CONTROVERSIE NELLE STRATEGIE TERAPEUTICHE DEL CARCINOMA PROSTATICO LOCALIZZATO AD ALTO RISCHIO

HYPOFRACTIONATION IN HIGH RISK PROSTATE CANCER: PRO

DI MUZIO NADIA

IRCCS OSPEDALE S. RAFFAELE - MILANO

HYPO FRACTIONATION IN PROSTATE CANCER

WHAT DO WE NEED TO JUSTIFY HYPOFRACTIONATION?

-LESS TOXICITY

-BETTER OUTCOME

-SAME EFFICACY IN A SHORT TIME

HYPO FRACTIONATION IN PROSTATE CANCER

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0360-3016/10/$–see front matter

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CLINICAL INVESTIGATION **Prostate**

ACUTE TOXICITY IN HIGH-RISK PROSTATE CANCER PATIENTS TREATED WITH ANDROGEN SUPPRESSION AND HYPOFRACTIONATED INTENSITY-MODULATED RADIOTHERAPY

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ACUTE TOXICITY

HIGH DOSE /HYPO
NO SIGNICANT DIFFERENCES
WITH CONVETIONAL
FRACTIONATION

PELVIC NODES

Study (reference)	Prescribed dose (Gy)/no. of fractions	EQD2 Gy§§	No. of patients	% of patients receiving concurrent AST	% of patients with acute GI toxicity				% of patients with acute GU toxicity			
					Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
Current study	68/25	82	60	83.30	13.30	51.70	35	0	13.37	46.67	33.33	6.67
Pollack *et al.* (30)*	70.2/26	84.2	50	44	42	40	18	0	8	44	40	8
Lim *et al.* (32)†	67.5/25	81	66	0	5	56	39	0	5	59	28.40	7.60
Kupelian *et al.* (31)‡	70/28	80	166	60	30	55	15	0	15	62	22	1
RTOG 9413§	70.2/39	66.2	309	100	—	—	44	2.6‡‡	—	—	27.50	3.9‡‡
RTOG 9406¶	79.2/44	74.7	67	69	49.30	29.60	20.90	0	31.82	42.42	25.76	0
Beckendorf *et al.* (9)**	80/40	80	153	None	32.70	37.30	28.10	1.97	20.26	42.48	30.07	7.19

HYPO FRACTIONATION IN PROSTATE CANCER

Latest IMRT clinical trials on prostate cancer with focus on toxicity assessment.

Trial/study design	Radiation dose and fraction size	Toxicity	Observations
Hypofractionated IMRT (with androgen suppression) (Pervez et al., 2010) [46]	68 Gy in 25 fractions (2.72 Gy/fraction) to the prostate with simultaneous delivery of 45 Gy in 25 fractions to the pelvic lymph nodes	3-months follow up: 13.6% – grade 1 gastrointestinal toxicity 18.97% – grade 1 genitourinary toxicity 8.62% – grade 2 genitourinary toxicity	Acutely well tolerated longer follow up needed for late toxicity and outcome assessment
Hypofractionated IMRT (five fields) (Coote et al., 2009) [47]	57–60 Gy to prostate in 19–20 fractions (3 Gy/fraction)	2-years post treatment: No grade 4 toxicity One patient – grade 3 bladder toxicity 4% – grade 2 bowel toxicity 4.25% – grade 2 bladder toxicity	Patients receiving 60 Gy were more likely to develop bowel toxicity than those receiving 57 Gy generally well tolerated
IMRT-SIB (retrospective toxicity analysis) (McCammon et al., 2009) [48]	70 Gy in 28 fractions (2.5 Gy/fraction) to the prostate with simultaneous delivery of 50.4 Gy in 28 fractions (1.8 Gy/fraction) to the pelvic lymph nodes	Acute toxicity: 36.7% – grade 2 cystitis 26.7% – grade 2 urinary frequency 2-years post treatment: 6.6% – grade 3 toxicity 3.3% – grade 4 toxicity	Acute or late bladder and rectal toxicity did not correlate with any of the dosimetric parameters
Hypofractionated intensity modulated arc therapy (with androgen suppression) (Fonteyne et al., 2009) [49]	69.3 Gy (median dose) in 25 fractions to the prostate (2.77 Gy/fraction) and 50 Gy in 25 fractions to the pelvic lymph nodes	3-months follow up: 45% – grade 2 lower gastrointestinal toxicity 45% – grade 2 genitourinary toxicity 6.45% – grade 3 genitourinary toxicity	Feasible treatment with low toxicity

ACUTE TOXICITY

HIGH DOSE /HYPO

NO SIGNICANT DIFFERENCES WITH CONVETIONAL FRACTIONATION

HYPO FRACTIONATION IN PROSTATE CANCER

EFFICIENCY : COMPARISON BETWEEN CONVENTIONAL AND HYPO

Table 2 — Comparison of the efficiency of hypofractionated treatments

Reference	α/β value (Gy)	Patients	Modified treatment	Conventional treatment	Results	Remarks
LIVSEY	1.3	705	16 fractions of 3.1 Gy each ($BED_3 = 102\ Gy_3$)	33 fractions of 2.0 Gy each ($BED_3 = 110\ Gy_3$)	✖ Comparable tumour results for similar or not higher late toxicity	Tumour control evaluated as the biochemical relapse-free survival at 5 years
AKIMOTO		53	23 fractions of 3 Gy each ($BED_3 = 138\ Gy_3$)	39 fractions of 2 Gy each ($BED_3 = 130\ Gy_3$)	✖ Similar late toxicity	Patients from different risk groups were pooled together
VALDAGNI	8.3	330	66 fractions of 1.2 Gy ($BED_3 = 111\ Gy_3$)	37 fractions of 2 Gy ($BED_3 = 123\ Gy_3$)	✖ Comparable tumour control efficiency with reduced late toxicity in the hyperfractionated arm	Bentzen and Ritter [57] advanced the hypothesis that incomplete repair might have influenced the results of the hyperfractionated arm
LUKKA	1.12–1.5	936	20 fractions of 2.6 Gy ($BED_3 = 98\ Gy_3$)	33 fractions of 2.0 Gy ($BED_3 = 110\ Gy_3$)	✖ Poorer results for the hypofractionated treatment and lower complications in the hypofractionated arm	Total dose too low in the hypofractionated arm
KUPELIAN	2.4	100 + 310	28 fractions of 2.5 Gy each ($BED_3 = 128\ Gy_3$)	39 fractions of 2.0 Gy each ($BED_3 = 130\ Gy_3$)	✖ Favourably comparable tumour control and rectal toxicity in the hypofractionated arm	Tumour control evaluated as the biochemical relapse-free survival at 66 months
YEOH	2.2	217	20 fractions of 2.75 Gy each ($BED_3 = 105\ Gy_3$)	33 fractions of 2.0 Gy each ($BED_3 = 110\ Gy_3$)	✖ Similar tumour control and radiation toxicity	Tumour control evaluated as the biochemical relapse-free survival at 48 months

COMPARABLE / BETTER

Is the α/β Value for Prostate Tumours Low Enough to be Safely Used in Clinical Trials?

