SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Ferrara
Arcispedale S. Anna

Società Medico Chirurgica di Ferrara

Università degli Studi di Ferrara

Innovazione e trattamenti mini invasivi in Proctologia

Radioterapia Esterna e Brachiterapia nel carcinoma anale

Ferrara 22 sett 2012

Dr. Antonio Stefanelli

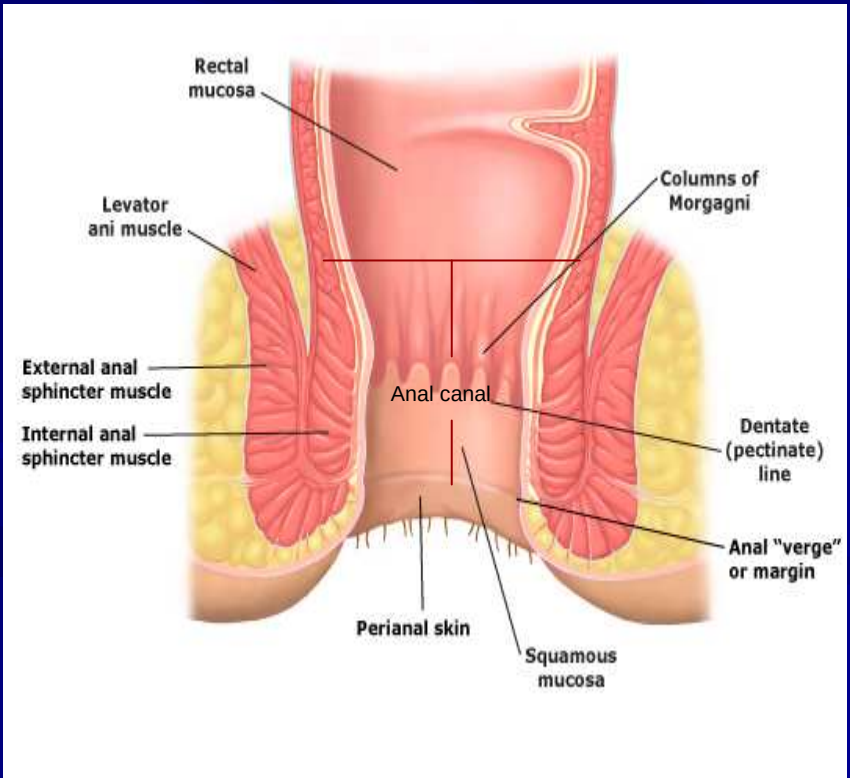
U.O. Radioterapia Ferrara

Anal Cancer

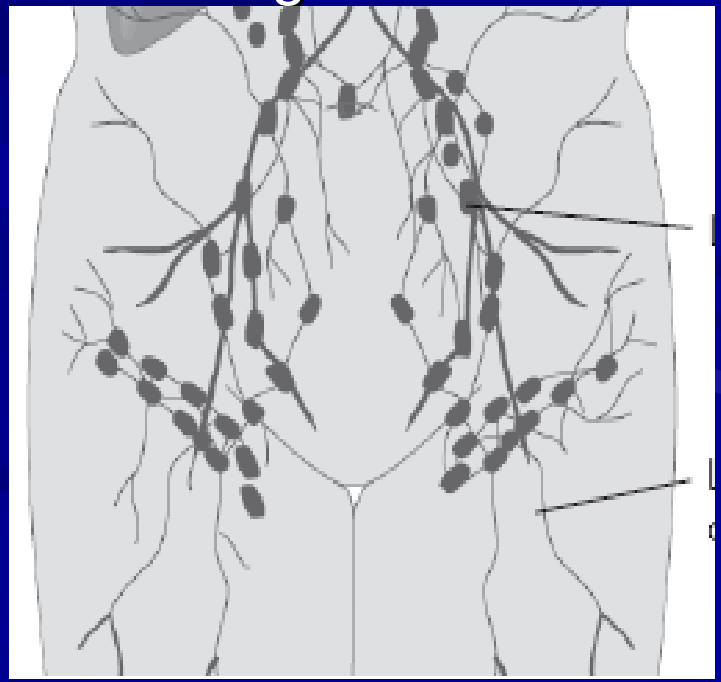
- Incidenza in Europa 1-3\100.000 per anno(doppia nelle donne)
- Anatomia patologica
  - ~80% ca a cellule squamose,
  - 20% adenoca o melanoma.
- HPV associato, stessi sierotipi del ca della cervice uterina, 16 & 18

Anal Cancer

- Anatomy:
  - 3-4 cm anal canal
  - Anal verge to dentate line



- Lymph node drainage:
  - Perirectal
  - Internal iliac
  - Inguinal nodes



Staging

- **T**
  - T0
  - Tis
  - T1 <2 cm
  - T2 >2 cm but <5 cm
  - T3 >5 cm
  - T4 invades adjacent organs
- **N**
  - N0
  - N1 perirectal
  - N2 unilateral internal iliac or inguinal
  - N3 perirectal and inguinal and/or bilateral inguinal and/or internal iliac
- **M**
  - M0
  - M1 distant metastases

Stage

0 Tis N0

I T1N0

II T2\3 N0

IIIA T1\2\3N1

T4N0

IIIB T4N1

Any T N2-3

IV M1

Ajcc six editon

Anal Cancer

CORNERSTONE

1974 Nigro observed complete tumor regression in some patients treted with preoperative 5-FU-based concurrent CT-RT including either Mito-C

that experience has suggested that was possible to cure anal carcinoma without surgery and permanent colostomy

Nigro ND Dis Colon Rect 1974

Current Standard is Definitive Chemoradiotherapy for Anal Cancer

- Radiotherapy alone vs.Chemoradiotherapy.
  - 45 Gy alone or w/ concomitant 5-FU and mitomycin
  - UKCCCR, 1996: 585 epidermoid anal cancer patients with any stage disease randomized
  - EORTC, 1997: 110 patients with stage IIIA-B anal cancer randomized

