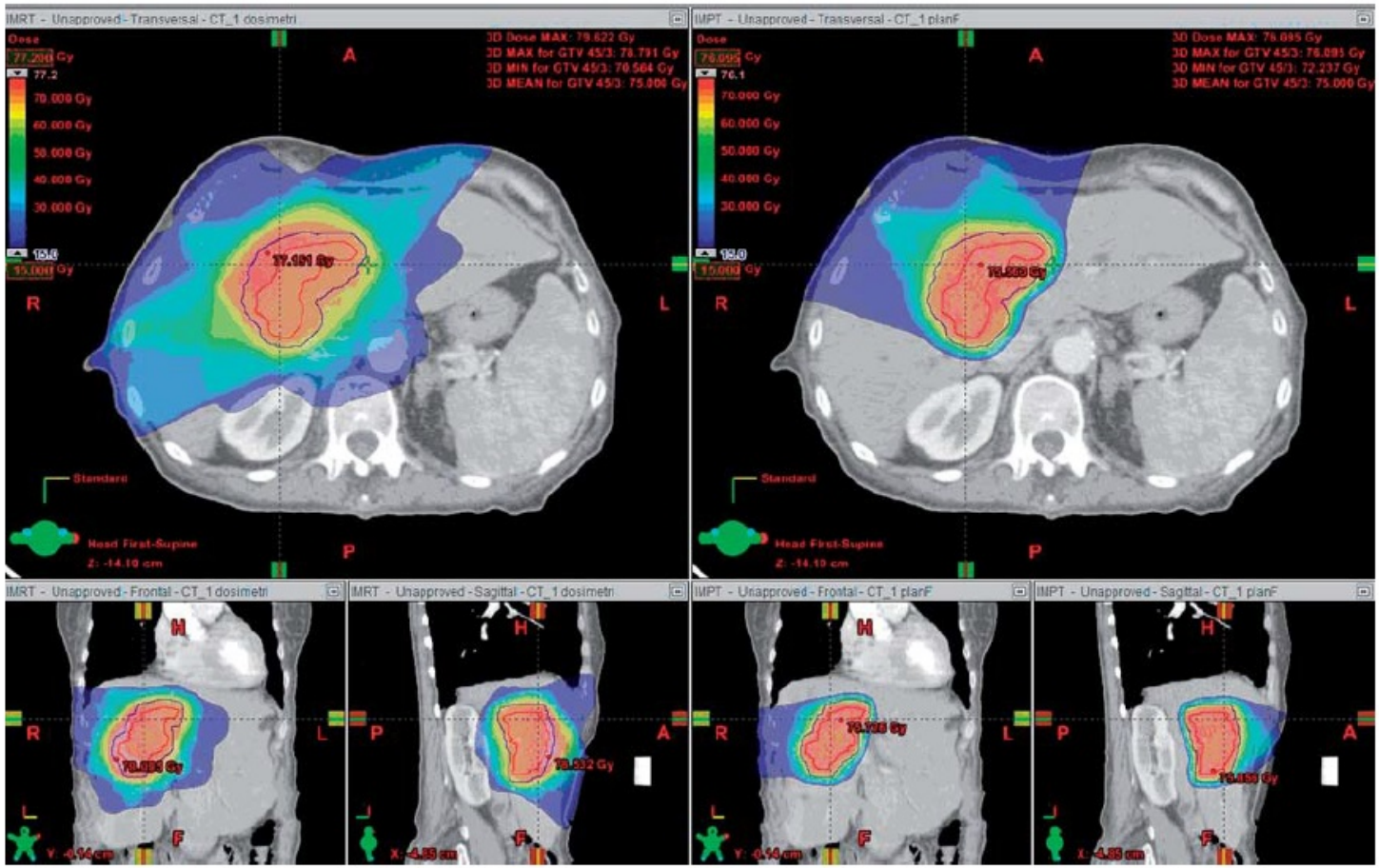

Figure 1. Patient with solitary liver metastasis (CTV = 84 cm^3) planned with IMRT (left) and IMPT (right). Threshold for dose colour wash is 15 Gy. Red and purple lines indicate CTV and PTV, respectively.

