GIVE ME FIVE

Report preliminare di uno schema marcatamente ipofrazionato per la cura della neoplasia prostatica organo-confinata mediante IG-IMRT

Esperienza dell' Istituto Europeo di Oncologia

Dr.ssa Sarah Colangione

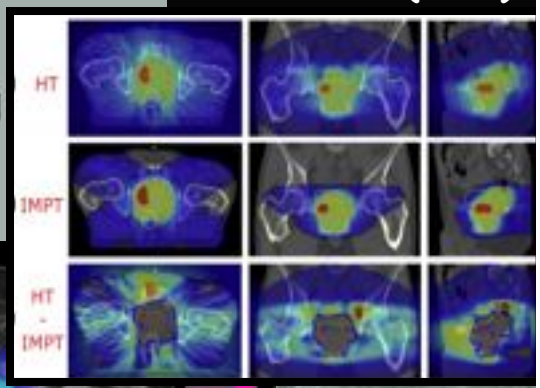
DOSE ESCALATION
High precision radiotherapy

Step of radiotherapy treatment planning and technique

to deliver high dose to a small target or dominant lesion

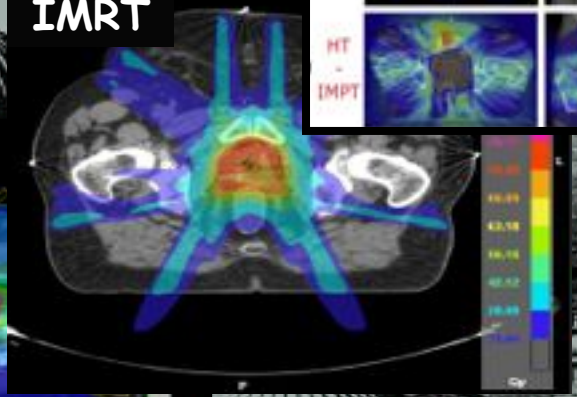
>90 Gy?

IG-IMRT (SIB)