A. Daşu

Clinical Oncology (2007) **19**: 289–301
doi:10.1016/j.clon.2007.02.007

HYPO FRACTIONATION IN PROSTATE CANCER

Randomised clinical trials of hypofractionated radiotherapy regimens for prostate cancer and associated therapeutic gain as compared to conventionally fractionated radiotherapy.

Trial/reference	Regimens compared	Treatment schedule	Treatment outcome	Therapeutic gain
Prospective phase III randomised trial 168 patients (Arcangeli et al., 2010) [35]	Hypofractionated versus Conventional	62 Gy in 20 fractions over 5 weeks, 4 fractions per week (3.1 Gy/fraction) versus 80 Gy in 40 fractions over 8 weeks	TCP: 3-year freedom from biochemical failure (FFBR) 87% hypofractionation 79% – conventional NTCP: no differences in late toxicity	Yes
Randomised trial 91 patients (Norkus et al., 2009) [36]	Hypofractionated 3D-CRT versus Conventional 3D-CRT	57 Gy in 17 fractions over 3.5 weeks: 13 fractions of 3 Gy + 4 fractions of 4.5 Gy versus 74 Gy in 37 fractions at 2 Gy/fraction over 7.5 weeks	NTCP: min. 3 months follow-up (acute toxicity) grade 2 GU: 19.1% (hypo) versus 47.7% (conventional) duration of acute GI toxicity shorter with hypofract (3 weeks versus 6 weeks)	Yes (but longer follow-up is needed for decisive results)
Randomised hypofractionated dose escalation trial 100 patients (Pollack et al., 2006) [37]	Hypofractionated IMRT versus Conventional IMRT	70.2 Gy in 26 fractions at 2.7 Gy/fraction versus 76 Gy in 38 fractions at 2.0 Gy/fraction	NTCP: small increase in GI toxicity in the hypofractionated arm	Not conclusive (the target endpoint was acute toxicity; longer follow-up is needed for decisive results).
Randomised trial 217 patients (Yeoh et al., 2006) [38]	Hypofractionated versus Conventional	55 Gy in 20 fractions over 4 weeks (2.75 Gy/fraction) versus 64 Gy in 32 fractions	TCP: similar in the two groups NTCP: GI toxicity worse in the hypofractionated group	No (the two schedules were equivalent in efficacy)

EFFICIENCY :

COMPARISON BETWEEN CONVENTIONAL AND HYPO

COMPARABLE / BETTER

RANDOMIZED TRIAL OF DOSE ESCALATON WITHOUT ADT:

- MD ANDERSON ➡ BENEFIT OF 78GY vs 70GY

PSA>10

-ZIETMAN ➡ BENEFIT OF 79.2GY vs 70.2GY

-Gleason 8-10

-- ROACH ➡ BENEFIT OF DOSE> 71GY
Gleason 8-10

TWO RANDOMIZED TRIALS WITH DOSE –ESCALATION + ADT

DUTCH RANDOMIZED STUDY ➡ BENEFIT OF 78GY vs 68GY +ADT (INTERMEDIATE RISK)

MEDICAL RESEARCH COUNCIL STUDY ➡ BENEFIT OF 74GY vs 64GY (GLEASON 8-10)

IN MVAs RT DOSE (>80GY) WAS A SIGNIFICANT DETERMINANT OF BF,DM,AND OM

+ ADT

CLINICAL INVESTIGATION

RADIOTHERAPY DOSES OF 80 GY AND HIGHER ARE ASSOCIATED WITH LOWER MORTALITY IN MEN WITH GLEASON SCORE 8 TO 10 PROSTATE CANCER

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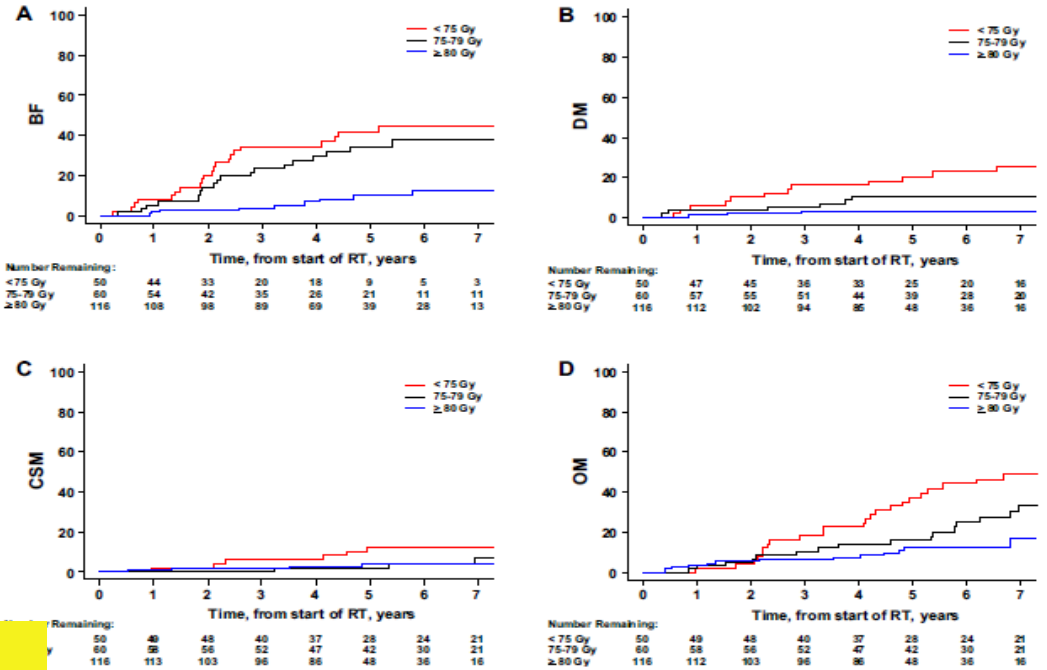

Fig. 2. Patient outcome by dose group. The cumulative incidence curves calculated from the start of radiotherapy by dose group are shown for biochemical failure (BF) (A), distant metastasis (DM) (B), and cause-specific mortality (CSM) (C) mpeting risks method, and for overall mortality (OM) (D) using the Kaplan-Meier approach. A significant is noted with higher RT dose and better outcome for BF ($p < 0.001$), DM ($p < 0.001$), and OM For CSM, results were not significant ($p = 0.387$). RT = radiotherapy.