Treviso, 7 Giugno 2013

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Sterilizzazione senza danno scrotale

Treviso, 7 Giugno 2013

Perché frazionare?.....

le 4 R della Radiobiologia

	TUMORE	TESSUTO SANO
RIPARAZIONE	bad	good
RIPOPOLAZIONE	bad	good
RIDISTRIBUZIONE	good	bad
RIOSSIGENAZIONE	good	bad

- La difficoltà principale è tradurre in parametri biologici realistici.

Modello Lineare Quadratico : Dose e Frazionamento in Radioterapia

- Il modello predittivo "*LINEARE QUADRATICO*" consente di valutare l'efficacia delle diverse schedule di frazionamento.

- Il *modello lineare quadratico* assume che vi siano 2 componenti da considerare per quanto concerne il cell-killing mediato da radiazioni ionizzanti

  1) una componente proporzionale alla dose
  2) una componente proporzionale al quadrato della dose

$$S = e^{-\alpha D - \beta D2}$$

- La formula più comunemente in uso per il calcolo della dose di isoeffetto con il *modello LQ* è:

$$BED = nd\,(1+d/[\alpha/\beta])$$

Dal punto di vista clinico, per esempio, la stessa dose totale di 40 Gy, erogata in 20 frazioni da 2 Gy, in 10 frazioni da 4 Gy, o in 4 frazioni da 10 Gy corrisponderà ai seguenti BEDs:

- 20 frazioni da 2 Gy → BED = 48 Gy
- 10 frazioni da 4 Gy → BED = 56 Gy
- 4 frazioni da 10 Gy → BED = 80 Gy

Modello lineare quadratico

E’ pratico (pochi parametri)

Valore predittivo ben documentato

Dubbia validità per frazioni >8-10Gy

Non è basato su modelli biologici

Ignora la presenza di sottopopolazioni cellulari

Ignora il danno vascolare e stromale

Ignora i meccanismi molecolari e le cellule staminali neoplastiche

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Seminars in
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The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction

David J. Brenner, PhD, DSc

The tool most commonly used for quantitative predictions of dose/fractionation dependencies in radiotherapy is the mechanistically based linear-quadratic (LQ) model. The LQ formalism is now almost universally used for calculating radiotherapeutic isoeffect doses for different fractionation/protraction schemes. In summary, the LQ model has the following useful properties for predicting isoeffect doses: (1) it is a mechanistic, biologically based model; (2) it has sufficiently few parameters to be practical; (3) most other mechanistic models of cell killing predict the same fractionation dependencies as does the LQ model; (4) it has well-documented predictive properties for fractionation/dose-rate effects in the laboratory; and (5) it is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction. To date, there is no evidence of problems when the LQ model has been applied in the clinic.
Semin Radiat Oncol 18:234-239