(UKCCCR, 1996; Bartelink et al., 1997)

Current Standard is Definitive Chemoradiotherapy for Anal Cancer

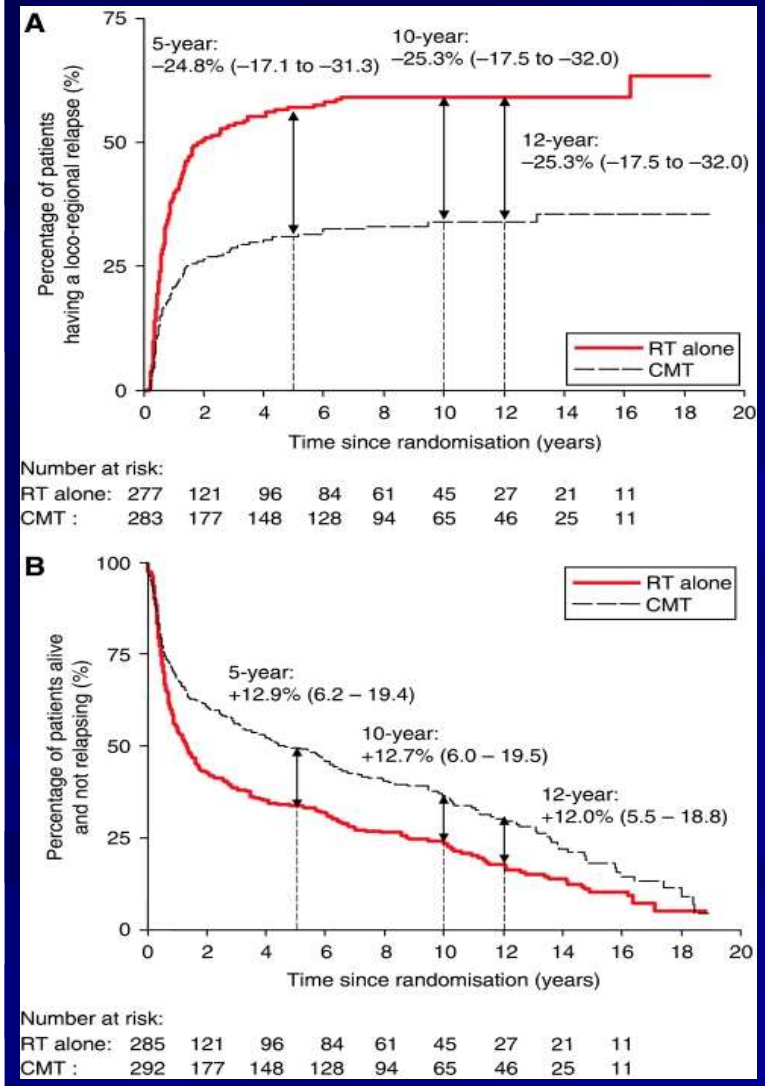
- UKCCCR
  - Significantly decreases local recurrence
    - 59%→ 36% local failure rate, Relative risk of 0.54
  - Decreases cancer related risk of death after 3 years
    - 39%→ 28% anal cancer mortality, Relative risk 0.71
  - No significant overall survival benefit after 3 years
    - Radiotherapy 58% and Chemoradiotherapy 65%

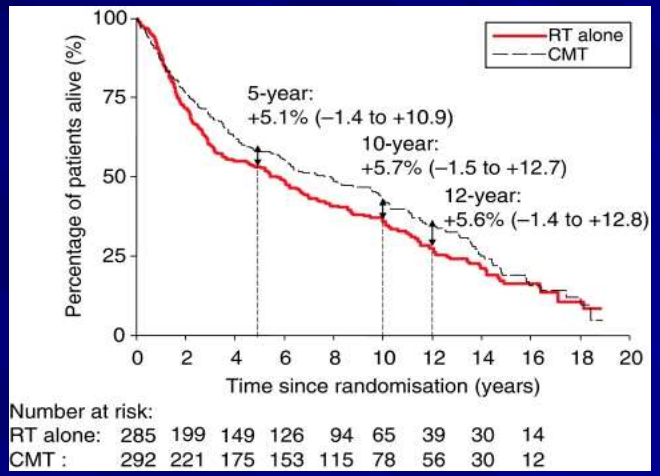
UKCCR 1996 2010

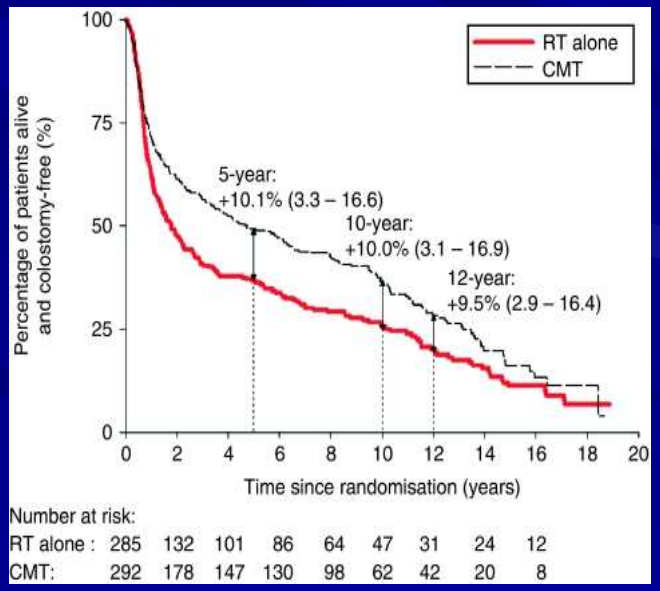
- EORTC
  - No significant difference in acute toxicity
    - Diarrhea and skin reaction most common
  - Better complete remission rates 54%→80%
  - 18% improvement in locoregional control
  - 32% improvement in Colostomy-free survival at 5 years

