Workshop Interdisciplinare
"radiazioni: biologia, clinica, ambiente e protezione"
Centro Ricerche Casaccia ENEA
Roma, 14 maggio 2009

basse dosi in radioterapia

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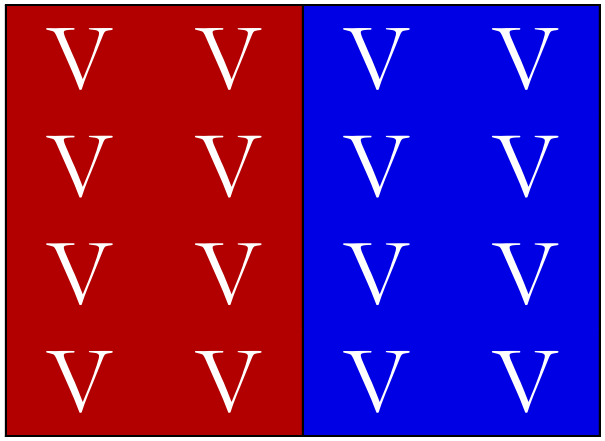
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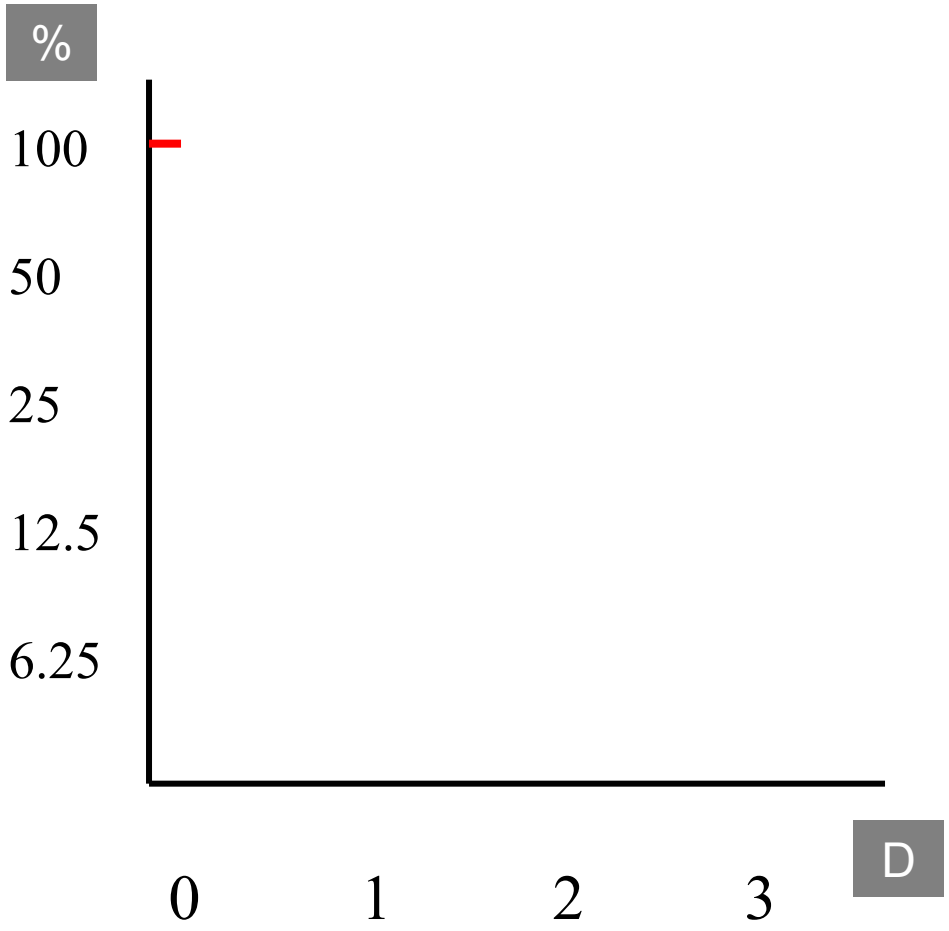
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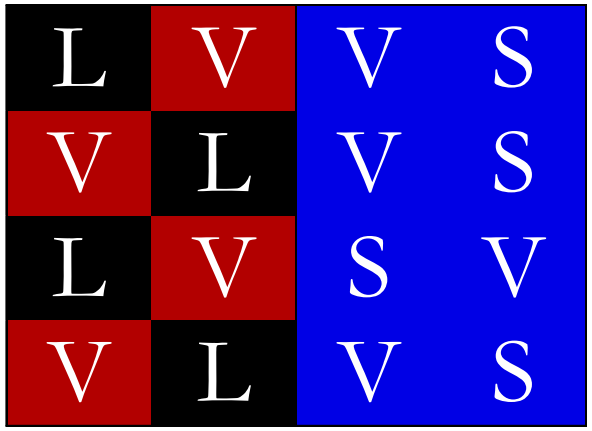
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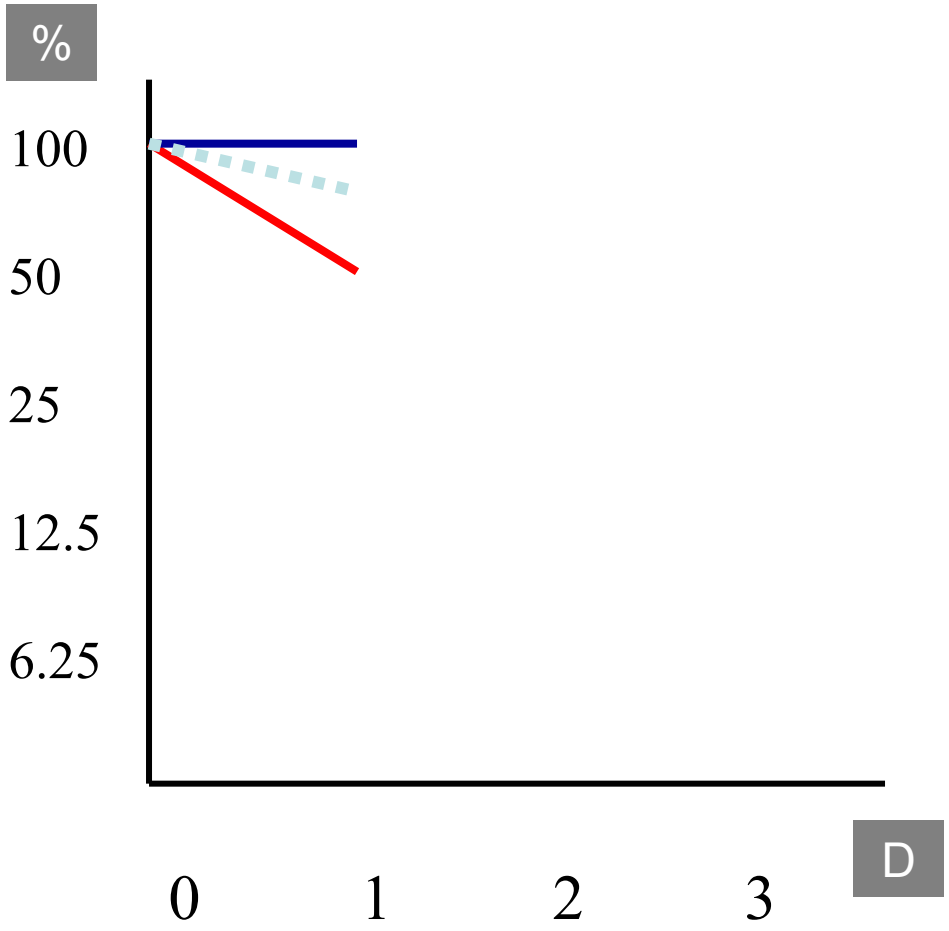
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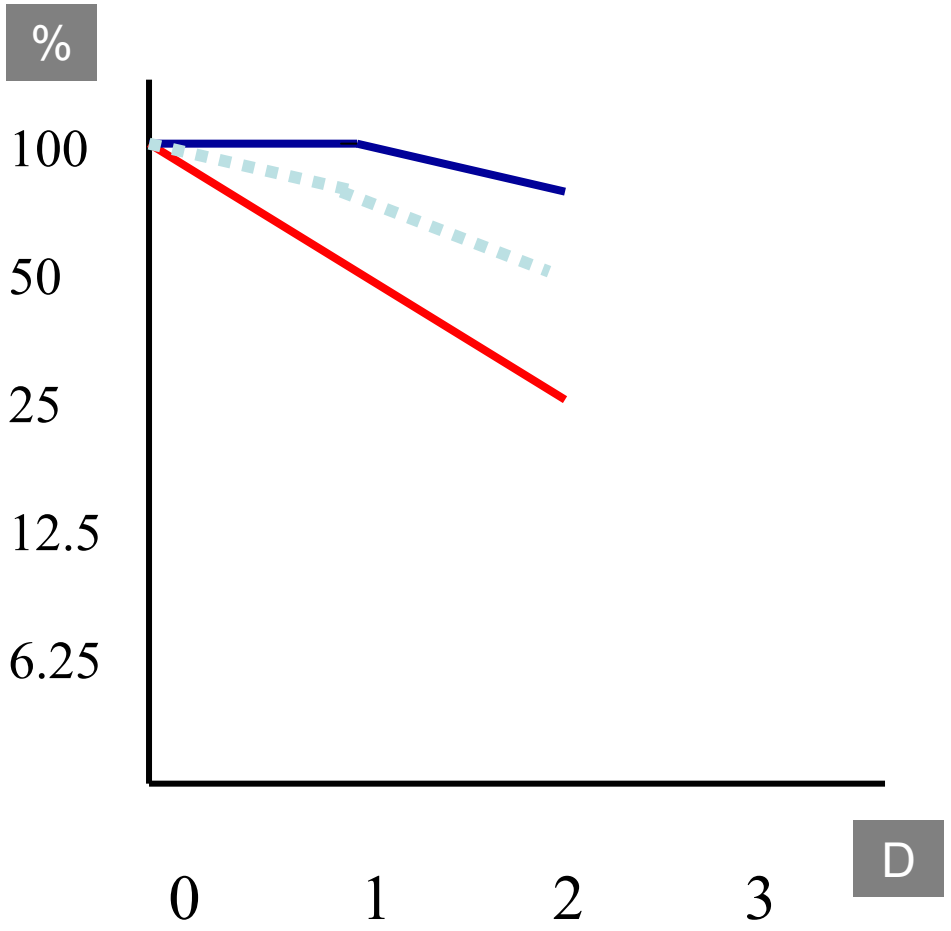