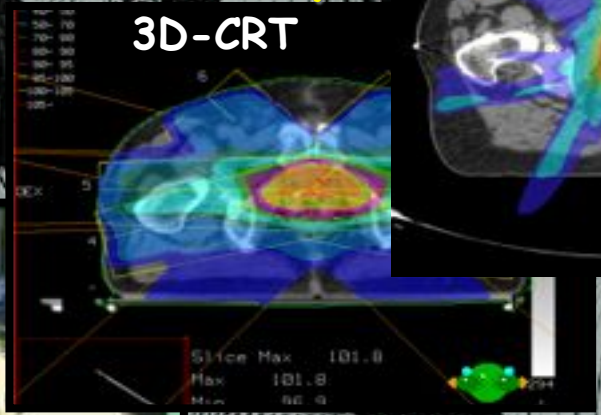
90 Gy

IMRT



80 Gy

3D-CRT

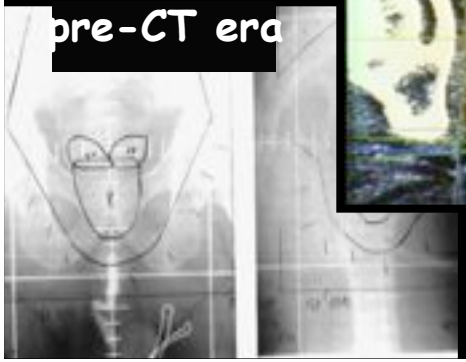


70 Gy

post-CT era

60 Gy

pre-CT era



PURPOSE of OUR REPORT

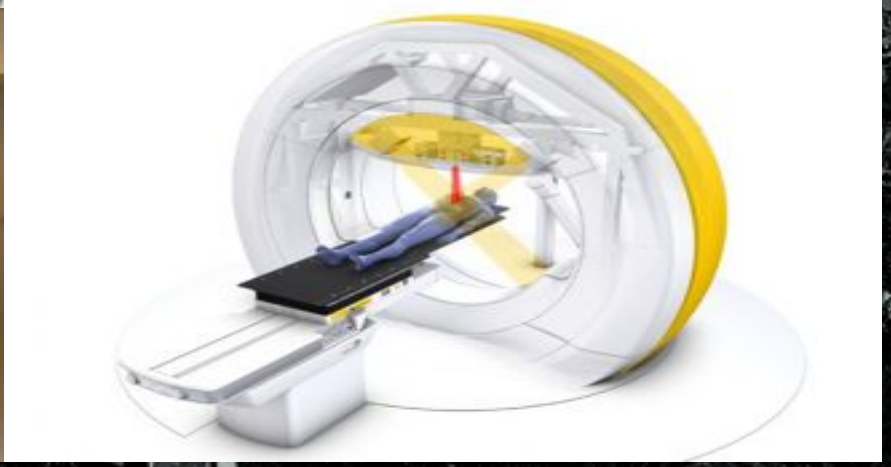
To evaluate feasibility and *safety*, in terms of early and late toxicity using a short course of radiotherapy for prostate confined tumor through IG-IMRT with non robotic linear accelerators:

- Vero - BrainLab system
- RapidArc - Varian

GIVE ME FIVE!

Volume	Dose/fr	N u m fr	Dtot	NTD (α/β=1,5Gy) d/fr 2Gy	B E D (α / β=1,5Gy)
PTVprostata	6,5 7	5 5	32,5 35	74,3 85	173 198

Give me five: OUR PROPOSAL



Materials and methods

April 2012 - October 2014

432 pts treated at IEO with non metastatic organ-confined PCa

140/pts received an extreme hypo-IG-IMRT regimen

Analyzed data on the first 120 pts with early stage Pca

118 pts with VERO-BrainLab system; 2 pts with Rapidarc-Varian

SUPPORTIVE MEASURES

PREMEDICATION with low dose steroids + IPP before each treatment

URINARY: symptomatic urinary are allowed (e.g. alpha-blockers like tamsulosin, silodosin)

BLADDER: full urinary bladder both during simulation and treatment

BOWEL: low gas and low motility diet. One Fleet's enema will be administered 2-3 hours before CT simulation and each treatment

Materials and methods

INCLUSION CRITERIA

- Histologically confirmed adenocarcinoma of prostate, according to the 2014 NCCN risk categories: low (T1-T2a, PSA <10 ng/ml, Gleason score <7) or intermediate (T2b or T2c, PSA between 10 and 20 ng/ml, Gleason score of 7)

- Personalized indication for high risk pts (PSA > 20 ng/ml, Gleason score> 7)

- Prostate volume <100 cc

- cN0 and cM0 stage

- Age > 18 years

- Specific informed consent *OUT TRIAL PATIENTS*