(EORTC, Bartelink et al., 1997)

13 anni follow-up UKCCCR trial







Current Standard is Definitive Chemoradiotherapy for Anal cancer

- RTOG 98-11:

Standard concomitant 5-FU/mitomycin RT vs. 5-FU/Cisplatin + RT

341 mito-5Fu
341 5Fu-Cisplatin
Follow-up median 2.5 years

DFS 60% vs 54% 5 years
OS 75% vs 70%
LRR 25% vs 33%
Colostomy 10% vs 19%
Severe hematologic toxicity mito arm

Jama 2008

Anal Cancer and RTE

- Corretto staging pre-RT
- Esplorazione ano-rettale
- RM pelvi +\- US transrettale
- TC
- US inguinale
- istologia
- Scinti ossea

Anal Cancer and RTE

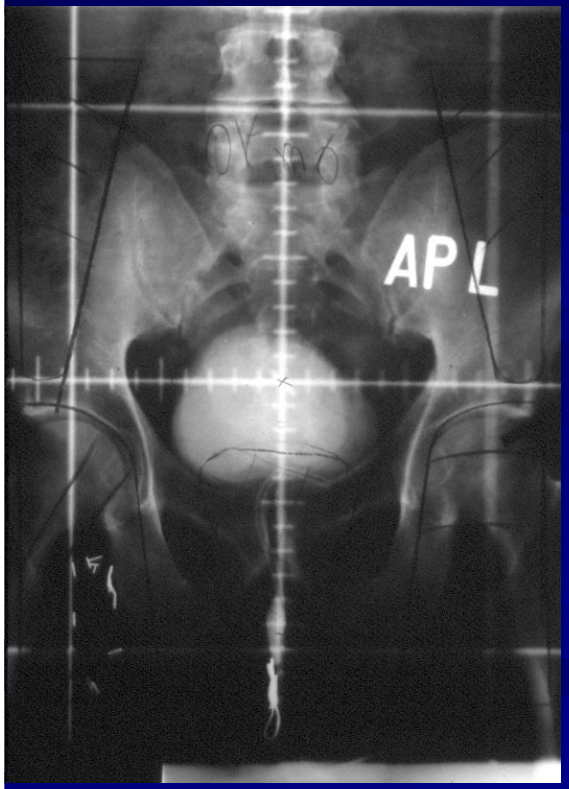
- Attualmente si usano tecniche multiportali conformate (3DRT-IGRT IMRT) con acceleratori lineari di alta energia (> 6 Mv) e l'erogazione di una dose di almeno 45 Gy in frazioni di 1.8-2 Gy die (frazionamento convenzionale) concomitante a CT
- Con le tecniche 2D dove il tasso di tossicità era molto elevato si inseriva una pausa (Split) di 1-2 settimane dopo 36 Gy .Attualmente si tende ad eseguire il trattamento senza pause a meno di tossicità importanti

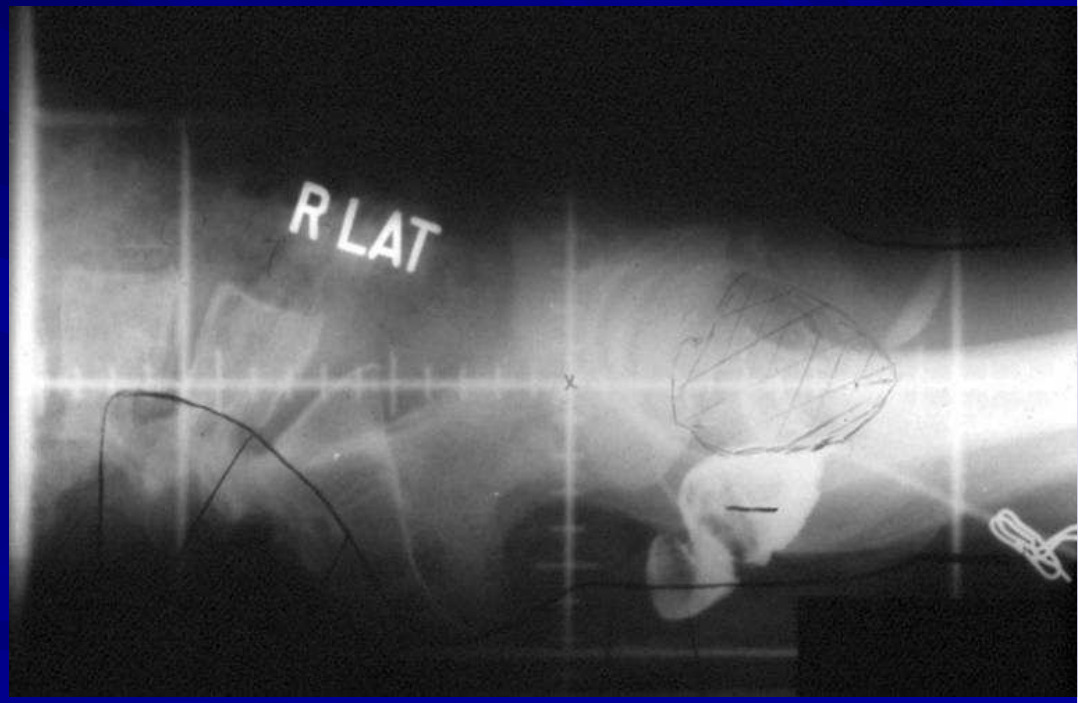
(cutanee, GU,GI,Ematologica)