		BF (competing risks)			DM (competing risks)			OM (Cox)		
Covariate	Group	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
RT Dose	Continuous	0.88	0.82–0.94	<0.001	0.83	0.75–0.92	<0.001	0.93	0.86–0.99	0.015
PSA	Continuous	1.01	1.00–1.02	0.053	1.01	0.99–1.03	0.420	1.01	1.00–1.02	0.092
T category	T1	Ref	—	—	Ref	—	—	Ref	—	—
	T2	1.28	0.51–3.23	0.596	0.77	0.15–3.90	0.755	1.11	0.51–2.42	0.794
	T3/T4	2.82	1.07–7.40	0.035	3.42	0.70–16.68	0.129	2.20	0.98–	
	TX	0.80	0.16–4.10	0.790	1.06	0.11–10.70	0.961			
ADT duration	Continuous	0.98	0.96–1.00	0.058	1.01					
Age	Continuous	0.97	0.92–1.01	0.136	0.9					
Technique	Conventional	0.92	0.27–3.11	0.894	0.63					
	3DCRT	Ref	—	—	Ref					—
	IMRT	0.83	0.29–2.39	0.732	—			1.03	0.29–3.75	0.890

at the time of this planned analysis. With a median follow-up of 5 years, there remain no statistically significant differences between the treatment arms in terms of BF, any failure, or late side effects. HIMRT is a reasonable option for men with intermediate to high-risk prostate cancer.

ASTRO

HYPO FRACTIONATION IN PROSTATE CANCER

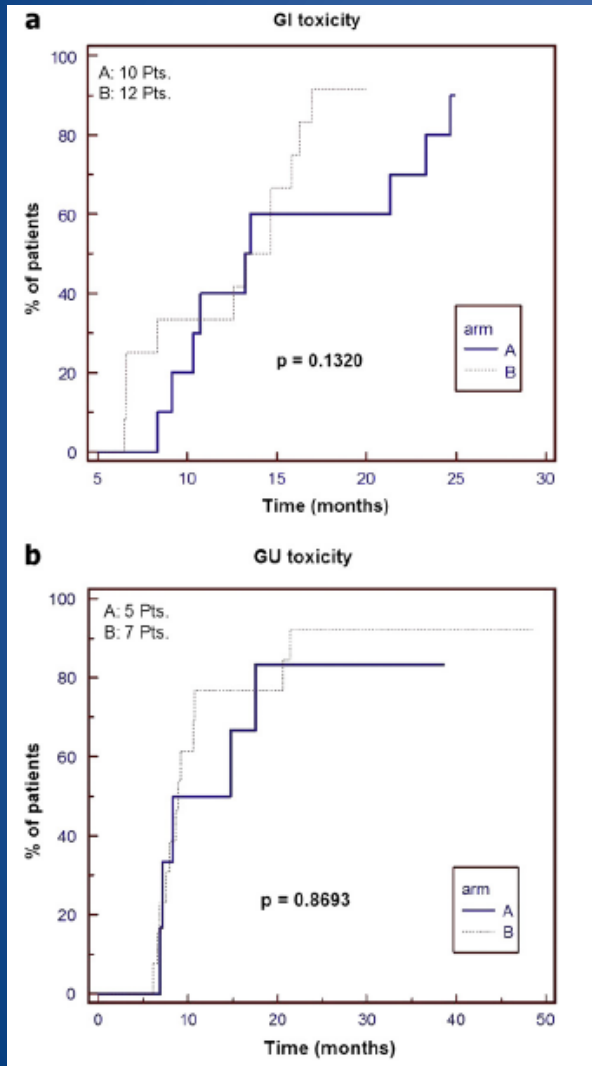

Fig. 5. Percentage of patients with late (a) gastrointestinal (GI) and (b) genitourinary (GU) Grade 2 or greater complications, normalized to maximal incidence, as function of time for conventional (solid line) and hypofractionation (dotted line) groups. Pts. = patients.

CLINICAL INVESTIGATION **Prostate**

ACUTE AND LATE TOXICITY IN A RANDOMIZED TRIAL OF CONVENTIONAL VERSUS HYPOFRACTIONATED THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY FOR PROSTATE CANCER

GIORGIO ARCANGELI, M.D.,* JACK FOWLER, PH.D.,† SARA GOMELLINI, M.D.,* STEFANO ARCANGELI, M.D.,* BIANCAMARIA SARACINO, M.D.,* MARIA GRAZIA PETRONGARI, M.D.,* MARCELLO BENASSI, PH.D.,‡ AND LIDIA STRIGARI, PH.D.‡

FFBF RATE WITH A MEDIAN FOLLOW UP OF 35 M WAS 79% FOR THE CONVENTIONAL ARM VS. 87% FOR THE HYPOFRACTIONATION ARM (STATISTICALLY SIGNIFICANT IMPROVEMENT : p = 0.035)

$\alpha/\beta = 1.8$

NO SIGNIFICANT CORRELATION FOR EITHER GI OR GU BETWEEN ACUTE AND LATE GI AND GU TOXICITY IN PTS TREATED WITH THE HYPOFRACTIONATE SCHEDULE