Materials and methods

EXCLUSION CRITERIA

-Extraprostatic tumor extension (T3) or locally advanced disease (T4)

-Pelvic lymph node metastasis (cN1)

-Distant metastasis (cM1)

-Severe urinary obstructive symptoms

-Previous pelvic radiotherapy

-Severe systemic disorders

- Concomitant disorders including: chronic urinary or intestinal inflammatory conditions (for example, ulcerous recto-colitis, Crohn disease)

- Psychiatric disorders or any other condition that can can make unreliable the informed consent

- Non conformity of the radiotherapy dose distribution when compared to the dose constraints

Materials and methods

TREATMENT PLANNING

IEO Istituto Europeo di Oncologia
Divisione di Radioterapia

Cognome ______________________
Nome ______________________
ID Paziente ______________________

REPORT DOSIMETRICO TRATTAMENTO IMRT

"PROSTATE EXTREME HYPOFRACTIONATION"

(dose/frazione: 6,5-7,5Gy; numero di frazioni: 5; dose totale 32,5-37,5Gy)

Limiti dose-volume: organi sani (OARs)

DOSE CONSTRAINTS

	Valori raccomandati per dose/frazione	Valori del piano di cura
Retto* V= ________ cm³	V <50%	%
	V < 20%	%
	V < 10%	%
	V < 5%	%
Volume di sovrapposizione PTV – retto	D <85%	%
Parete post. retto/canale anale[§§]	D_{mean}<45%	%
Canale anale[§]	D_{mean}<10Gy	Gy
Vescica urinaria* V= ________ cm³	V <10% oppure V < 5cm³	% cm³
	V < 40%	%
Uretra**	V <50%	%
	D_{max}<110%	%
Teste femorali*	V < 5%	%
Intestino/cavità peritoneale V= ________ cm³	**V <1cm³	cm³
	[§§]D_{max}<15%	%
	[§§] V < 195cm³	cm³
Bulbo penieno**	V < 50%	%
Pene[§§]	V <1cm³	cm³
Testicoli	D < 2Gy	Gy
Cauda equina[§§]	D_{max}<19Gy	Gy

* King CR, Brooks JD, Gill H, et al. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012; 82:877-882.