Anal Cancer and RTE

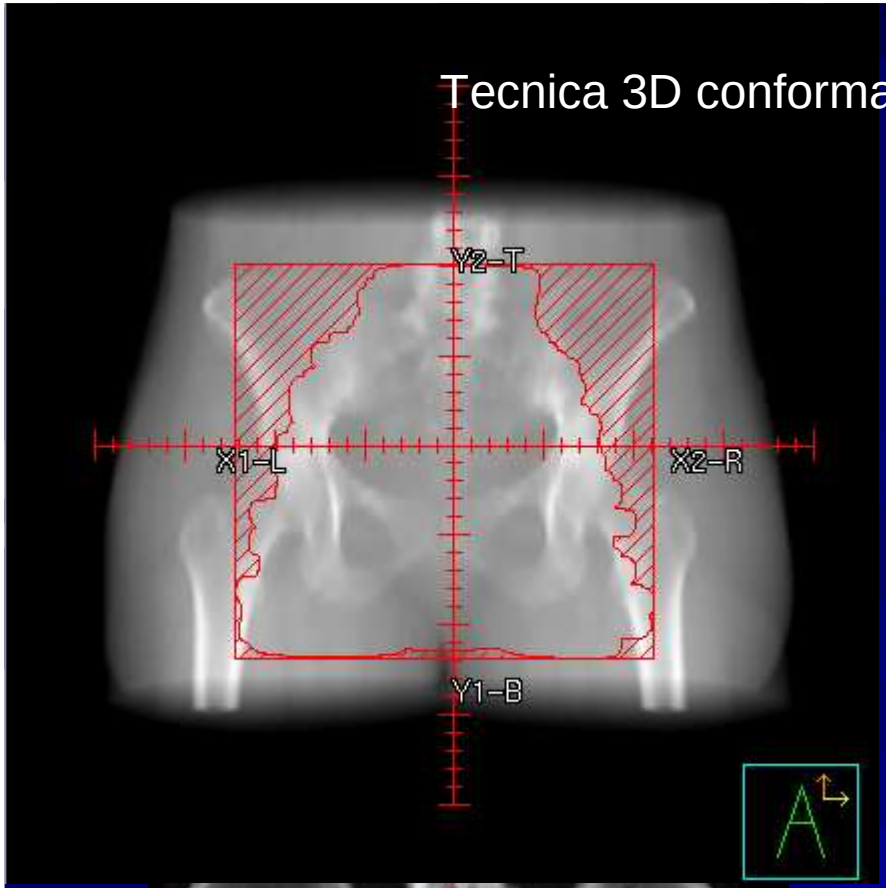
- I volumi da trattare sono il canale anale i linfonodi pararettali, iliaci interni , esterni ed inguinali