HYPO FRACTIONATION IN PROSTATE CANCER

Table 1 — Radiobiological analysis of clinical data

Reference	α/β value (Gy)	95% confidence interval	Patient number	Conditions	Assumptions
[1]	1.5	0.8–2.2 Gy	367 patients from two centres	Comparison between high dose rate external beam radiotherapy at 1.8 or 2.0 Gy per fraction and low dose rate brachytherapy with permanent I-125 implants	No proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[2]	4.96	4.1–5.6 Gy	367 patients from two centres	Reanalysis of the data used in [1]	Partial heterogeneity, no proliferation, unity relative biological effectiveness for the brachytherapy radiation
[3]	2.1		367 patients from two centres	Reanalysis of the data used in [1]	Full heterogeneity, no proliferation, unity relative biological effectiveness for the brachytherapy radiation
[6]	1.49	1.25–1.76 Gy	1471 patients from 10 centres	Comparison between high dose rate external beam radiotherapy and low dose rate brachytherapy with permanent I-125 and P-103 implants	No proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[8]	0.97–27				Non-unity relative biological effectiveness for the brachytherapy radiation, no proliferation, no parameter heterogeneity
[36]	0.52				1.75 relative biological effectiveness for the brachytherapy radiation, no proliferation, no parameter heterogeneity
[37]	0.89–1.1				Ranges of values for the relative biological effectiveness for the brachytherapy radiation, no proliferation, no parameter heterogeneity
[10]	1.2	0.03–4.1 Gy	192 patients from one centre	Comparison between high dose rate external beam radiotherapy and high dose rate brachytherapy	No proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[23]	3.1	1.7–4.5 Gy	1471 patients from 10 centres	Comparison between high dose rate external beam radiotherapy and low dose rate brachytherapy with permanent I-125 and P-103 implants	Very fast onset of accelerated proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[25]	3.1–3.9		1471 patients from 10 centres	Comparison between high dose rate external beam radiotherapy and low dose rate brachytherapy with permanent I-125 and P-103 implants	Very fast onset of accelerated proliferation, no parameter heterogeneity, unity relative biological effectiveness for the brachytherapy radiation
[38]	8.4	1.2–15.5 Gy		*In vitro* irradiation of cells	
[47]	1.33		705 patients from one centre	Comparison between hypofractionated and conventional treatments	
[57]	1.12	–3.3–5.6 Gy	936 patients from one centre	Comparison between hypofractionated and conventional treatments with external beam irradiation	
[57]	8.3	0.7–16 Gy	330 patients from one centre	Comparison between hyperfractionated and conventional treatments with external beam irradiation	
[46]	2.38		282 (100) patients from one centre	Comparison between hypofractionated and conventional treatments with external beam irradiation	
[52]	2.2	–6–10.6 Gy	217 patients from one centre	Comparison between hypofractionated and conventional treatments with external beam irradiation	

A. Daşu

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α/β derived from clinical data 5.000 pts

PREDOMINANT LOW α/β RATIO

The α/β ratio of prostate cancer ● A. E. NAHUM *et al.*

I. J. Radiation Oncology ● Biology ● Physics Volume 57, Number 2, 2003

fraction. For a total dose 76–78 Gy administered in 2 Gy fractions (currently considered the optimal treatment for intermediate-stage prostate cancer), cell killing by β-inactivation alone would produce an SF of about 0.0004. Given that realistic estimates of the density of clonogens in human tumors fall in the range 10^5–10^7/g (16), the probability that reducing the number of clonogens by a factor between 1,000 and 10,000 (often termed "3–4 logs" of cell kill) could produce tumor cure would be zero. If we now add the cell killing expected from the single-hit component (α) to that of the β-component, values of $\alpha \geq 0.20$ Gy^{-1} are required to yield an *SF* of $\sim 10^{-8}$, at which the probability of cure becomes significantly greater than zero. This demonstrates that the success of standard fractionated radiotherapy depends strongly upon the single-hit (α) inactivation coefficient of individual tumor clonogens (17–19).

HYPO FRACTIONATION IN PROSTATE CANCER

CLINICAL INVESTIGATION **Prostate**

INCORPORATING CLINICAL MEASUREMENTS OF HYPOXIA INTO TUMOR LOCAL CONTROL MODELING OF PROSTATE CANCER: IMPLICATIONS FOR THE α/β RATIO

ALAN E. NAHUM, PH.D., BENJAMIN MOVSAS, M.D., ERIC M. HORWITZ, M.D., CORINNE C. STOBBE, B.SC., AND J. DONALD CHAPMAN, PH.D.

Table 1. α- and β-coefficients reported for asynchronous populations of human prostate cancer cell lines

Cell line	α (Gy^{-1})*	β (Gy^{-2})*	α/β	SF_2*	Reference
TSU	0.06	0.050	1.24	0.70	Algan *et al.* (33)
TSU-Pr1	0.115	0.015	7.66	0.62	DeWeese *et al.* (34)
PC-3	0.064	0.017	3.76	0.71	DeWeese *et al.* (34)
PC-3	0.24	0.069	3.48	0.48	Algan *et al.* (33)
PC-3	0.521	0.055	9.47	0.32	Leith *et al.* (35)
PPC-1	0.1	0.026	3.84	0.56	DeWeese *et al.* (34)
DU-145	0.099	0.009	11	0.63	DeWeese *et al.* (34)
DU-145	0.31	0.048	6.45	0.48	Algan *et al.* (33)
DU-145	0.155	0.0521	2.98	0.60	Leith *et al.* (35)
LnCap	0.68	0.0053	~128	0.25	Leith (36)
LnCap	0.29	0.013	22.3	0.27	DeWeese *et al.* (34)
LnCap	0.49	0.0144	34.0	0.25	Chapman (15)
Average (± SE)	0.2603 ± 0.059	0.03115 ± 0.0064			

α/β DERIVED FROM CELL LINES

PREDOMINANT HIGH α/β RATIO

HYPO FRACTIONATION IN PROSTATE CANCER

CLINICAL INVESTIGATION **Prostate**

INCORPORATING CLINICAL MEASUREMENTS OF HYPOXIA INTO TUMOR LOCAL CONTROL MODELING OF PROSTATE CANCER: IMPLICATIONS FOR THE α/β RATIO

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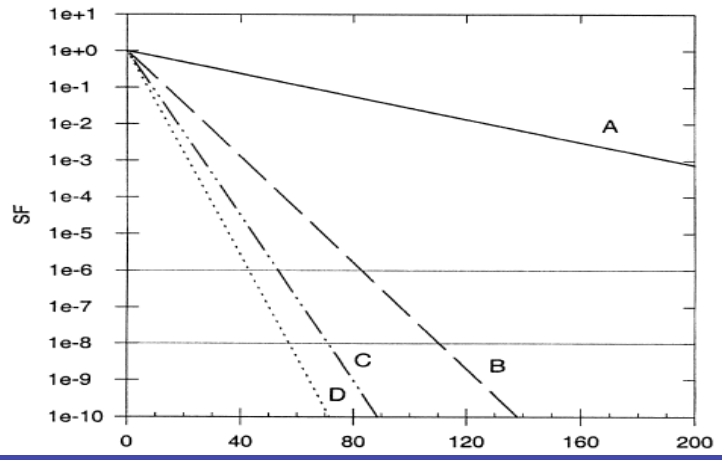
I. J. Radiation Oncology ● Biology ● Physics Volume 57, Number 2, 2003