**Chen et al. Stereotactic Body Radiation Therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. Radiat Oncol 2013;8:58.

§ Alsadius D, Hedelin M, Lundstedt D, et al. Mean absorbed dose to the anal-sphincter region and fecal leakage among irradiated prostate cancer survivors. Int J Radiat Oncol Biol Phys. 2012;84:e181-5. (valore riscalato per la dose attuale di prescrizione con α/β=3Gy cui viene sottratto il 20%)

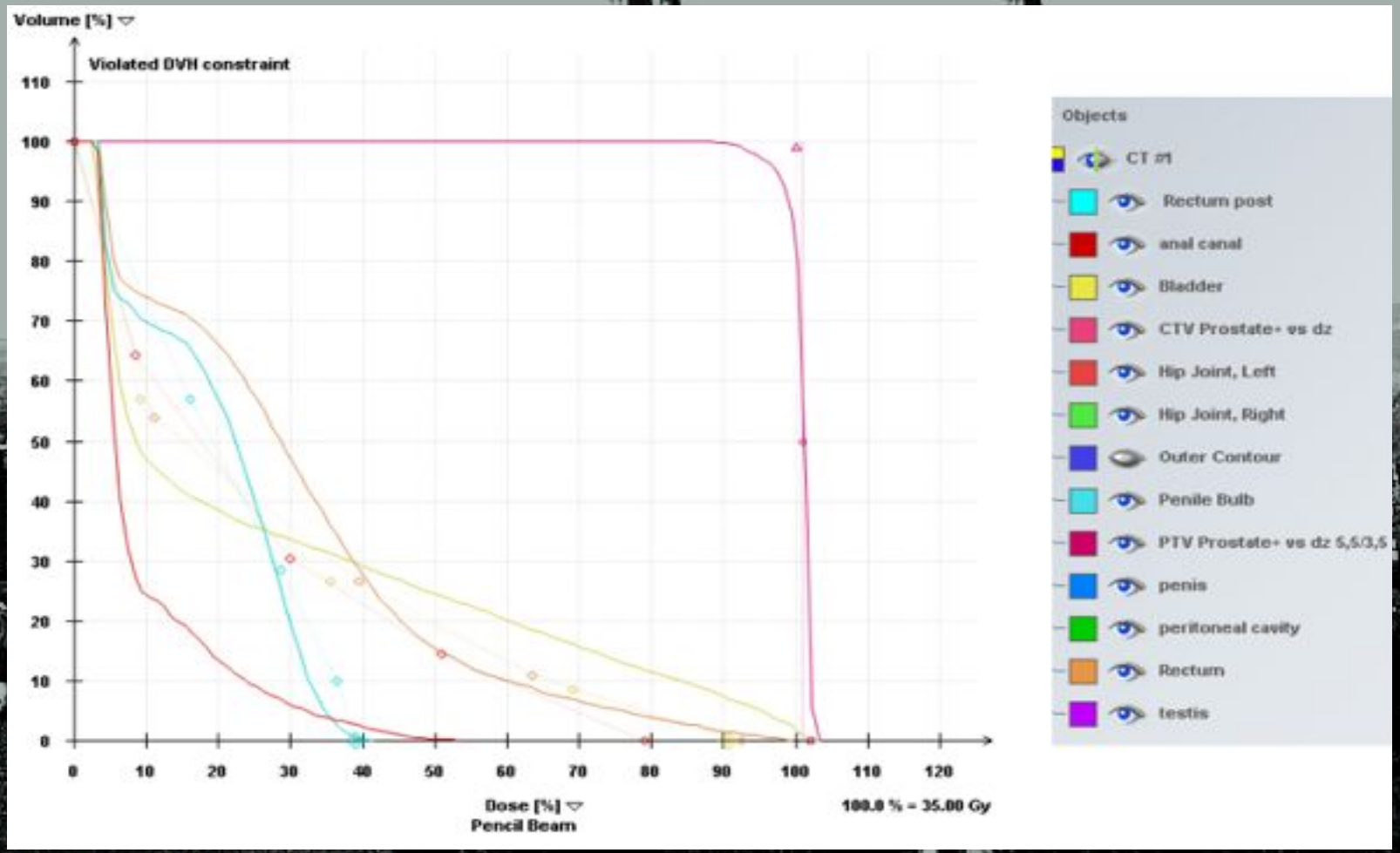
§§ Valore da protocollo IEO (linee guida interne) e da Kavanagh BD, Pan CC, Dawson LA, et al. Radiation dose-volume effects in the stomach and small bowel. Int J Radiation Oncology Biol. Phys. 76: S101–S107, 2010; valore riscalato per la dose attuale di prescrizione con α/β=3Gy cui viene sottratto il 20%.