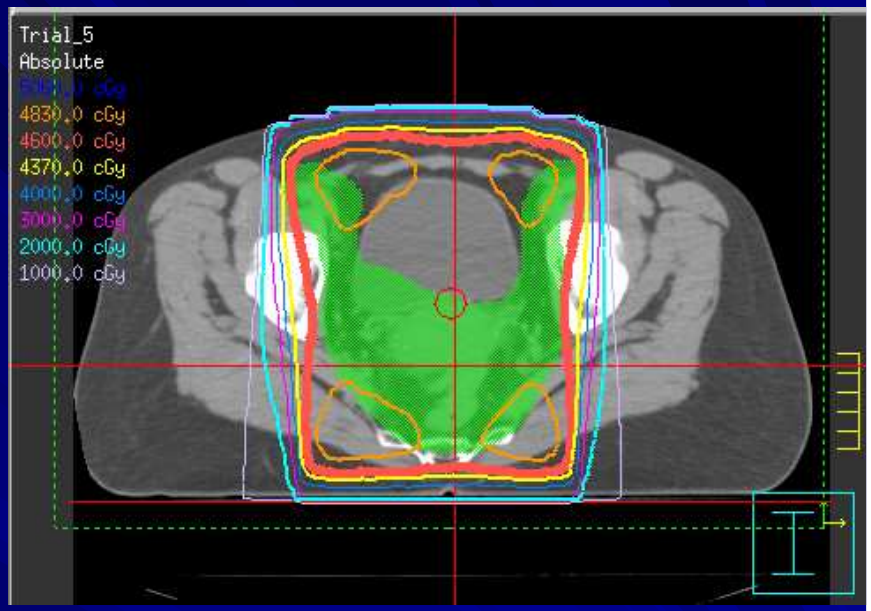
Tecnica 2D

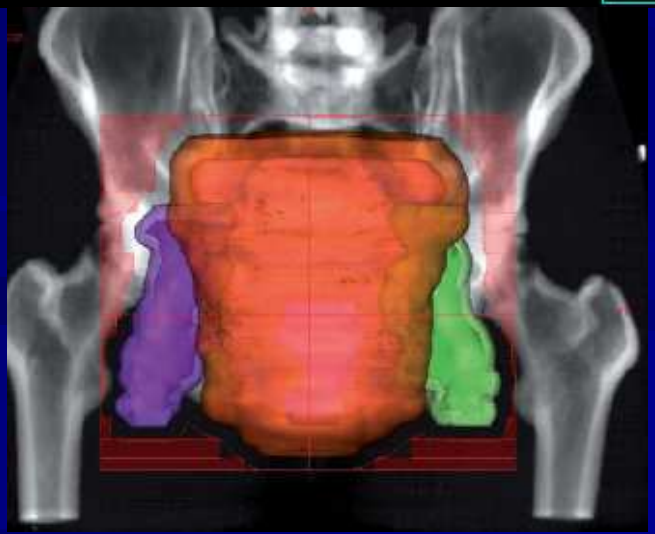


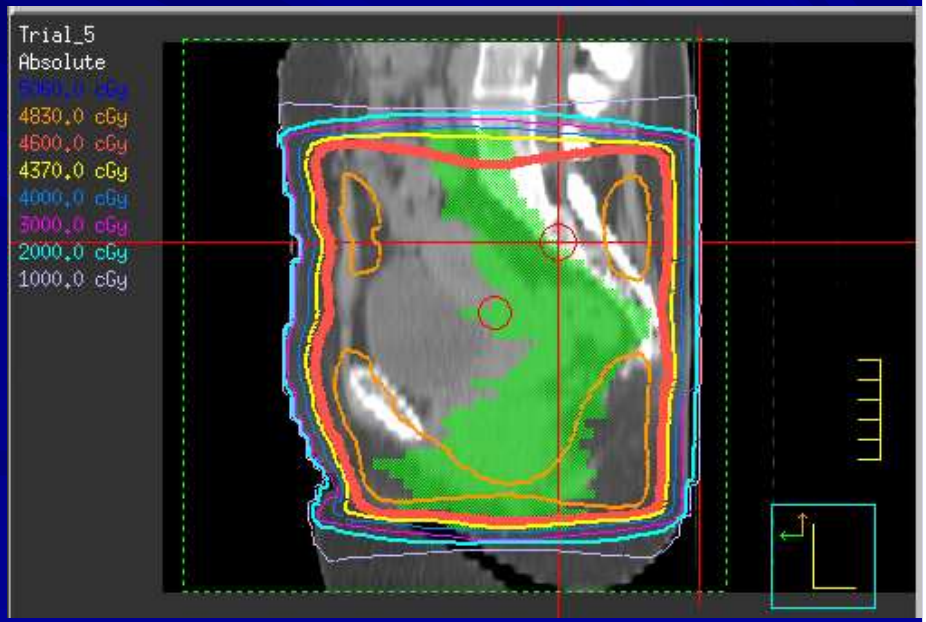


Tecnica 3D conformata





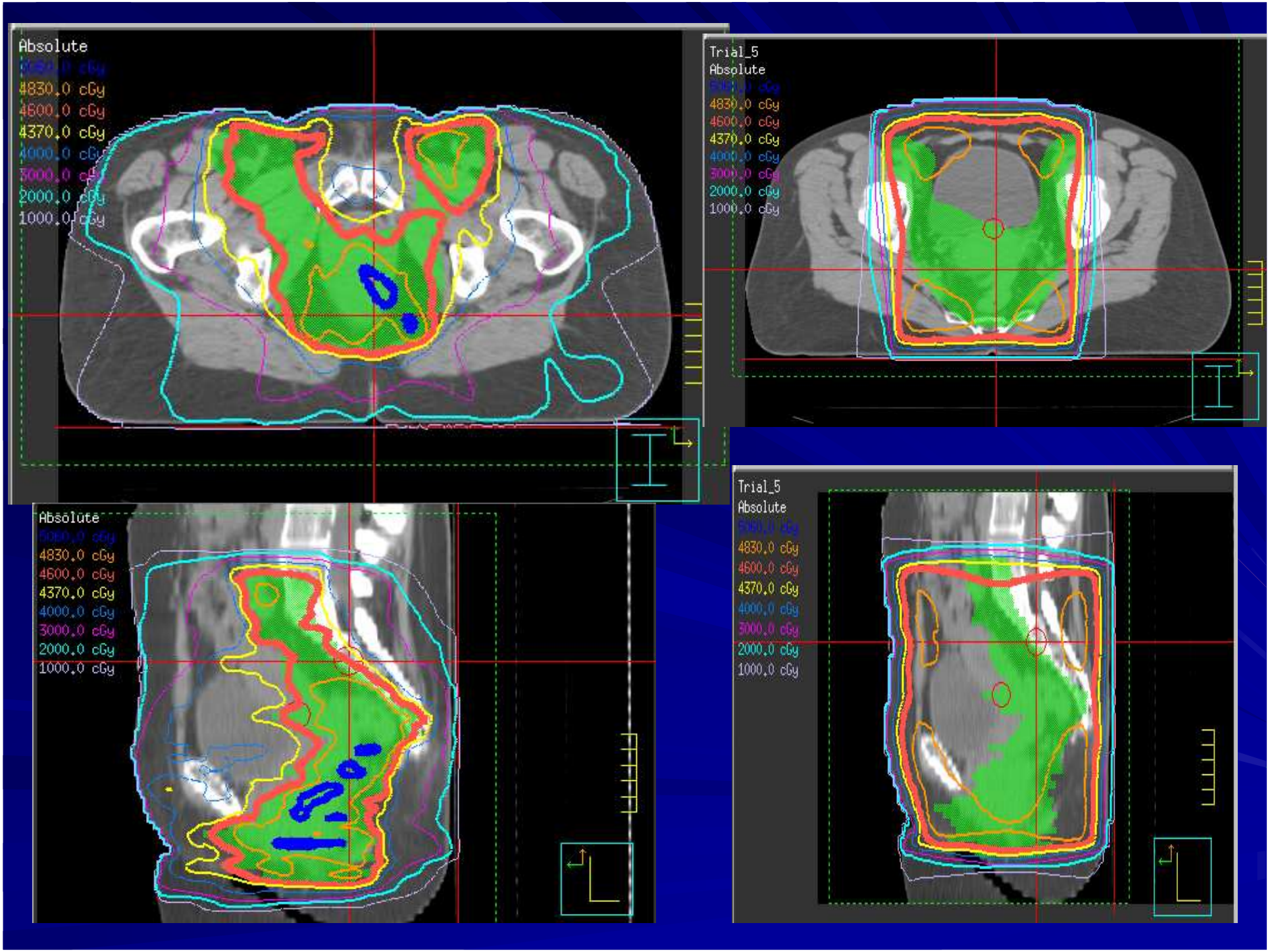


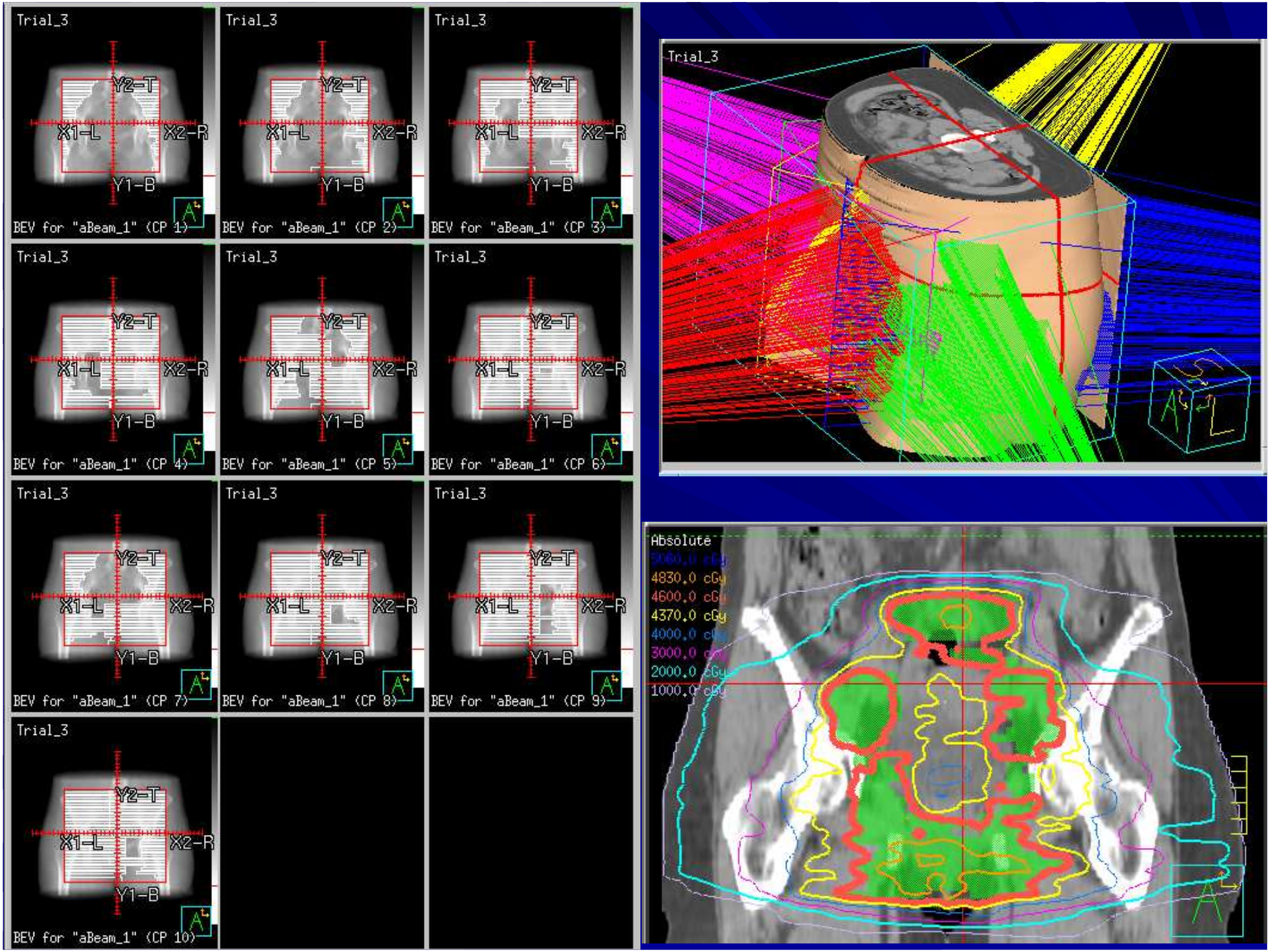


IMRT in anal cancer

- L’approccio radioterapico tradizionale 2D era gravato da alto tassi di tossicità soprattutto cutanea e GI che va n un tasso di tossicità 5 fino al 18% nelle ca
- La tecnica a modula ne come una relativam risparmiare gli orga significativo gli effet il controllo di malattia


VARIAN
medical systems
DHX


Absolute
4830.0 cGy
4600.0 cGy
4370.0 cGy
2000.0 cGy
1000.0 cGy
Trial_5
Absolute
4830.0 cGy
4600.0 cGy
4370.0 cGy
2000.0 cGy
1000.0 cGy
Absolute
4830.0 cGy
4600.0 cGy
4370.0 cGy
3000.0 cGy
2000.0 cGy
1000.0 cGy
Trial_5
Absolute
4830.0 cGy
4600.0 cGy
4370.0 cGy
3000.0 cGy
2000.0 cGy
1000.0 cGy


Trial_3
Y2-T
X1-L
X2-R
Y1-B
BEV for "aBeam_1" (CP 1)
BEV for "aBeam_1" (CP 2)
BEV for "aBeam_1" (CP 3)
BEV for "aBeam_1" (CP 4)
BEV for "aBeam_1" (CP 5)
BEV for "aBeam_1" (CP 6)
BEV for "aBeam_1" (CP 7)
BEV for "aBeam_1" (CP 8)
BEV for "aBeam_1" (CP 9)
BEV for "aBeam_1" (CP 10)
Absolute
4830.0 cGy
4600.0 cGy
4370.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
1000.0 cGy

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ORIGINAL REPORT

Concurrent Chemotherapy and Intensity-Modulated Radiation Therapy for Anal Canal Cancer Patients: A Multicenter Experience

Joseph K. Salama, Loren K. Mell, David A. Schomas, Robert C. Miller, Kiran Devisetty, Ashesh B. Jani, Arno J. Mundt, John C. Roeske, Stanley L. Liauw, and Steven J. Chmura

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doi:10.1016/j.ijrobp.2005.02.030