SF < 10-10 FOR AEROBIC CELLS (CURVE D)

SF 10-5 FOR HYPOXIC CELLS (CURVE B)

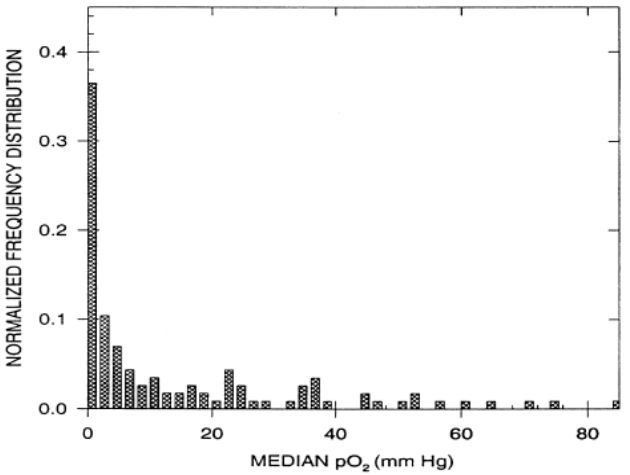
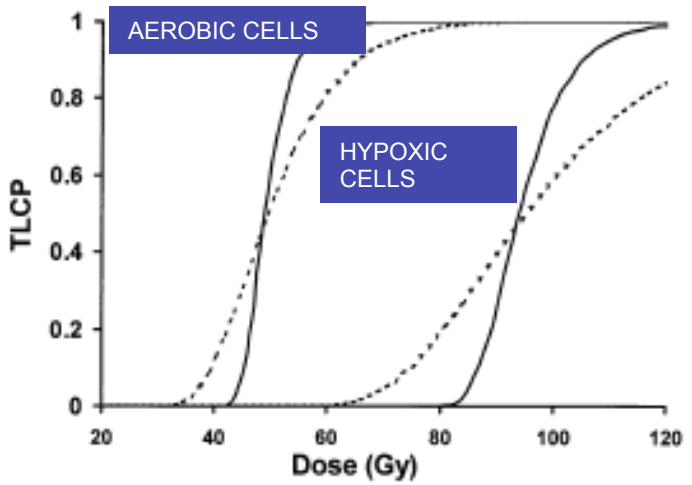


Fig. 2. A normalized distribution function of median Po_2 (mm Hg) measured by microelectrodes in 115 prostate cancer patients before receiving LDR or high-dose-rate brachytherapy at the Fox Chase Cancer Center.



LARGE PROPORTION OF PTS WITH EARLY DISEASE EXHIBITED EXTREMELY LOW VALUES OF PO2 (PARKER: IJROBP,2001; DASU: RO,2002)

? CAN THE IMAGING PROBE SIGNIFICANTLY INFLUENCE THE OXIGEN LEVEL MEASURED IN PROSTATE TUMOR?

LOW PO2 VALUES CORRELATE SIGNIFICANTLY WITH INCRESING TUMOR STAGE (MOSVAS : CANCER,2000)

RADIORESISTANT HYPOXIC TUMORS GOVERN THE OVERALL RESPONSE RATE OF PROSTATE CANCER TO OUR CURRENT THERAPIES

HYPO FRACTIONATION IN PROSTATE CANCER

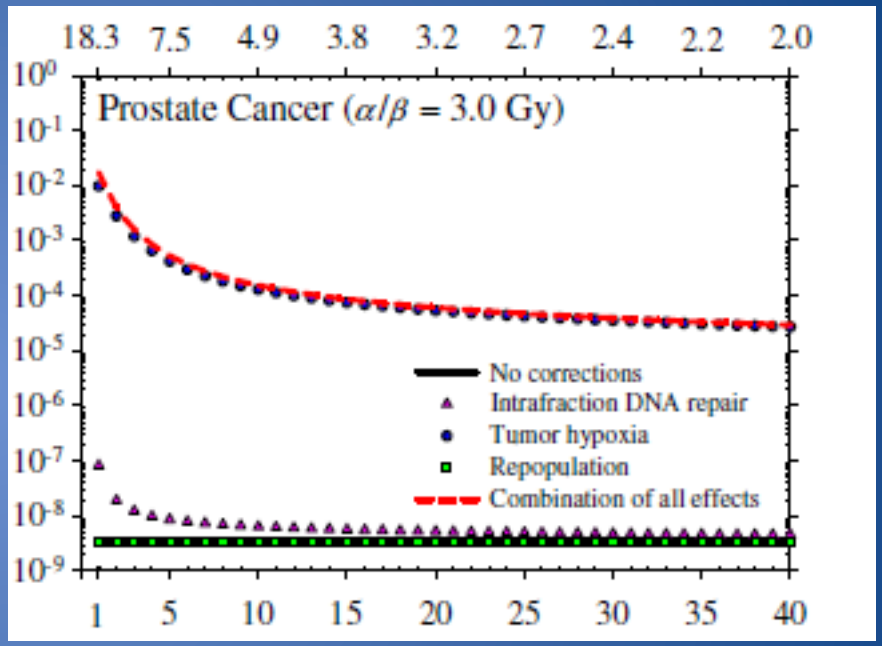
DECREASE IN CELLS KILLING WITH INCREASING DOSE PER FRACTION:

- CHANGES IN THE EFFECTIVE RADIOSENSITIVITY WITH HETEROGENEOUS OXYGENATION

-REDUCTION IN INTERFRACTION REOXYGENATION

-INCREASED IMPORTANCE OF MAXIMALLY RESISTENT CELLS (HYPOXIC FRACTION) IN DETERMINING OVERALL DOSE –RESPONSE AS THE TOTAL DOSE IS DELIVERED IN FEWER FRACTIONS

POTENTIAL LARGE ERROR WHEN CALCULATING ALTERNATE FRACTIONATIONS USING BED FORMALISMS THAT NOT ACCOUNT FOR TUMOR HYPOXIA



Effects of hypoxia in hypofractionated radiotherapy ● D. J. CARLSON *et al.*

I. J. Radiation Oncology ● Biology ● Physics Volume 79, Number 4, 2011

MODERATE HYPOFRACTIONATION

HYPO FRACTIONATION IN PROSTATE CANCER

OVERALL TREATMENT TIME (OTT)