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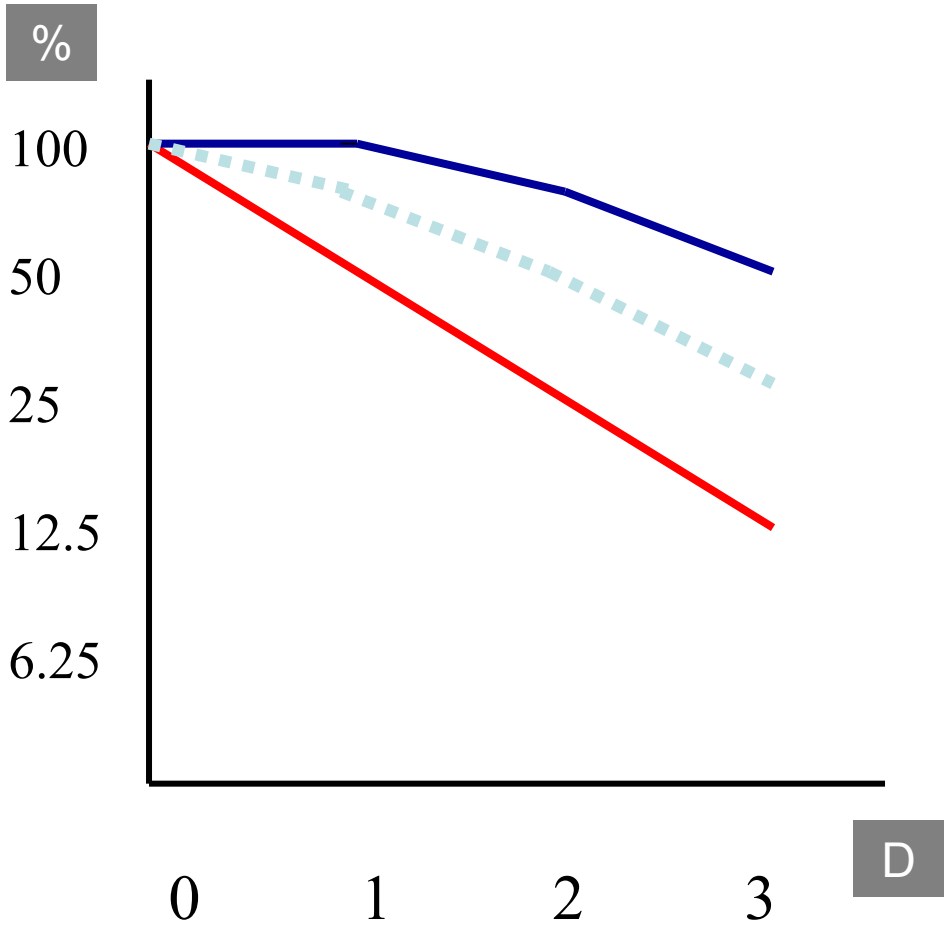
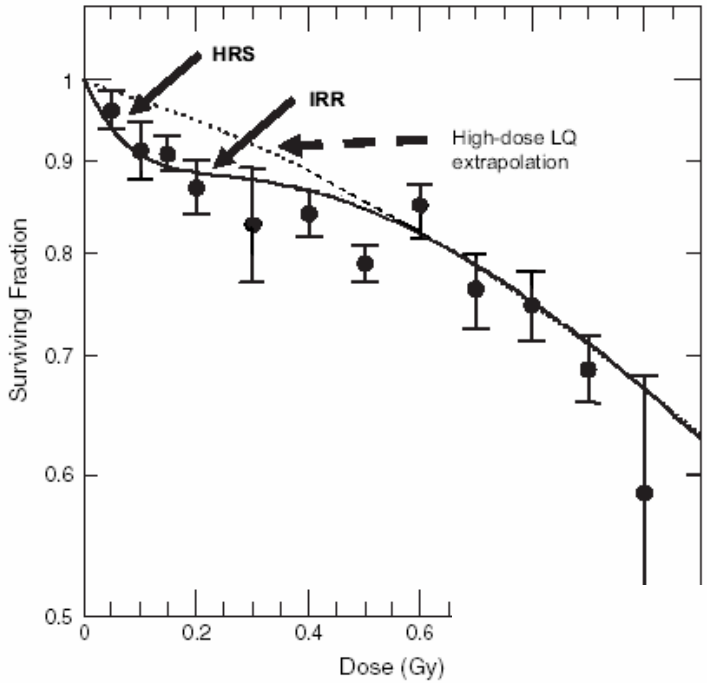
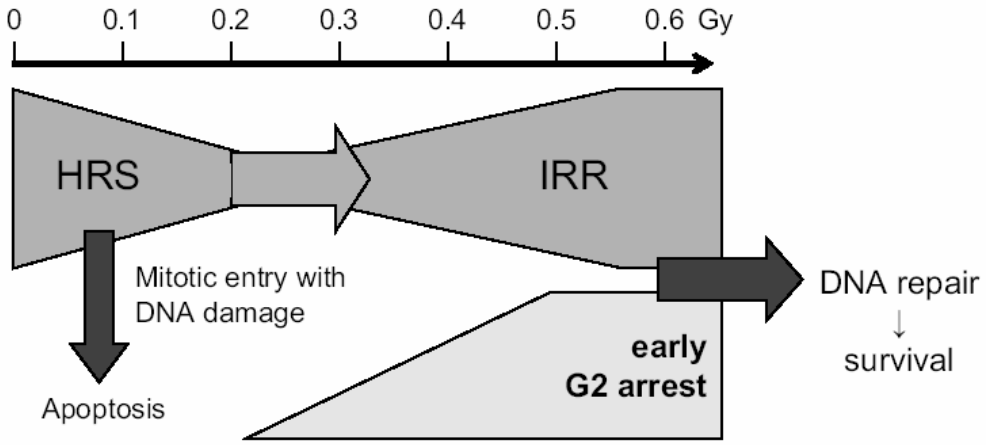
L	LL	V	S



Joiner's Induced Repair model





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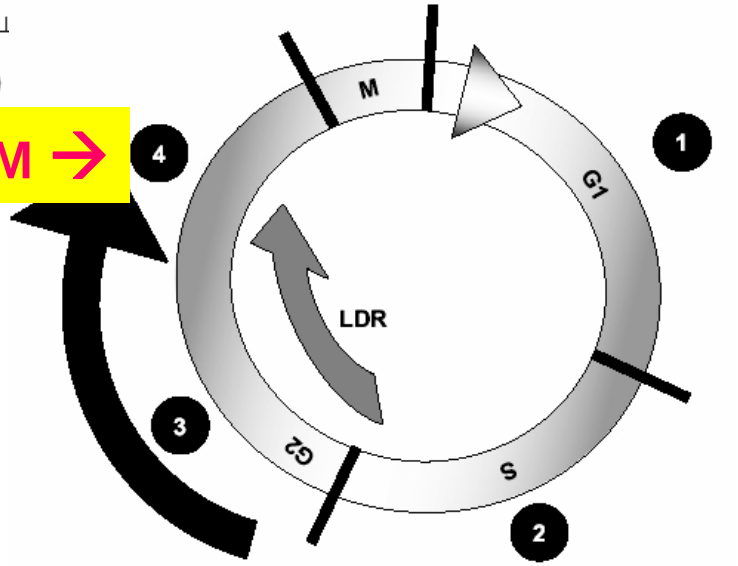
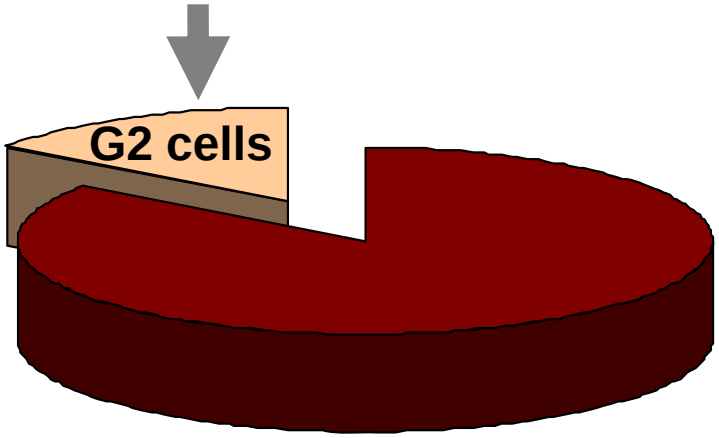