CLINICAL INVESTIGATION — **Anus**

INTENSITY-MODULATED RADIATION THERAPY (IMRT) IN THE TREATMENT OF ANAL CANCER: TOXICITY AND CLINICAL OUTCOME

MICHAEL T. MILANO, M.D., PH.D.,* ASHESH B. JANI, M.D.,* KARL J. FARREY, M.S.,* CARLA RASH, C.M.D.,* RUTH HEIMANN, M.D., PH.D.,† AND STEVEN J. CHMURA, M.D., PH.D.*

*Department of Radiation and Cellular Oncology, University of Chicago, Chicago, IL; †Division of Radiation Oncology, University of Vermont, Burlington, VT

IMRT sembra diminuire in modo significativo gli effetti collaterali senza un negativo impatto sul controllo di malattia

Intensity-Modulated Radiation Therapy Versus Conventional Radiation Therapy for Squamous Cell Carcinoma of the Anal Canal

Jose G. Bazan, MD, MS[1]; Wendy Hara, MD[1]; Annie Hsu, PhD[1]; Pamela A. Kunz, MD[2]; James Ford, MD, PhD[2]; George A. Fisher, MD, PhD[2]; Mark L. Welton, MD[3]; Andrew Shelton, MD[3]; Daniel S. Kapp, MD[1]; Albert C. Koong, MD, PhD[1]; Karyn A. Goodman, MD[4]; and Daniel T. Chang, MD[1]

Table 2. Comparison of Treatment Breaks, Toxicity, and Outcome in Patients With Squamous Cell Carcinoma of the Anus Treated With IMRT

	Bazan (N=46)	Salama (N=53)	Pepek (N=29)[a]
Median follow-up, mo	32 (IMRT) 26 (CRT)	14.5	19
Treatment breaks, %	34.5 (IMRT) 88.0 (CRT)	41.5	NR[b]
Acute GI toxicity, grade 3-4, %	7 (IMRT) 29 (CRT)	15.1	10
Acute skin toxicity, grade 3-4, %	21 (IMRT) 41 (CRT)	37.7	0
Acute hematologic toxicity, grade 3-4, %	21 (IMRT) 29 (CRT)	58.5	24
Overall survival, %	88 (3 y) IMRT	93.4 (1.5 y)	100 (2 y)
LRC, %	92 (3 y) IMRT	83.9 (1.5 y)	95 (2 y)
CFS, %	91 (3 y) IMRT	83.8 (1.5 y)	91 (2 y)

IMRT indicates intensity-modulated radiotherapy; CRT, conventional radiotherapy; NR indicates not reported; GI, gastrointestinal; LRC, locoregional control; CFS, colostomy-free survival.

[a] Includes only patients with squamous histology.

[b] Reports a value of 18% for all patients but not separately for patients with squamous histology.