RECENT STUDIES HAVE SUGGESTED A CLINICALLY SIGNIFICANT REPOPULATION EFFECT EXLUSIVELY FOR LOW RISK PTS WITH AN ONSET TIME OF ACCELERATED REPOPULATION OF 30-35 DAYS AND AN EFFECTIVE CLONOGEN DOUBLING TIME OF 12 DAYS (D'AMBROSIO DJ: IJROBP 2008, GAO M: IJROBP 2009)

4839 PTS OF NINE INSTITUTIONS →

DOSE AND OVERALL TIME ABOVE 52 DAYS (7 W) SIGNIFICANT IN LOW AND INTERMEDIATE-RISK PTS ONLY FOR >70GY (THAMES HD:RAD. ONCOL. 2010)

→ **MOST OF HYPO TREATMENT ARE DELIVERED IN <6 WEEKS**

HIGH RISK PTS MAY BE MORE LIKELY TO PRESENT WITH SUBCLINICAL METASTASES WICH MIGHT OVERSHADOW THE OTT MODULATION EFFECT (D'AMBROSIO DJ: IJROBP 2008) →

LOCALLY ADVANCED TUMORS MAY REQUIRE A LONGER TIME (69 DAYS) TO IMPROVE BLOOD/ NUTRIENT SUPPLY AND TRIGGER ACCELERATED REPOPULATION WHILE ON TREATMENT: NEGLEGIBLE EFFECT ON OUTCOME TO PROTRACT THE TREATMENT UP TO 10 WEEKS (GAO M: IJROBP 2009)

Table 2. Patient distribution according to dose/fraction and centers stratified by risk group and androgen deprivation (AD) status

		Without AD			With AD			
Author	Dose/fraction	Low risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk	Total
Kupelian*	2 Gy	70	113	6	5	140	227	561
	2.5 Gy	198	108	4	59	210	213	792
Leborgne†	2 Gy	195	216	131	52	108	165	867
Logue‡	3.125 Gy	311	516	409	111	323	412	2,082
Lukka§	2 Gy	113	278	79	–	–	–	470
	2.62 Gy	113	265	88	–	–	–	466
Madsen et al (20)*	6.7 Gy	40	–	–	–	–	–	40
Miralbell‖	1.8/2 Gy	57	118	50	–	71	107	403
	4 Gy	21	30	20	–	–	–	71
Yeoh¶	2 Gy	34	63	12	–	–	–	109
	2.75 Gy	26	57	25	–	–	–	108
Total		1178	1764	824	227	852	1124	5,969

Table 3. Five-year biochemical relapse–free survival probability stratified by risk groups and androgen deprivation (AD) status

		Without AD			With AD		
Author	Dose/fraction	Low Risk	Intermediate risk	High risk	Low risk	Intermediate risk	High risk
Kupelian*	2 Gy	0.95	0.83	1.00	1.00	0.87	0.74
	2.5 Gy	0.95	0.84	0.65	0.95	0.84	0.65
Leborgne†	2 Gy	0.85	0.90	0.58	0.94	0.82	0.73
Logue‡	3.125 Gy	0.79	0.63	0.59	0.69	0.57	0.53
Lukka§	2 Gy	0.66	0.38	0.28	–	–	–
	2.62 Gy	0.59	0.47	0.29	–	–	–
Madsen et al (20)*	6.7 Gy	0.93	–	–	–	–	–
Miralbell‖	1.8/2 Gy	0.87	0.67	0.32	–	0.74	0.67
	4 Gy	0.90	0.72	0.74	–	–	–
Yeoh¶	2 Gy	0.76	0.57	0.42	–	–	–
	2.75 Gy	0.73	0.67	0.64	–	–	–

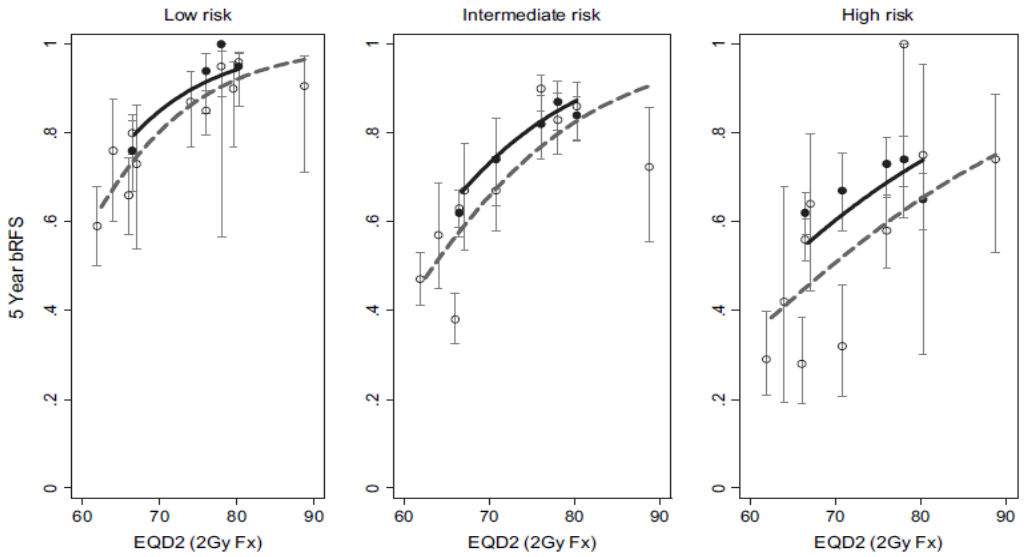


Fig. 1. Outcomes for each patient/treatment group along with fitted values from Model B. Error bars represent 95% CI on the binomial proportions in each group. Solid lines and filled symbols represent AD-treated patients; and broken lines and open symbols represent non–AD-treated patients. Data are normalized to 2-Gy fractions using the fitted α/β values.

ANDROGEN DEPRIVATION

α/β VALUE FOR THE POOLED DATA IS 1.4

-0.6 FOR LOW-RISK

-1.7 FOR INTERMEDIATE RISK

-1.6 FOR HIGH RISK

SIGNIFICANT IMPROVEMENT OF bRFS WITH DOSE IN ALL RISK GROUP INDEPENDENTLY OF THEIR AD STATUS

AD + RT IMPROVED SIGNIFICANTLY bRFS IN ALL RISK GROUPS BY 5%

CAN AD MEDIATED T REOXYGENATION IN NEOADJUVANT SETTING BEFORE RT INFLUENCE CELL REPOPULATION IN ADVANCED STAGE??????