Marples et al. *Int J Radiat Oncol Biol Phys* 2008

therapeutic gain

rapidly proliferating tissue

1th LD fraction

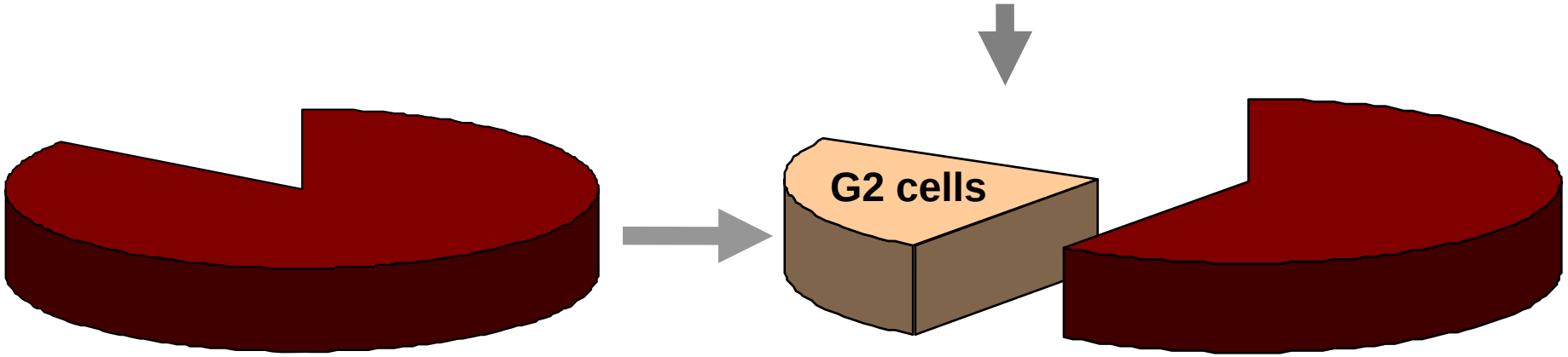


therapeutic gain

rapidly proliferating tissue

1th LD fraction

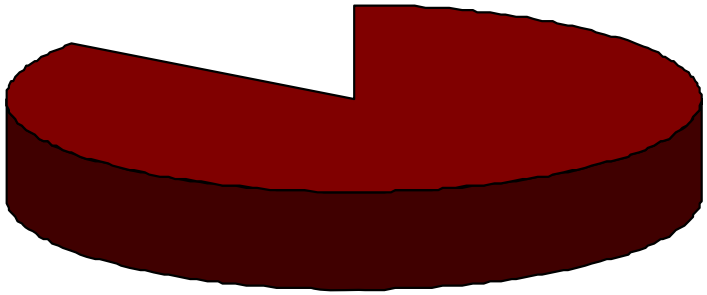
2th LD fraction



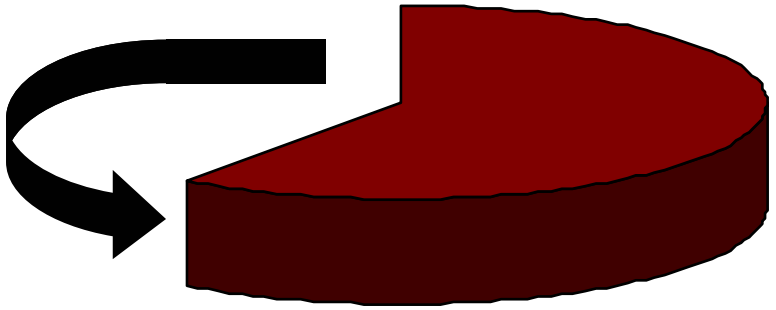
therapeutic gain

rapidly proliferating tissue

1th LD fraction



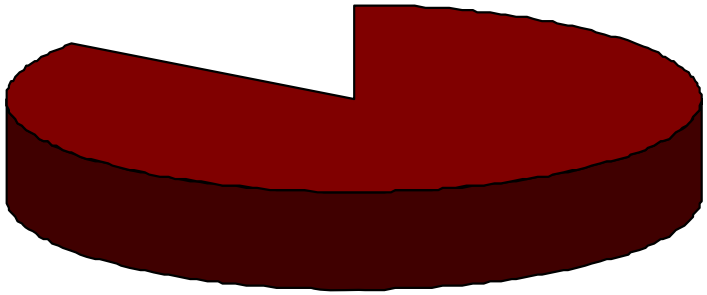
2th LD fraction



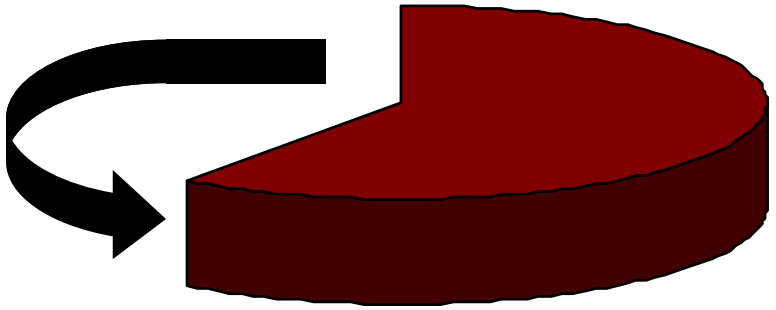
therapeutic gain

rapidly proliferating tissue

1th LD fraction

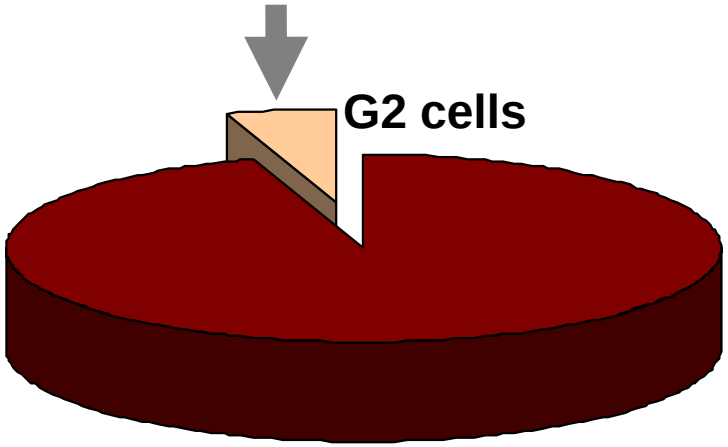


2th LD fraction



slowly proliferating tissue

1th LD fraction



therapeutic gain

rapidly proliferating tissue

1th LD fraction

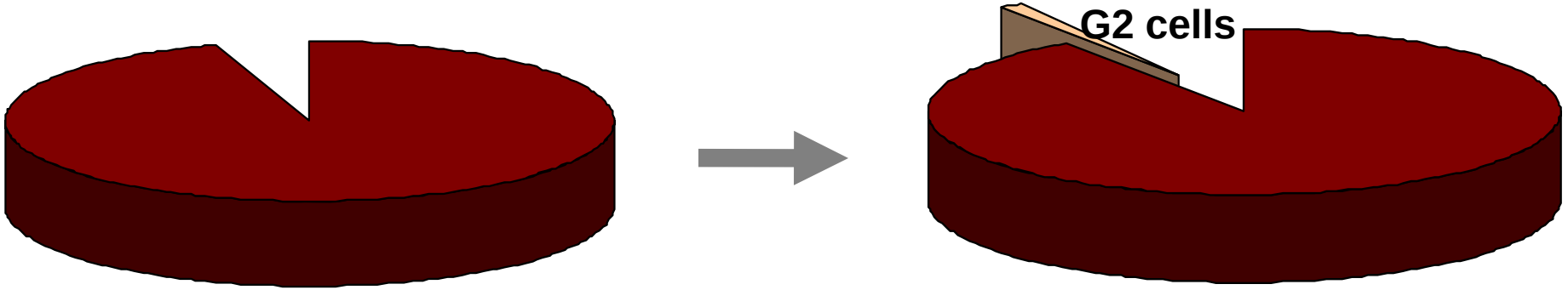
2th LD fraction

slowly proliferating tissue

1th LD fraction

2th LD fraction

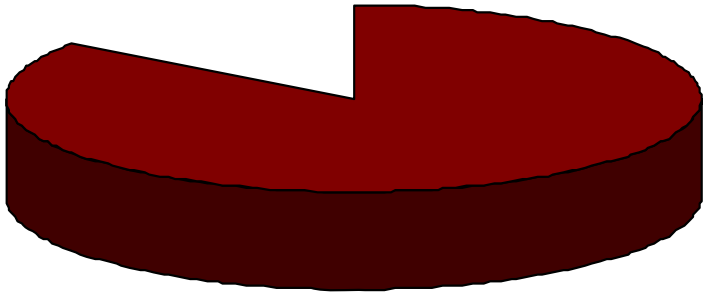
G2 cells



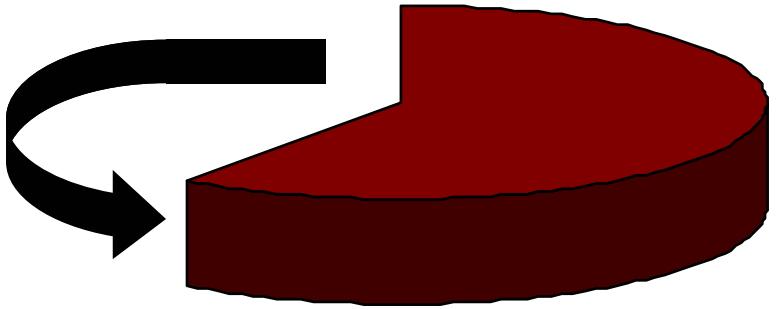
therapeutic gain

rapidly proliferating tissue

1th LD fraction

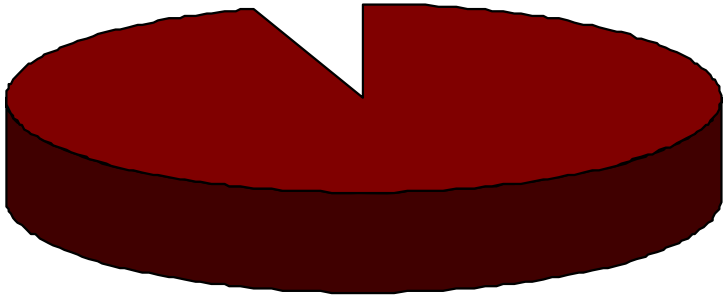


2th LD fraction

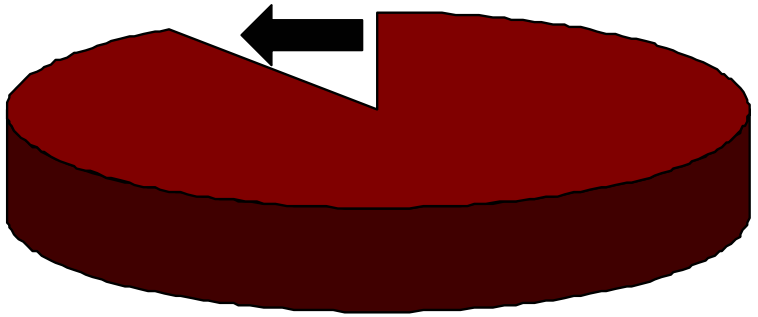


slowly proliferating tissue

1th LD fraction



2th LD fraction



in vivo studies

normal tissues

Author	Normal tissue type	Effect
Joiner et al. *Int. J. Radiat. Biol* 1986	Mouse skin	Lower X-ray doses were **more effective** per gray than predicted by LQ
Parkins et al. *Br J Cancer* 1986	Mouse lung	Lower X-ray doses were **more effective** per gray than predicted by LQ
Joiner et al. *Radiat Res.* 1988	Mouse kidney	Lower X-ray doses were **more effective** per gray than predicted by LQ
Wong et al. *Radiother Oncol* 1992	Mouse spinal cord	Lower X-ray doses were **less effective** per gray than predicted by LQ
Hamilton et al. *Radiother Oncol* 1996	Erythematous response of human skin	Lower X-ray doses were **more effective** per gray than predicted by LQ
Harney et al. *Radiother Oncol.* 2004	Basal cells of human skin	LDHRS **does not occur** in skin following doses of approximately 0.5Gy/fraction when regimens of equal dose/time intensity are compared.