Data ___/___/___ Firma Fisico ______________________ Firma Medico ______________________

Give me five: IEO protocol

6.5/7 Gy/fraz x 5 frazioni: 32.5/35 Gy a giorni alterni mediante IG-IMRT con 7 campi di fotoni X 6 MV

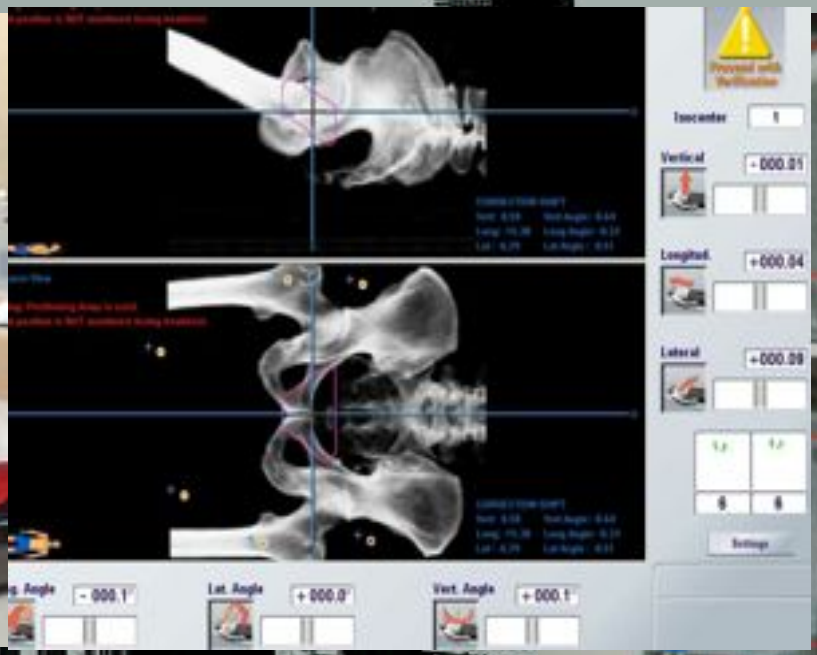
Give me five: IEO protocol

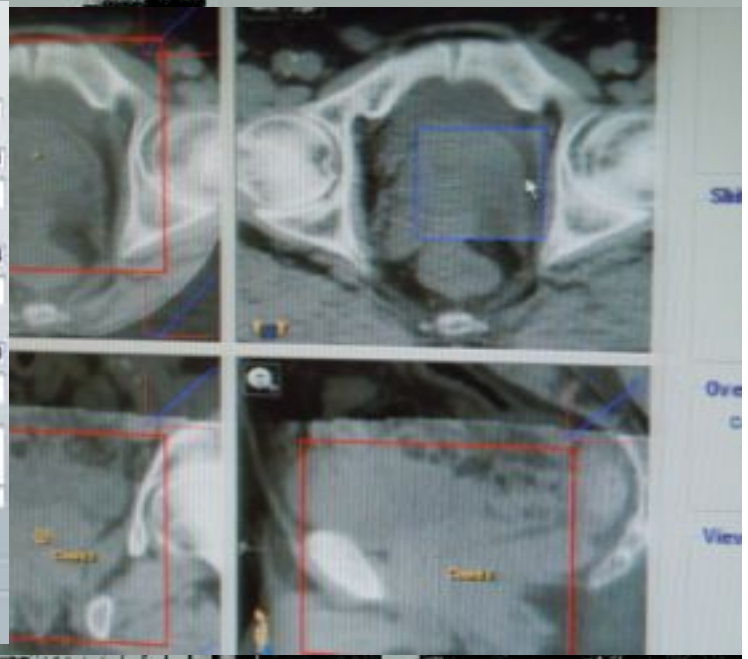


7 Gy x 5 fx: 35 Gy on alternate days

Give me five: IEO protocol

VERO - BrainLab





1. Daily ExacTrac (positioning array or surface markers)

2. Daily IGRT with CBCT

Just couple of minutes, imaging dose 1.9 cGy

Materials and methods

ACUTE TOXICITY ASSESSMENT

TOSSICITA' ACUTA (< 3 mesi F.U.) URINARIA E RETTALE (RTOG/ EORTC)

TOSSICITA' ACUTA URINARIA

G0	G1	G2	G3	G
Invariato rispetto pre RT	Pollachiuria e nicturia 2 volte più frequenti rispetto pre-RT	Pollachiuria con freq > 1 ora,disuria, urgenza, tenesmo vescicale trattabile con farmaci	Pollachiuria con urgenza, freq <1ora, disuria, dolore pelvico, tenesmo vescicale che richiedono terapia maggiore. Macroematuria	Ema importante trasfusione; vescicale a catetere in u ulcerazione

TOSSICITA' ACUTA INTESTINALE/RETTALE

G0	G1	G2	G3	G4
Invariato rispetto pre RT	Alvo accelerato o modifica della consistenza delle feci che non richiede trattamento farmacologico	Mucorrea lieve tale da non richiedere trattamenti. Diarrea, dolore rettale e/o addominale che richiedono trattamento farmacologico	Diarrea profusa che richiede terapia parenterale. Mucorrea severa o proctorragia tali da richiedere intervento medico. Distensione addominale (valutata ad Rx in posizione orizzontale).	Ostruzione acuta o subacuta,perforazione;sanguinamento che richiede trasfusione; dolore addominale;tenesmo che richiede diversione intestinale o drenaggio chirurgico.

Materials and methods

LATE TOXICITY ASSESSMENT

TOSSICITA' TARDIVA (> 3 mesi F.U.) URINARIA E RETTALE (RTOG/EORTC)

TOSSICITA' TARDIVA URINARIA

G0	G1	G2	G3	G4
Invariato rispetto pre-RT	Ematuria microscopica, alla cistoscopia minima atrofia della mucosa vescicale e qualche teleangiectasia	Ematuria macroscopica intermittente pollachiuria con ora	Pollachiuria (IL<1ora) e disuria	Ritenzione acuta d'urina con necessità di

TOSSICITA' TARDIVA INTESTINALE/RETTALE

G0	G1	G2	G3	G4
Invariato rispetto pre-RT	Diarrea moderata < 5 scariche/die e dolori Addominali crampi formi modesti; minima mucorrea o sanguinamento.	Diarrea > 5 scariche/ die; marcata mucorrea rettale e sanguinamento intermittente in assenza di grave anemizzazione	Sanguinamento rettale che richiede terapia laser e/o trasfusione; ostruzione intestinale che richiede intervento chirurgico	Necrosi Perforazione intestinale e/o fistolizzazione