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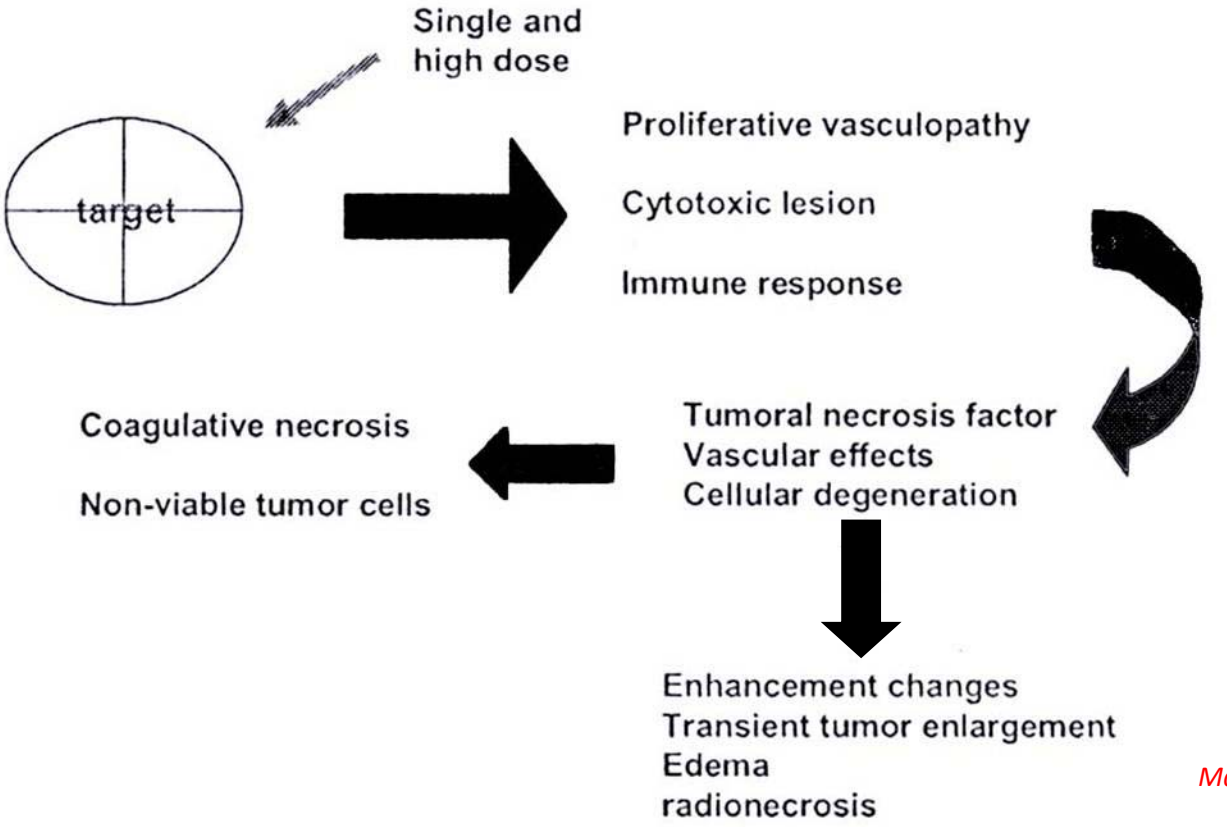
The Linear-Quadratic Model Is Inappropriate to Model High Dose per Fraction Effects in Radiosurgery

John P. Kirkpatrick, MD, PhD, Jeffrey J. Meyer, MD, and Lawrence B. Marks, MD

The linear-quadratic (LQ) model is widely used to model the effect of total dose and dose per fraction in conventionally fractionated radiotherapy. Much of the data used to generate the model are obtained in vitro at doses well below those used in radiosurgery. Clinically, the LQ model often underestimates tumor control observed at radiosurgical doses. The underlying mechanisms implied by the LQ model do not reflect the vascular and stromal damage produced at the high doses per fraction encountered in radiosurgery and ignore the impact of radioresistant subpopulations of cells. The appropriate modeling of both tumor control and normal tissue toxicity in radiosurgery requires the application of emerging understanding of molecular-, cellular-, and tissue-level effects of high-dose/fraction-ionizing radiation and the role of cancer stem cells.
Semin Radiat Oncol 18:240-243

Fisiopatologia della Radiochirurgia



Maldaun M.V.C. Neurosurg Rev 2008

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Exploring the Possibility of Unique Molecular, Biological, and Tissue Effects With Hypofractionated Radiotherapy

Michael Story, PhD, Reinhard Kodym, MD, and Debabrata Saha, PhD

1. Alte dosi -> Perdita massiva di cell. tumorali -> Influenza su sopravv. in regioni a basse dosi
2. Effetto bystander oltre il PTV
3. Alte dosi -> Perdita massiva di cell. tumorali -> Perdita stimolo crescita autocrina e paracrina

Perché tossicità inferiore a quella attesa?

1. Pochi dati a lungo termine
2. Modello LQ non applicabile all'ipofrazionamento "estremo"
3. Il rapporto alfa/beta conosciuto proviene dall'era RT 2D
4. Dosi molto alte a volumi molto piccoli

Prospettive di studio

- Effetto inibitorio sulle cellule dello stroma tumorale

Morte cellulare in gran parte per danno alla vascolarizzazione tumorale

- Attivazione di cellule CD8+ T tumore-specifiche

Combinazione ipofrazionamento/agenti biologici (antiangiogenici-immunomodulatori)

Ko EC Cancer/Radiotherapie 2013

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Giardini Naxos - Taormina, 26 - 29 ottobre

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