in vivo studies

tumour

Author	Tumor type	Radiation Schedule	Efficacy
Short et al. *Int J Radiat Biol*. 1999	T98G glioma xenografts in mice	UF[1] (0.4 Gy 3 times/day for 30 days) *versus* CF[2] (1.2 Gy once daily for 30 days).	**Non significant increase in tumor growth delay with UF**
Beauchesne et al. *Int J Cancer*. 2003	G152 glioma xenografts in mice	UF (0.8 Gy 3 times/day 4 days/week, total dose 19.2 Gy) *versus* CF (2 Gy once/day 4 days/week, total dose 16 Gy).	**UF resulted in a significant increase in tumor growth delay**
Krause et al. *Int J Radiat Biol*. 2003	A7 glioma xenografts in mice	UF (0.4 Gy per fraction, 126 fractions in 6 weeks) *versus* CF (1.68 Gy per fraction, 30 fractions in 6 weeks)	**UF resulted in a significant decrease in tumor growth delay**
Harney et al. *Int J Radiat Oncol Biol Phys*. 2004	Metastatic tumor nodules to human skin	UF (0.5 Gy 3 times/day, for 12 days) *versus* CF (1.5 Gy/day, for 12 days)	**UF resulted in a significant increase in tumor growth delay in melanoma and sarcoma nodules**
Krause et al. *Strahlenther Onkol*. 2005	Radioresistant murine DDL1 T-cell lymphoma in mice	UF (0.4 Gy per fraction 3 times/day, 7 days per week) *versus* CF (1.68 Gy once/day 5 days/ week)	**Non significant increase in tumor growth delay with UF**
Krause et al. *Int J Radiat Biol*. 2005	T98G or HGL21 glioma xenografts in mice	UF (0.4 Gy per fraction 3 times/day, 7 days per week) *versus* CF (1.68 Gy once/day 5 days/ week)	**Non significant increase in tumor growth delay with UF in HGL21 glioma xenograft. UF resulted in a significant increase in tumor growth delay in T98G glioma**

[1] UF, ultrafractionation
[2] CF, conventional fractionation

in vivo studies

tumour

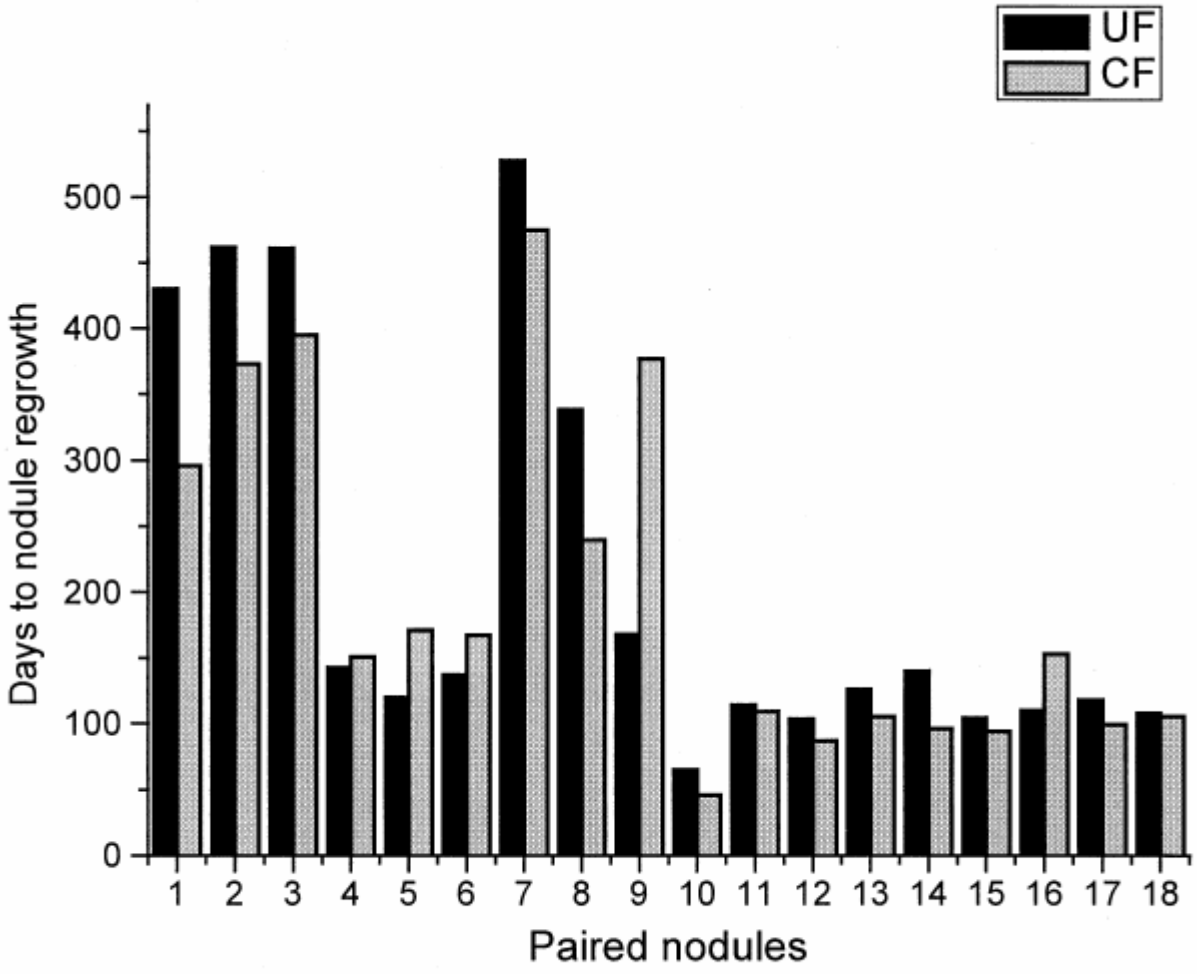


Fig. 1. Analysis of all nodule data demonstrates a trend toward greater tumor control in the "ultrafractionated" group. $p = 0.14$. UF (dark bars) = ultrafractionation; CF (light bars) = conventional fractionation.