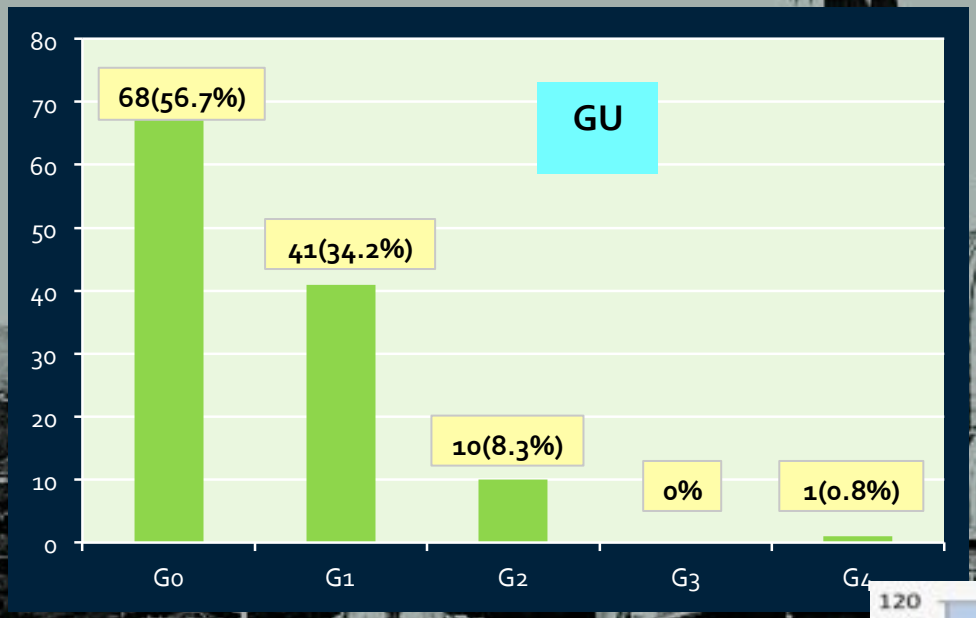
BIOCHEMICAL OUTCOME:

bRFS according to Phoenix's definition
(PSA nadir + 2)

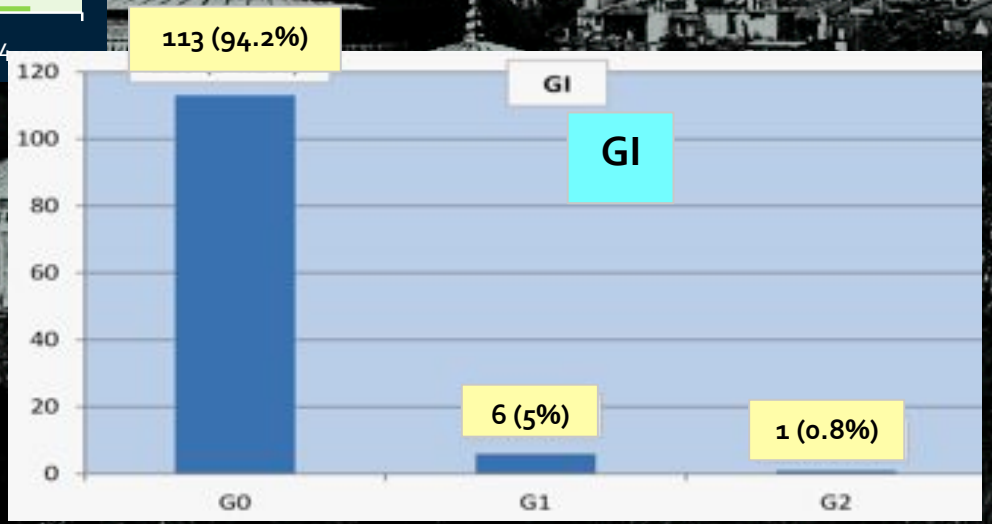
Give me five: RESULTS

FEATURES	PATIENTS (n= 120)
Age (years)	
Mean	73.2
Median (range)	74 (51.4-89)
Initial PSA (ng/mL)*	
Mean	9.9
Median (range)	7.2 (2.8 – 55.7)
Initial Gleason Score (x 101 patients)	
Median (range)	6 (4-9)
Initial disease category	
Low	45 (37.5%)
Intermediate	56 (46.7%)
High	18 (15%)
Unknown	1 (0.8%)
ADT	35 (29%)