MIRABELL,IJROBP,2011

e presumed cell proliferation trigger from reoxygenation because of the enhanced tumor-cell kill-ing effect may be prevented by an enhanced recruitment of tu-mor cells into the non-proliferative phase of the cell cycle ("G_0") as a consequence of the same AD therapy. Also, this argues against the higher estimated α/β value of 7.1 Gy (95% CI = 2.8–28.8) as reported by Williams *et al.* (41).

HYPO FRACTIONATION IN PROSTATE CANCER

TREATMENT OF PELVIC LYMPH NODES ??

YES → MODERATE HYPOFRACTIONATION

Table 1. Radiotherapy characteristics, by first author

Author	Dose/fraction	Total dose	No. fractions	No. fractions/wk	OTT (wk)	Pelvic nodes RT	Technique
Kupelian	2 Gy	78 Gy	39	5	7.5	No	3d-CRT
	2.5 Gy	70 Gy	28	5	5.5	No	IMRT-BAT
Leborgne	2 Gy	76 Gy	38	5	7.5	No	3d-CRT
Logue	3.125 Gy	50 Gy	16	5	3	No	3d-CRT
Lukka	2 Gy	66 Gy	33	5	6.5	No	2d-CRT
	2.62 Gy	52.4 Gy	20	5	4	No	2d-CRT
Madsen et al (20)	6.7 Gy	33.5 Gy	5	5	1	No	SRT-IGRT
Miralbell	1.8–2 Gy	74–74.4 Gy	37–40	5	7.5–8	No/yes	3d-CRT
	4 Gy	56 Gy	14	2	6.5	No	SRT
Yeoh	2 Gy	64 Gy	32	5	6.5	No	2d-RT
	2.75 Gy	55 Gy	20	5	4	No	2d-RT

Abbreviations: BAT = transabdominal ultrasound system; IGRT = image guided radiotherapy; OTT = overall treatment time; SRT = stereotactic radiotherapy; 2D-RT = two-dimensional radiotherapy treatment planning; 3D-CRT = three-dimensional conformal radiotherapy.

5969 PTS :

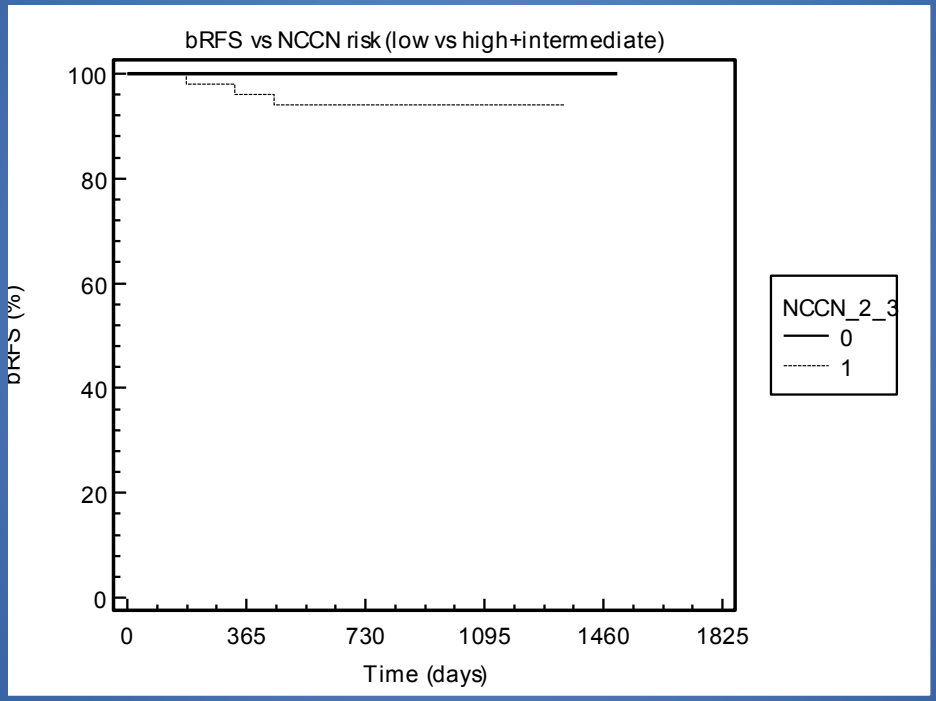
23% LOW RISK;

44% INTERMEDIATE RISK;

33% HIGH RISK

HYPO FRACTIONATION IN PROSTATE CANCER

HSR EXPERIENCE



MEDIAN FOLLOW UP 36 M

MODERATE HYPOFRACTIONATION : 74.2 GY (51.8GY ON PELVIC NODES) 28 FR AD 50% PTS

Feasibility of safe ultra-high (EQD_2>100 Gy) dose escalation on dominant intra-prostatic lesions (DILs) by Helical Tomotherapy

ANGELO MAGGIO[1], CLAUDIO FIORINO[1], PAOLA MANGILI[1], CESARE COZZARINI[2], FRANCESCO DE COBELLI[3], GIOVANNI MAURO CATTANEO[1], TIZIANA RANCATI[4], ALESSANDRO DEL MASCHIO[1], NADIA DI MUZIO[2] & RICCARDO CALANDRINO[1]