Harney et al. Int J Radiat Oncol Biol Phys. 2004

in vivo studies

tumour

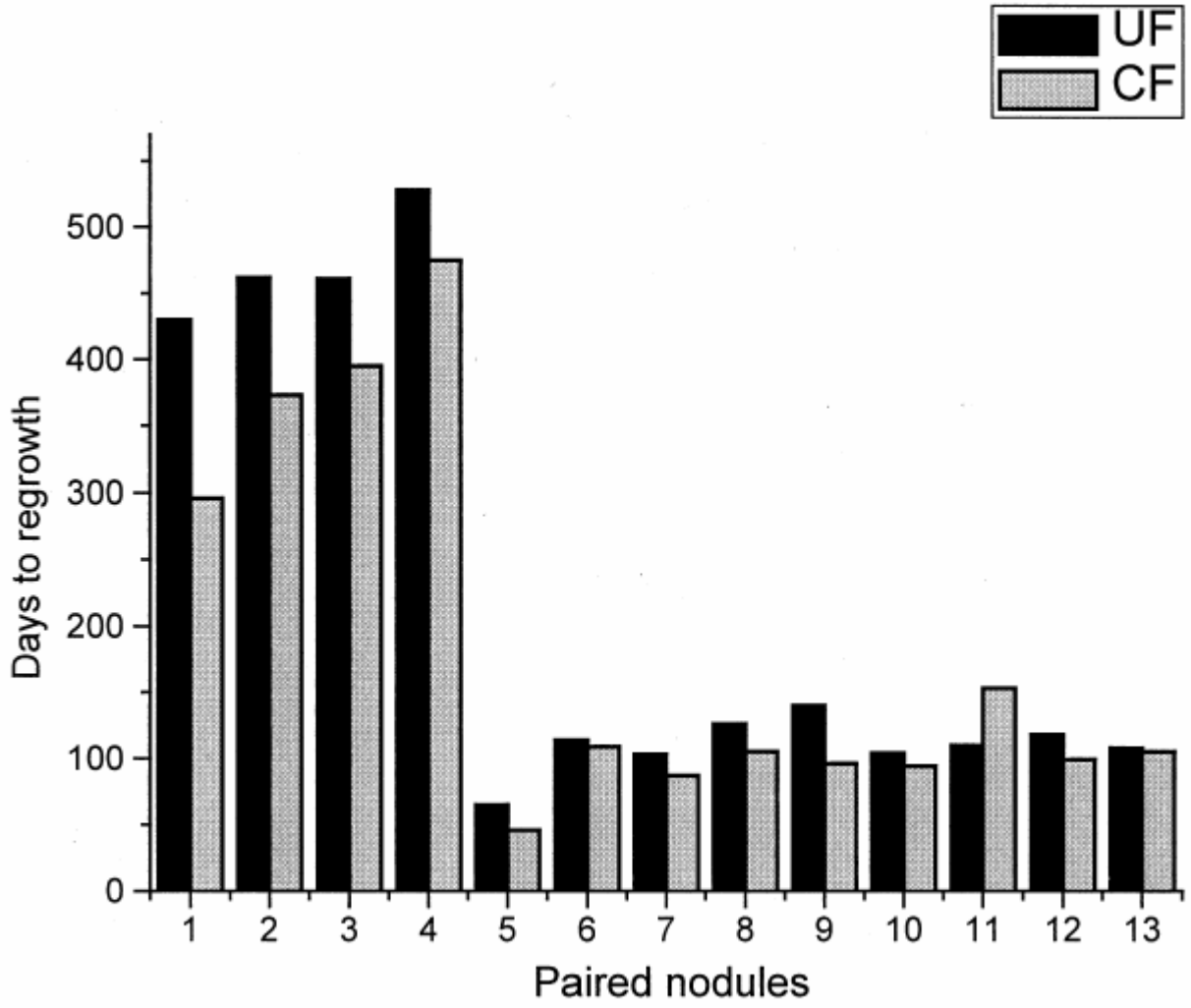
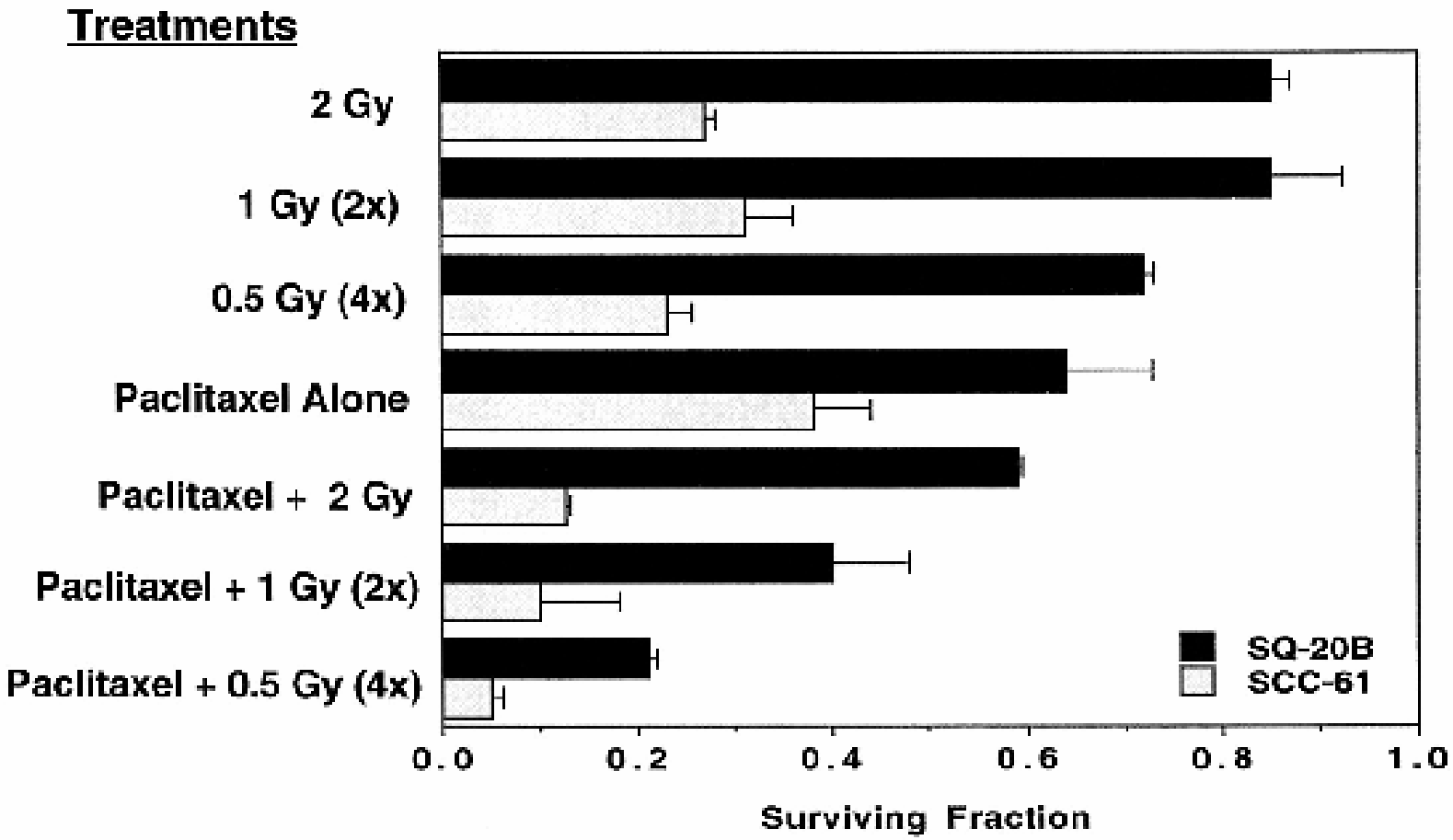


Fig. 2. Analysis of sarcoma and melanoma tumor nodules demonstrates a statistically significant growth delay in those treated with the "ultrafractionated" regime. $p = 0.009$. UF (dark bars) = ultrafractionation; CF (light bars) = conventional fractionation.

Harney et al. Int J Radiat Oncol Biol Phys. 2004

chemosensitization by radiotherapy

preclinical studies

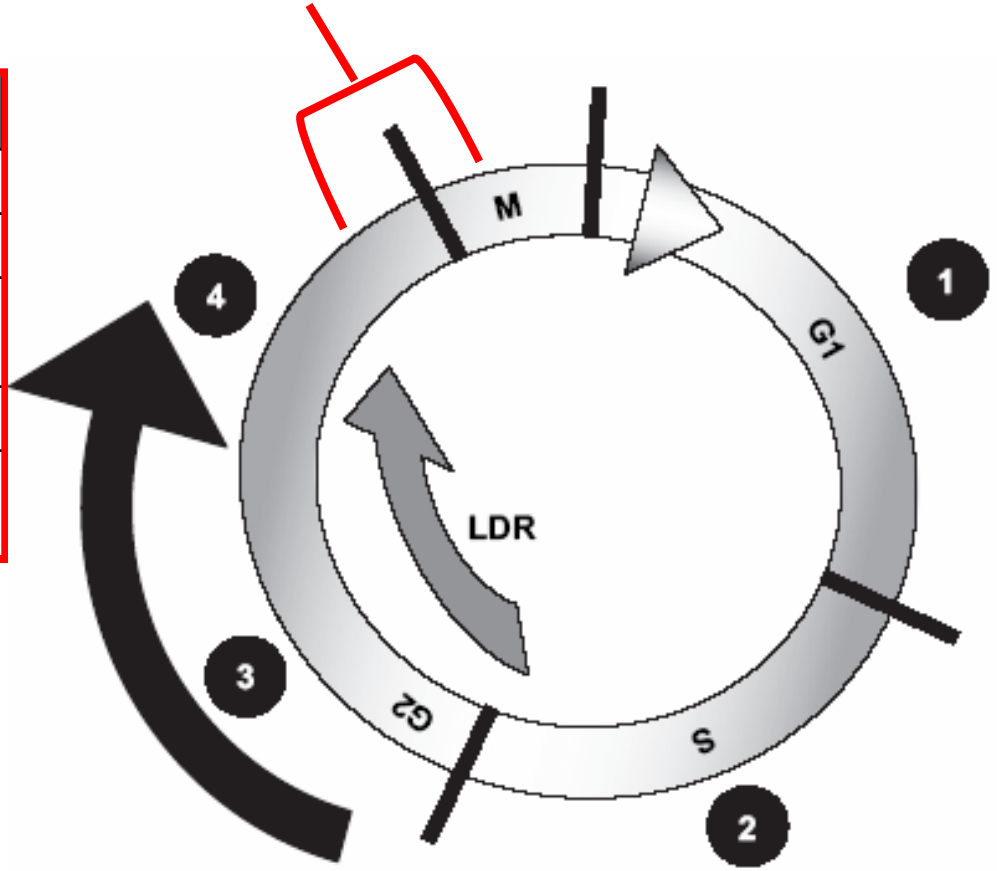


Dey, Clin Cancer Res 2003

chemosensitization by radiotherapy

preclinical studies

Author	Drug
Dey S et al. *Clin Cancer Res* 2003	*Paclitaxel*
Beauchesne PD et al. *Int J Cancer* 2003	*Etoposide*
Gupta S et al. *Proc Am Assoc Cancer Res* 2004	*Cisplatin*
Chendil D et al. *Cancer*2000	*Paclitaxel*
Spring PM. et al *Cell Cycle* 2004	*Taxotere*



a new treatment paradigm?