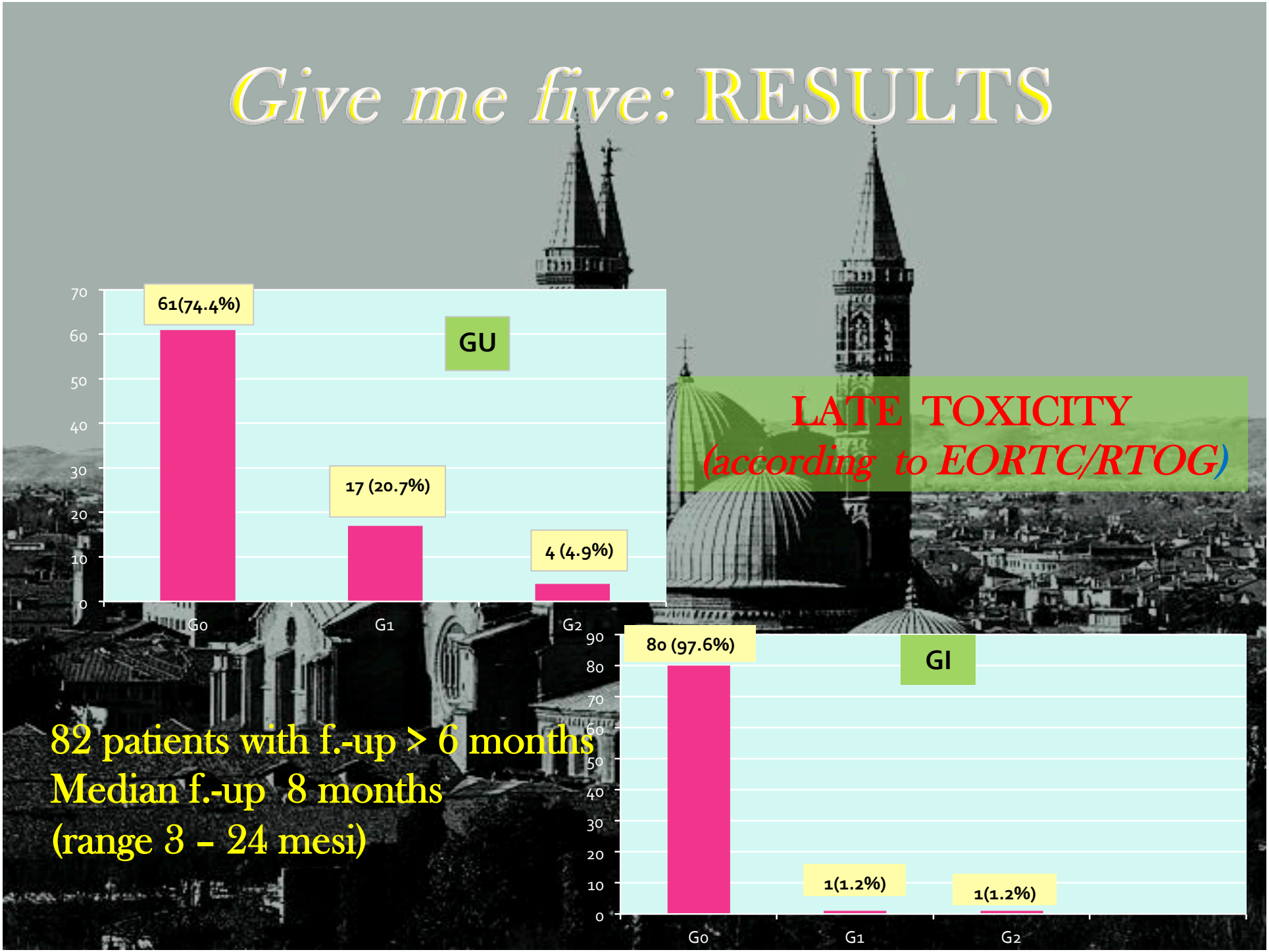
Give me five: RESULTS



ACUTE TOXICITY
(according to EORTC/RTOG)



Give me five: RESULTS



Give me five
Promising RESULTS

- GU Acute Toxicity G4: 1 patient /120 (0.8 %)
- No late toxicity G3 and G4
- Currently ... 81 pazienti/82 NED *(median f.-up: 8 months)*
- Clinical and biochemical progression disease: 1 patient /82(1.2 %)