Acta Oncologica, 2011; 50: 25–34

PTV(p+sv)
✓ 71,4 Gy; 2,55 Gy/fr

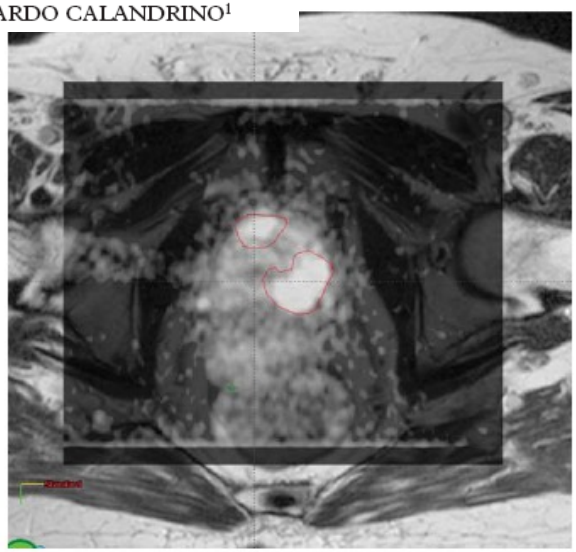
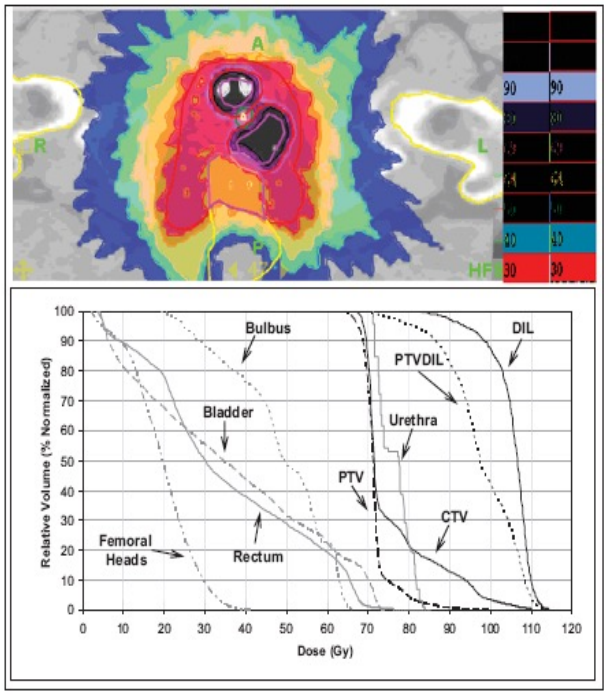
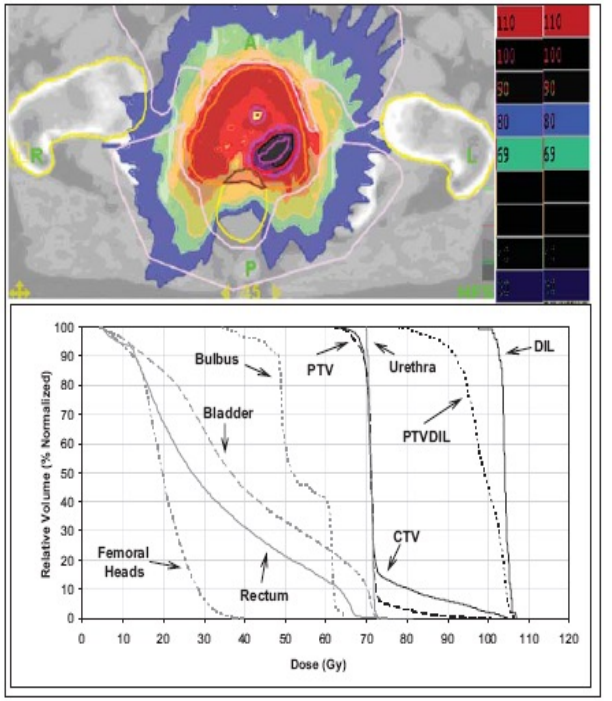


Figure 1. DWI superimposed to T2WI for a patient with two DILs in peripheral zone.



PTVDIL
- ✓ 71,4 Gy; 2,55 Gy/fr (EQD_2=75 Gy)
- ✓ 80 Gy; 2,86 Gy/fr (EQD_2=86 Gy)
- ✓ 90 Gy; 3,21 Gy/fr (EQD_2=99 Gy)
- ✓ 100 Gy; 3,57 Gy/fr (EQD_2=113 Gy)
- ✓ 120 Gy; 4.29 Gy/fr (EQD_2=143 Gy)*



EQD_2 calculated with $\alpha/\beta=10$

HYPO FRACTIONATION IN PROSTATE CANCER

CONCLUSIONS

HIGH RISK PATIENTS → MODERATE HYPOFRACTIONATION

GOOD TOXICITY PROFILE

BETTER OUTCOME DOSE RELATED

LOW IMPACT OF HYPOXIA

TREATMENT OF PELVIC LYMPH NODES + AD IINCREASE BDFS

ALLOWS THE DELIVERY OF HIGHER DOSE WITH HYPO TO THE DIL :
BETTER LOCAL CONTROL

PROSTATE CANCER HAS BEEN CONSIDERED BY MANY TO BE A VERY SLOW-GROWING CANCER WITH NEGLIGIBLE TUMOR CLONOGENIG REPOPULATIN DURING THE FIRST 8-9 WEEKS OF TREATMENT (LAI PP: IJROBP 1991, PEREZ CA: CANCER 2004)

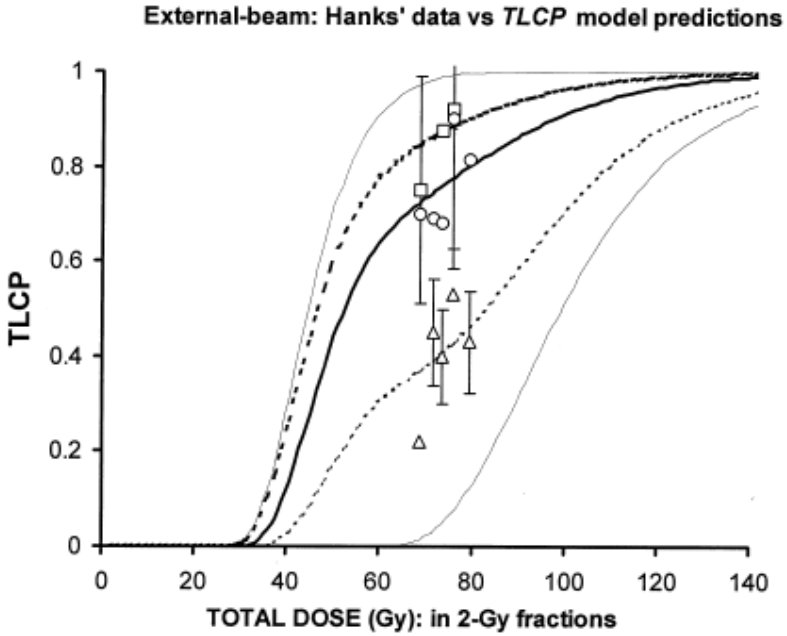


Fig. 4. *TLCP* vs. total external beam radiotherapy dose delivered in 2-Gy fractions for aerobic (left-most) and hypoxic (right-most) tumors whose clonogens have the same variable α (i.e., nonzero σ_α) and fixed β radiosensitivities as those of Fig. 3. The three intermediate curves describe patient populations whose hypoxic tumor/aerobic tumor ratios are 15/85 (dashed), 25/75 (full), and 60/40 (dotted) from left to right, respectively. The data points are local-control rates (bNED) for prostate cancers of increasing stage, with PSA levels of ≤10 (□□), 10–20 (○○), and ≥20 (△△) ng/ml from Hanks *et al.* (40). Error bars ($\pm\sqrt{n}/n$) were computed where n is the number of patients for treatment groups with $n \geq 20$.

Dosimetric and biological indeces: 7 PTs data