radiosensitizing chemotherapy → chemosensitizing radiotherapy

LD-RT

- new systemic agent
- referred as “r”
- examples:
  - -rT = LDRT + docetaxel
  - -rG = LDRT + gemcitabine
  - -rABVD = LDRT + ABVD

Regine WF et al. Int J Radiat Oncol Biol Phys. 2007

chemosensitization by radiotherapy

clinical studies

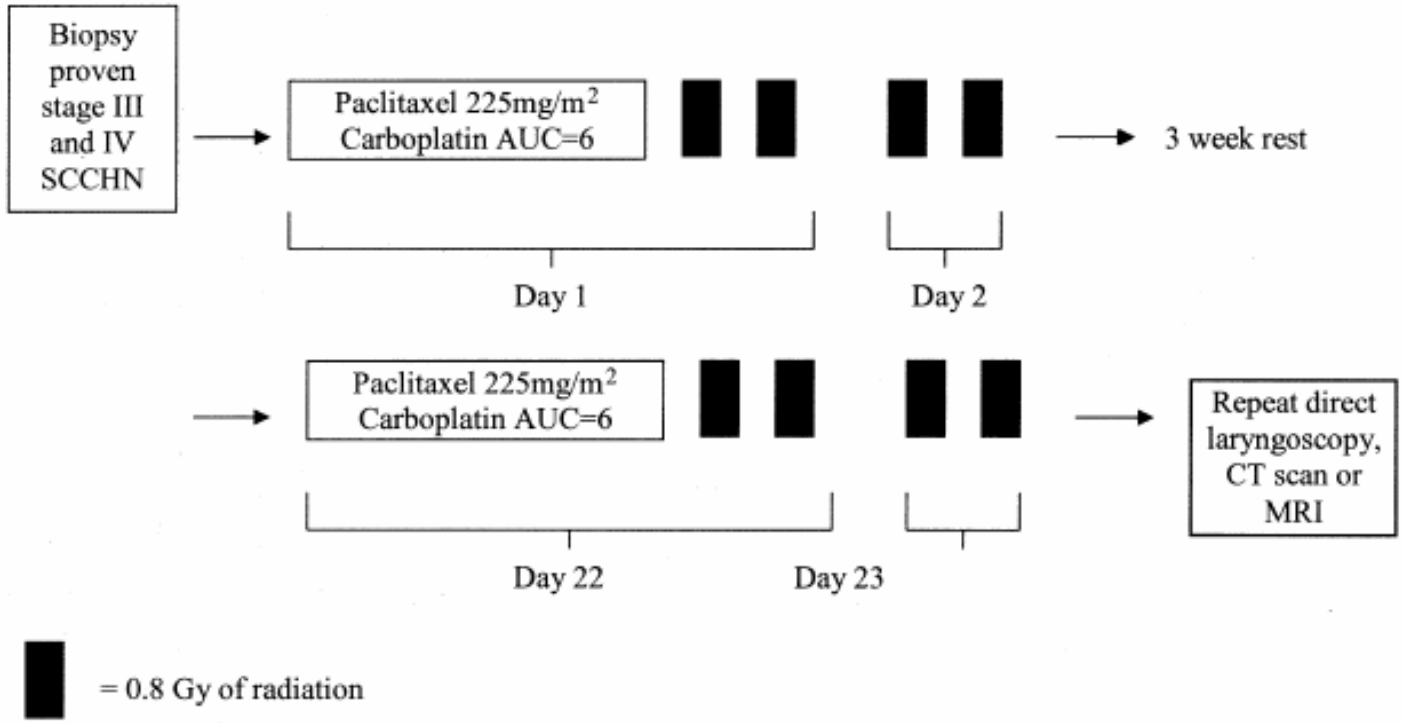


Fig. 1. Regimen for low-dose fractionated radiotherapy, carboplatin, and paclitaxel. Solid bars represent 80-cGy fractions of RT.

Arnold SM et al: Int J Radiat Oncol Biol Phys 2004

chemosensitization by radiotherapy

clinical studies

Table 5. Comparison of response to induction therapy with carboplatin and paclitaxel

	Stage (%)				Dose		Primary site response (%)					Neck response (%)				
First author	2	3	4	Cy	C (AUC)	P (mg/m²)	CR	PR	SD	PD	RR	CR	PR	SD	PD	RR
Dunphy (22) (n = 62)	4	19	76	3	7.5	150–265	34	32	18	16	66	33	21	NR	NR	53
Bouillet (24) (n = 20)	NR	NR	NR	2	6	175	0	55	40	5	55	NR	NR	NR	NR	NR
Machtay (23) (n = 53)	0	35	65	2	6	200	13	76	NR	NR	89	NR	NR	NR	NR	NR
Vokes† (15) (n = 69)	0	4	96	2	2* (6)	135* (405)	30/35	45/57	3/3	3/3	75/87	NR	NR	NR	NR	NR
Present study (n = 39)	0	23	77	2	6	225	28	62	10	0	90	31	38	28	3	69

Abbreviations: Cy = cycles; C = carboplatin; P = paclitaxel; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; RR = response rate; NR = not reported.

* Weekly doses; total for 3 weeks in parentheses.

† All patients/assessable patients only.

Arnold SM et al: Int J Radiat Oncol Biol Phys 2004

chemosensitization by radiotherapy

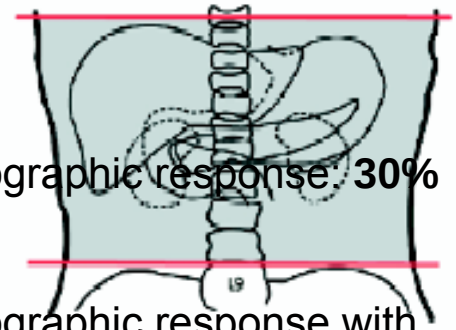
clinical studies

Table 2. Toxicity of LDFRT plus gemcitabine by dose level

Toxicity	Dose level 1 (60 cGy/fraction) (n = 6) Grades 1–2	Dose level 1 (60 cGy/fraction) (n = 6) Grades 3–4	Dose level 2 (70 cGy/fraction) (n = 4) Grades 1–2	Dose level 2 (70 cGy/fraction) (n = 4) Grades 3–4*
Leucopenia	1	10	1	0
Neutropenia	2	7	0	1
Thrombocytopenia	0	5	2	1
Fatigue	1	0	1	0
Anemia	1	0	0	1
Infection	0	1	0	1
Fever	1	0	0	0
Diarrhea	0	0	1	2
Hyperpigmentation	0	0	1	0
Dehydration	0	0	0	1
DLT	0	1	0	2

Abbreviations: LDFRT = low-dose fractionated radiotherapy; DLT = dose-limiting toxicity.
* No Grade 4 events.

Tumors without Peritoneal Carcinomatosis:



overall radiographic response: **30%**

overall radiographic response with Gemcitabine alone: 5.1-16%

Bramhall SRBr J Cancer. 2002
Oettle H Ann Oncol. 2005
Heinemann V J Clin Oncol. 2006
Abou-Alfa GK J Clin Oncol. 2006
Stathopoulos GP Br J Cancer. 2006

Regine WF et al. Int J Radiat Oncol Biol Phys. 2007

chemosensitization by radiotherapy

clinical studies

Table 2. Patient characteristics and response

Patient	Tumor site	Tumor type	Previous radiotherapy (total dose)	Previous chemotherapy (no. of cycles)	Chemotherapy with LD-FRT	Response
1	Lung	Non–small-cell	No	No	Gemcitabine	PD
2	Lung	Non–small-cell	No	No	Cisplatin and Gemcitabine	CR
3	Lung	Non–small-cell	No	Yes (3)	Pemetrexed	PD
4	Lung	Non–small-cell	No	Yes (9)	Pemetrexed	PD
5	Lung	Non–small-cell	No	Yes (4)	Pemetrexed	PD
6	Lung	Non–small-cell	Yes (43 Gy)	Yes (6)	Pemetrexed	NC
7	Lung	Non–small-cell	Yes (50 Gy)	Yes (4)	Gemcitabine	PD
8	Lung	Non–small-cell	Yes (50 Gy)	Yes (4)	Pemetrexed	PD
9	Lung	Non–small-cell	Yes (65 Gy)	Yes (3)	Pemetrexed	PR
10	Lung	Small cell	Yes (40 Gy)	Yes (3)	Pemetrexed	CR
11	Lung	Small cell	Yes (30 Gy)	Yes (2)	Carboplatin	PR
12	Lung	Small cell	Yes (30 Gy)	Yes (2)	Carboplatin	PR
13	Head and neck	Occult primary	No	No	Cisplatin and Fluorouracil	CR
14	Head and neck	Occult primary	No	Yes (5)	Cisplatin and Fluorouracil	PD
15	Head and neck	Pharynx	Yes (56 Gy)	No	Cisplatin and Fluorouracil	CR
16	Head and neck	Pharynx	Yes (60 Gy)	Yes (2)	Cisplatin and Fluorouracil	PR
17	Head and neck	Larynx	Yes (50 Gy)	Yes (2)	Cisplatin and Fluorouracil	PD
18	Head and neck	Larynx	Yes (50 Gy)	Yes (2)	Cisplatin and Fluorouracil	PD
19	Head and neck	Salivary gland	Yes (70 Gy)	Yes (3)	Cisplatin and Fluorouracil	PR
20	Breast	Ductal carcinoma	Yes (50 Gy)	No	Capecitabine	PR
21	Breast	Ductal carcinoma	Yes (60 Gy)	Yes (>10)	Fluorouracil	PD
22	Esophagus	Adenocarcinoma	Yes (50 Gy)	Yes (2)	Docetaxel	NC

Abbreviations: PD = progression of disease; CR = complete response; NC = no change; PR = partial response.