Discussion and Conclusion

Review – Prostate Cancer

A Systematic Review of Hypofractionation for Primary Management of Prostate Cancer

Bridget F. Koontz[a,], Alberto Bossi[b], Cesare Cozzarini[c], Thomas Wiegel[d], Anthony D'Amico[e]*

Table 2 – Prospective studies of extreme hypofractionation for intact prostate with at least 50 participants

	n	Median FU, mo	Risk, NCCN	Technique	Regimen	BED, Gy	Outcome	Toxicity
Aluwini et al. [46]	162	28	Low/intermediate	n.s.	38 Gy/4 fx	119.6	3 yr BC 98%	Gr 2 GU 15% Gr 2 GI 3%
Bolzicco et al. [27]	100	36	41% low 42% intermediate 17% high	Robotic IGRT	35 Gy/5 fx 29% ADT	85	BC 96%	Gr 1/2/3 GU 4%/3%/1% Gr 1/2/3 GI 2%/1%
Chen et al. [47]	100	28	37% low 55% intermediate 8% high	Robotic IGRT	35–36.25 Gy/5 fx 11% ADT	85-90.6	2 yr BRFS 99%	2 yr Gr ≥2 GU 31% 2 yr Gr ≥2 GI 1%
D'Alimonte et al. [48]	84	50	100% low	IMRT/IGRT	35 Gy/5 fx	85	BC 98%	Gr 2/≥3 GU 5/1% Gr 2/≥3 GI 5/1%
Puller et al. [39]	260	20	45% low 55% intermediate	n.s.	38 Gy/4 fx	119.6	3 yr BRFS 98%	Gr 3 GU 2% (any Gr 44%) Gr 3 GI 0% (any Gr 11%)
Katz and Kang [24]	515	54	67% low 26% intermediate 7% high	Robotic IGRT	35–36.25 Gy/5 fx	85-90.6	6 yr FFBF 97% 92% 70%	Gr ≥2 GU 9% Gr ≥2 GI 4%
King et al. [34]	67	32	100% low	Robotic IGRT	36.25 Gy/5 fx	90.6	4 yr BRFS 94%	Gr ≥2 GU 7% Gr ≥2 GI 12%
Loblaw et al. [25]	84	55	100% low	IMRT/IGRT	35 Gy/5 fx	85	5 yr BC 98%	5 yr Gr ≥2 GU 5% 5 yr Gr ≥2 GI 7%
Meier et al. [38,49]	129	30	100% intermediate	Robotic IGRT	40 Gy/5 fx No ADT	108.8	3 yr BRFS 99%	Gr 2 GU 10% Gr 2 GI 2%
Menkarios et al. [29]	80	33	100% low	IMRT/IGRT	45 Gy/5 fx	135	3 yr BC 97%	Gr ≥2 GU 14% Gr ≥2 GI 16%
Ouon et al. [50]	84	18	100% low	IMRT/IGRT	35 Gy/5 fx	85	n.s.	Gr 2 GU 2% Gr 2 GI 5%
IEO, 2014	**120**	**8**	**All risk categories**	**IG-IMRT**	**32.5-35 Gy/5 fx**	**74.3-85**	**8 mp BC 99.2%**	**Gr 2 GU 4.9% Gr 2 GI 1.2%**

European Urology, August 2014

Give me five
TAKE HOME MESSAGES

Our preliminary report has showed that ...

- Short time commitment regarding to treatment planning and dose delivery
- Excellent patient compliance (non invasive technique, NO fiducial markers)
- Excellent availability of RT staff (radiation oncologists, physicists, technicians)
- Reduction of waiting list
- IG-IMRT short course was well-tolerated

Longer follow-up is needed to corroborate our preliminary findings in terms of low late toxicity profiles, bDFS and OS

MAIN LIMIT

NEXT FUTURE

- AIRC -

Associazione Italiana per la Ricerca sul Cancro

Investigator Grant - IG 2012

Tailored very short hypofractionated RT

Task 1: In-silico planning study (based on patient- and tumor- parameters)

Task 2: Two-stage phase II, prospective, single-arm, monocentric clinical trial (65 pts)

Task 3: Modeling and organ motion

Task 4: Molecular biomarker study

Grazie per l'attenzione