Response rate in lung cancer : **41.6%**

Response rate to second line chemotherapy in lung cancer: 5-10%

Shepherd FA, J ClinOncol 2000
Fossella FV, J Clin Oncol 2000
Hanna N, J ClinOncol 2004

Response rate in Head & Neck cancer : **57%**

Response rate to chemotherapy in advanced head and neck cancer: 10-35%

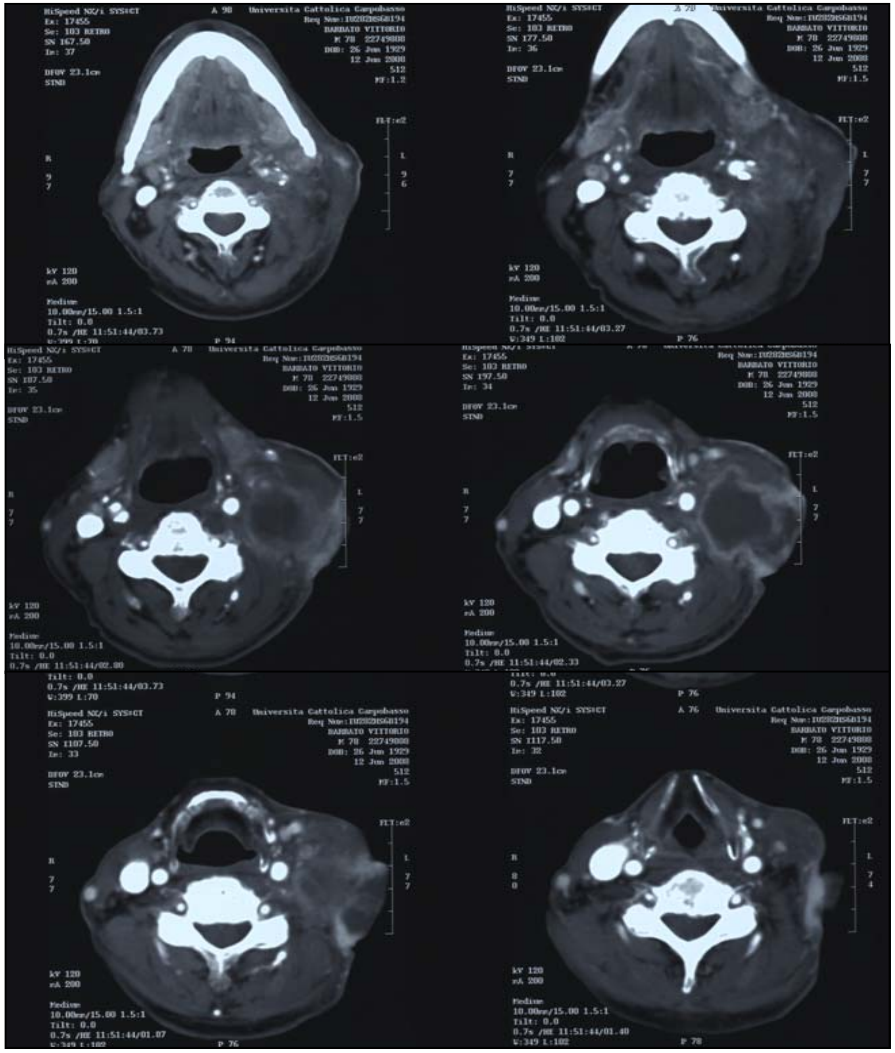
Forastiere AA, J ClinOncol 1992
Forastiere AA, J Clin Oncol 2001
Gibson MK, J ClinOncol 2005

Valentini V et al.: Int J Radiat Oncol Biol Phys 2009 in press

RACHEL: **RA**dio-**CHE**motherapy with **L**ow fractionation acute toxicity (17 pts)

grade	1	2	3	4
haemat	4 (Hb)	1 (Hb) 1 (Plt) 1 (WB)	1 (neu)	0
GI sup	1	1	0	0
GI inf	0	0	0	0
skin	3	0	0	0
other	1 (lung) 2 (mucositis)	1 (mucositis)	0	0

05/2008



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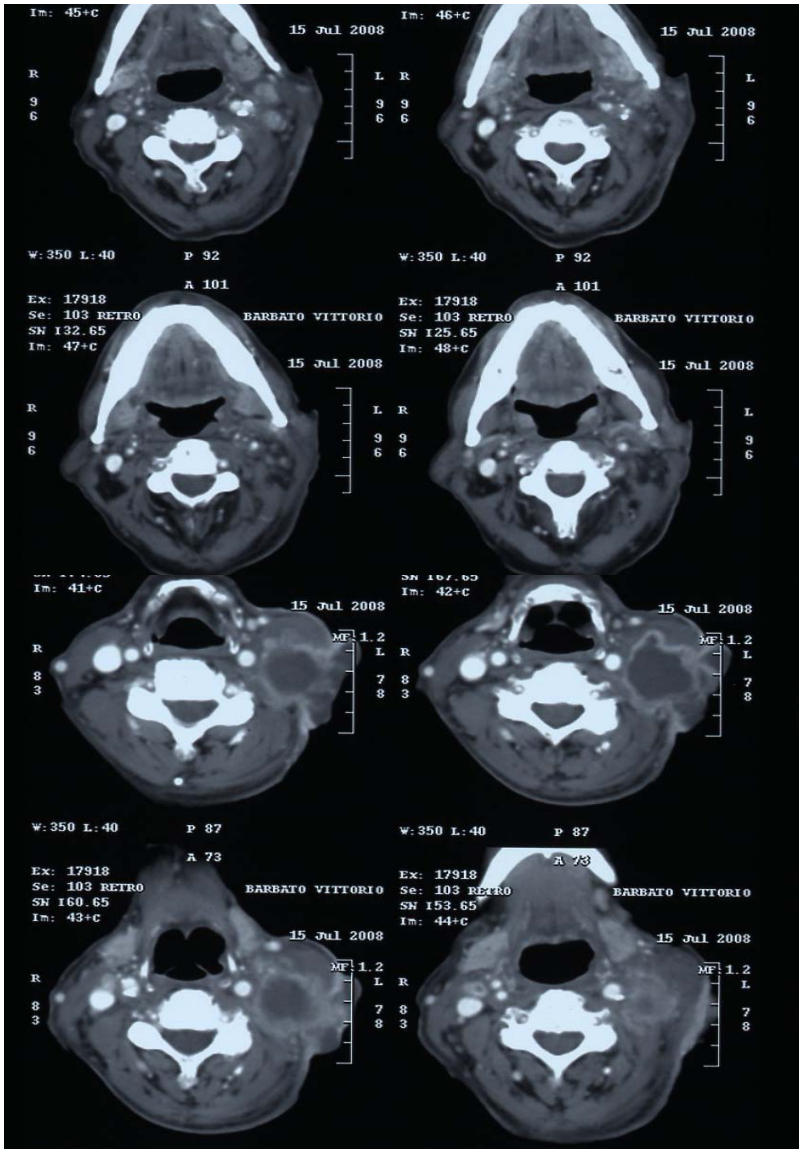

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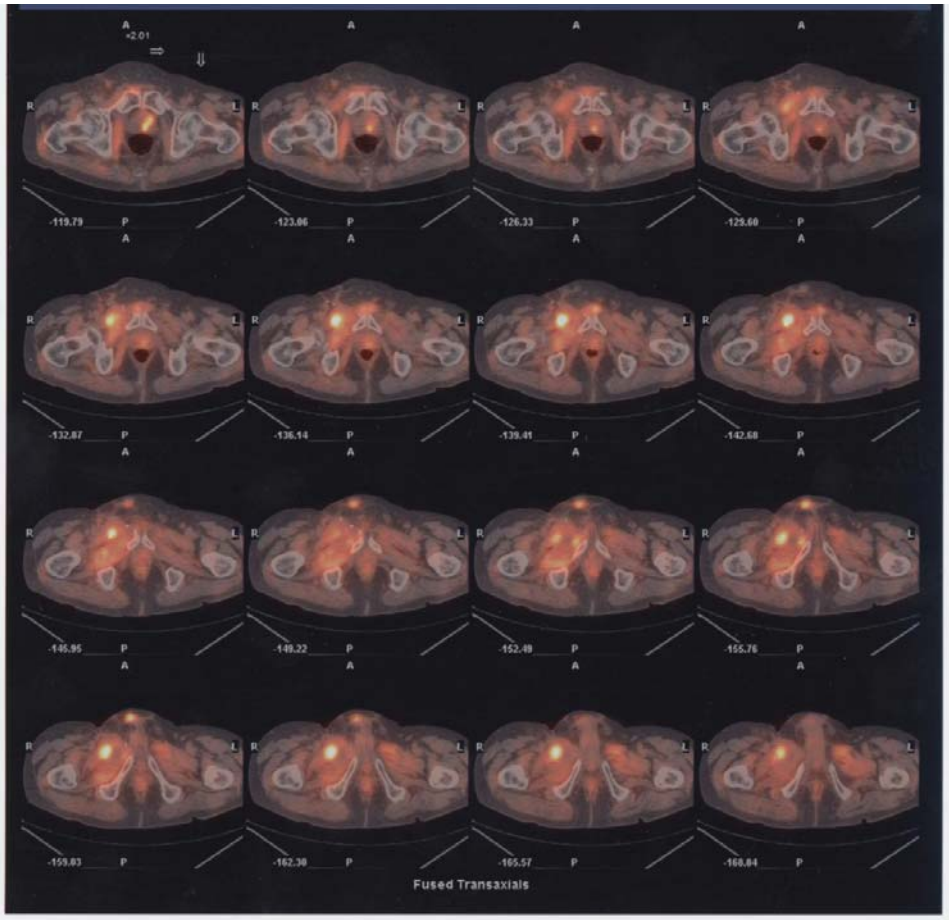

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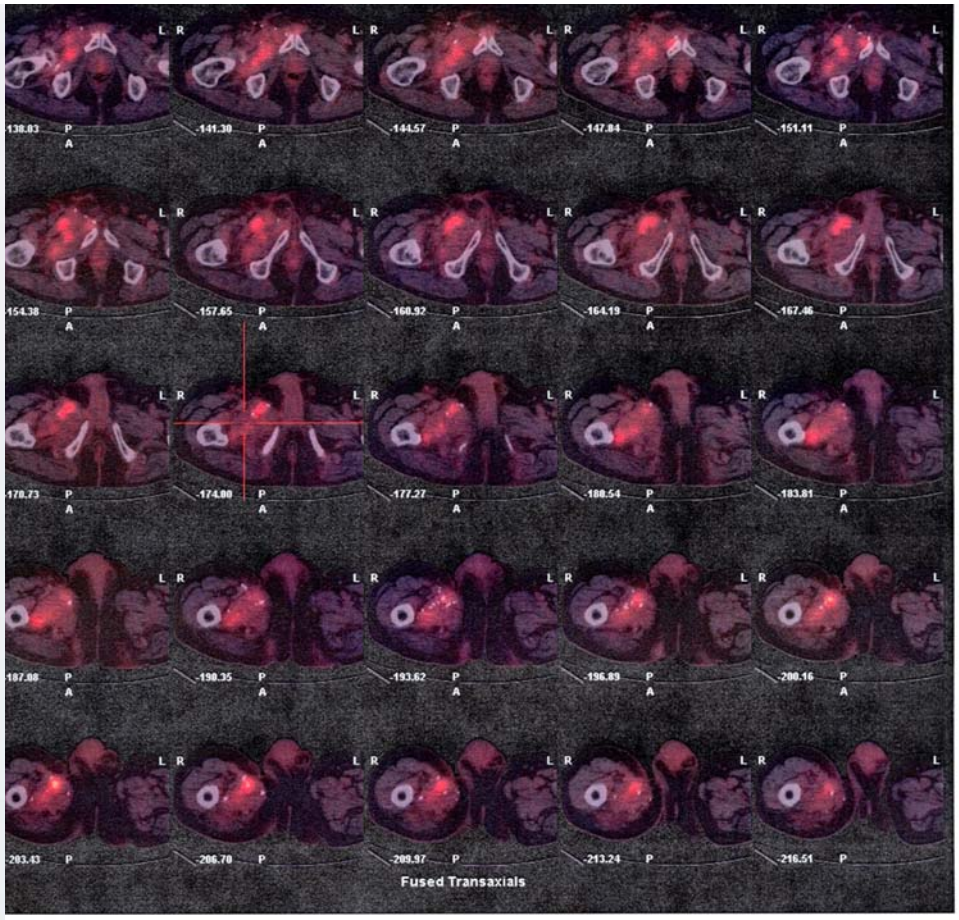

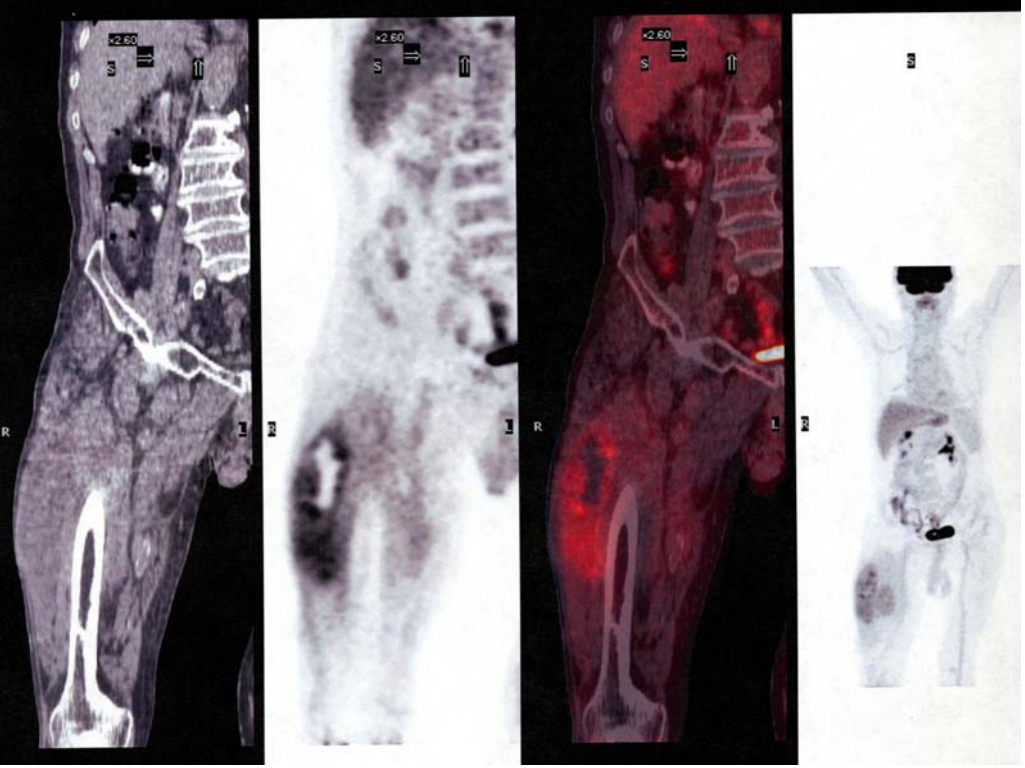

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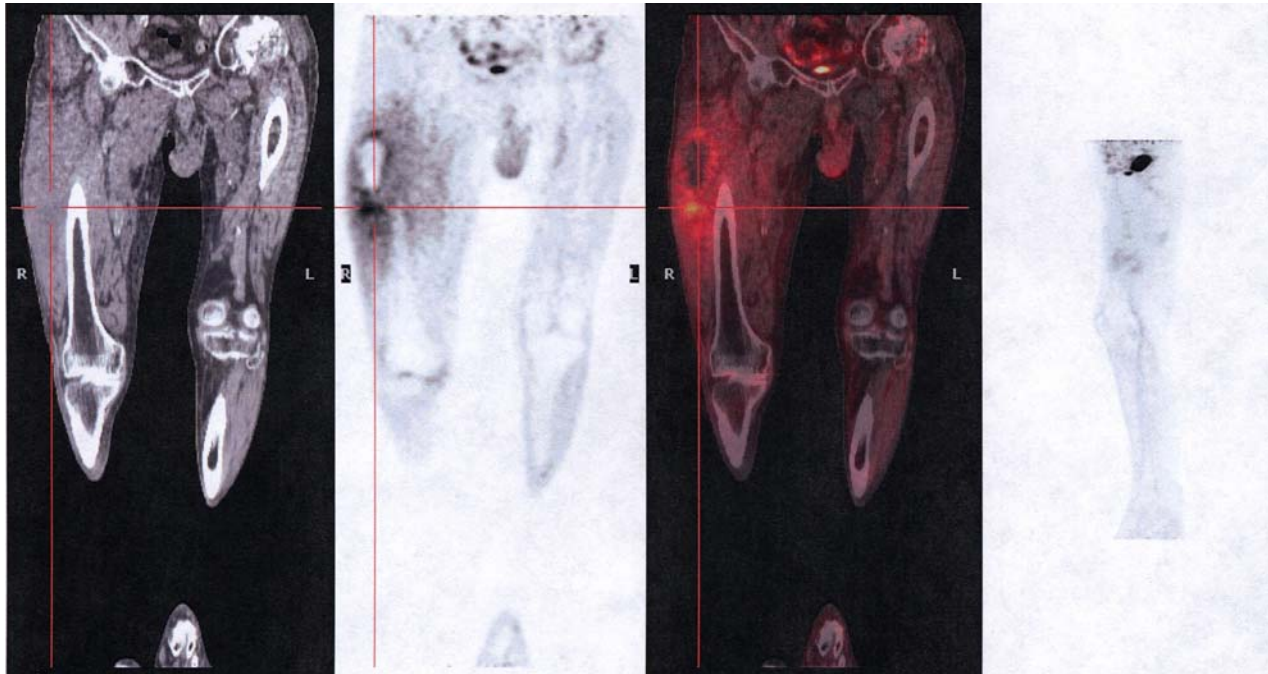

conclusions

- RT doses **< 0.5 Gy**: more effective than predicted by LQ model
- G2 checkpoint → **HRS/IRR** (***induced repair*** model)
- in vivo studies: improved outcome by ***ultrafractionation***?
- chemotherapy → > G2-phase fraction
- LD-FRT as ***chemopotentiator***?
- new treatment paradigm?