Cancer August 1, 2011

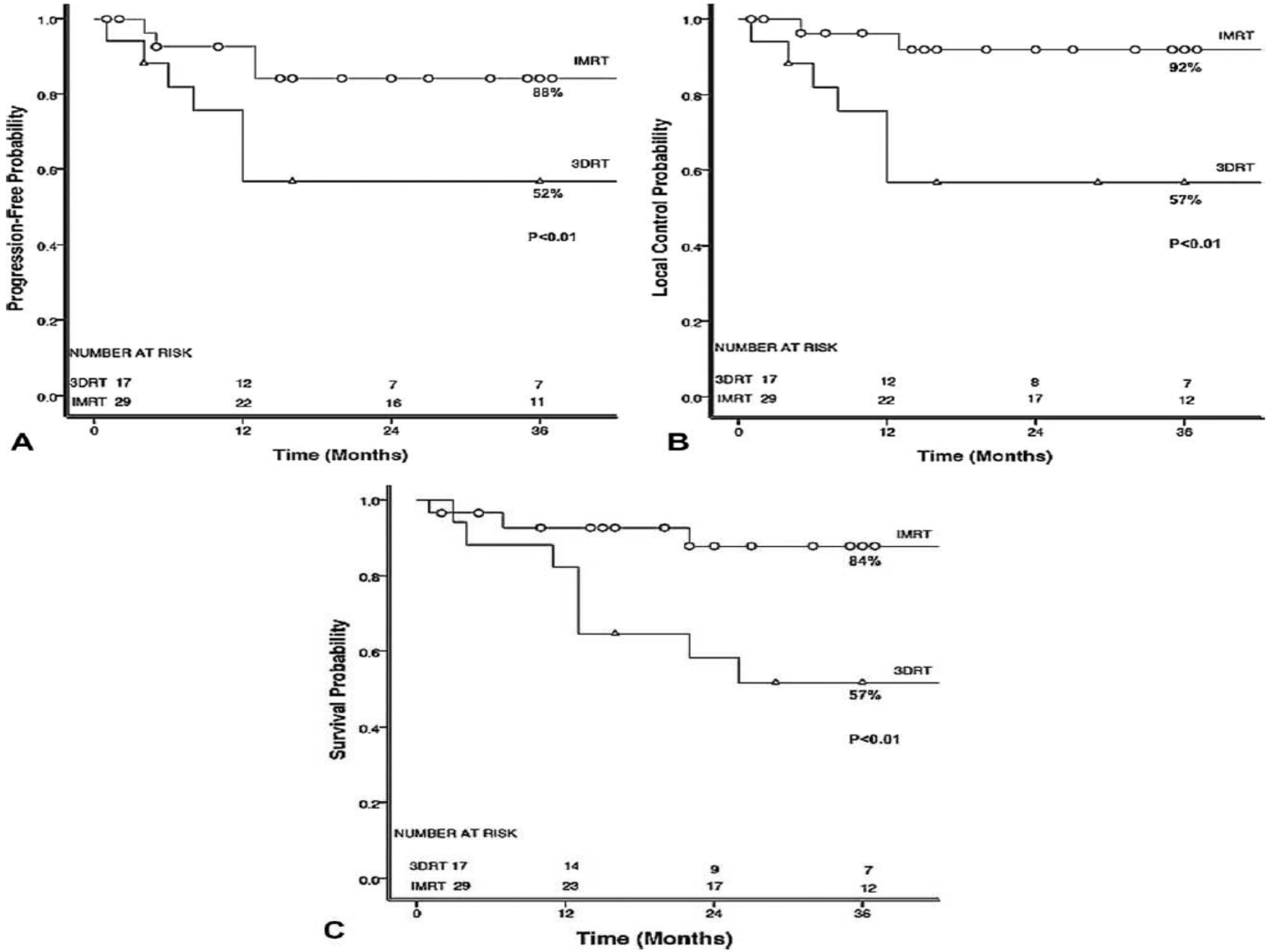


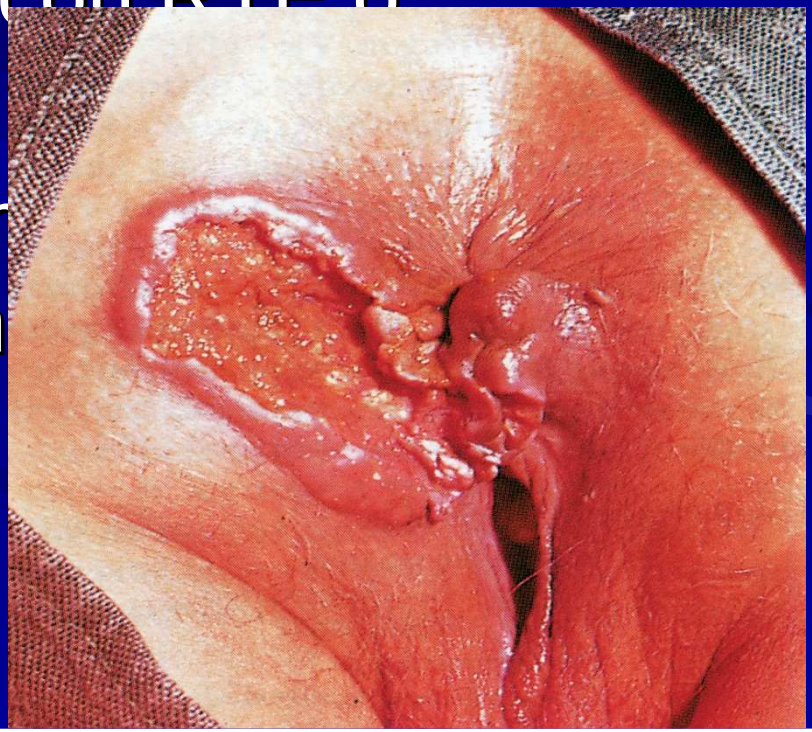
Figure 2. (A) Overall survival by radiation technique, (B) locoregional control by radiation technique, and (C) progression-free survival by radiation technique are depicted.

Restaging after ERT+CT

- TA US
- Clinical Examination
- MRI

Anal Cancer and RTE

- In caso di residuo di malattia sul T dopo la prima fase del trattamento è indicato un supplemento di dose di 15 -20 Gy che puo' essere erogato con RTE o brachiterapia
- In caso di interessam della circonferenza n brachiterapia



BRACHITERAPIA

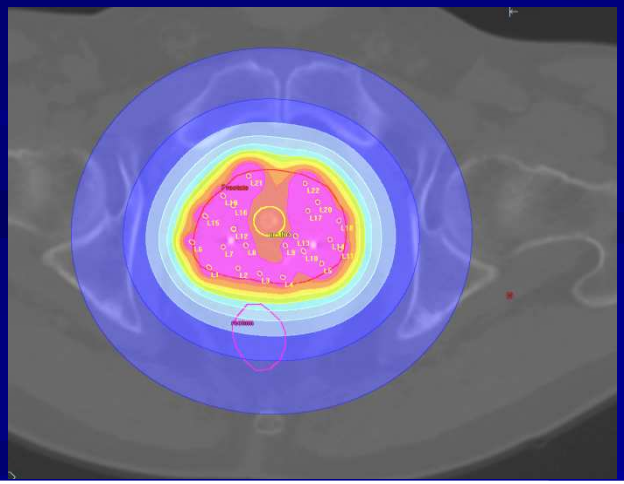
ha come caratteristica fondamentale:

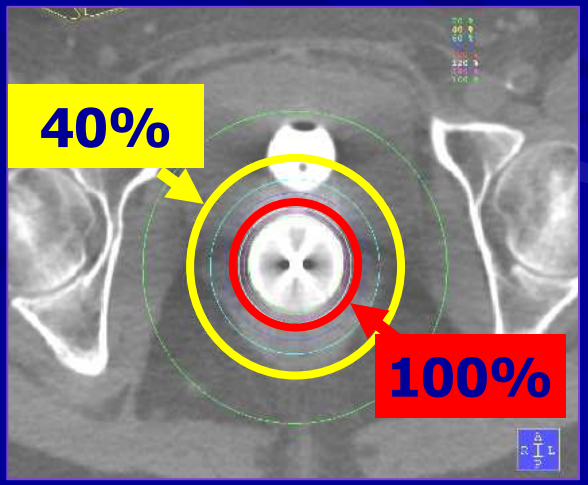
una rapida caduta del“gradiente di dose”

che consente di adattare la dose al volume

da irradiare, risparmiando i tessuti sani

circostanti.





Definizioni

- Brachiterapia a basso dose rate (LDR = low dose rate): 0.4 – 2 Gy/h
- Brachiterapia a medio dose rate (MDR = medium dose rate): 2 – 12 Gy/h
- Brachiterapia ad alto dose rate (HDR = high dose rate): > 12 Gy/h (Ir 192)
- pulsed dose rate(PDR) in cui viene simulato un low dose rate mediante una serie di “dose pulse” di breve durata

BRT Timing

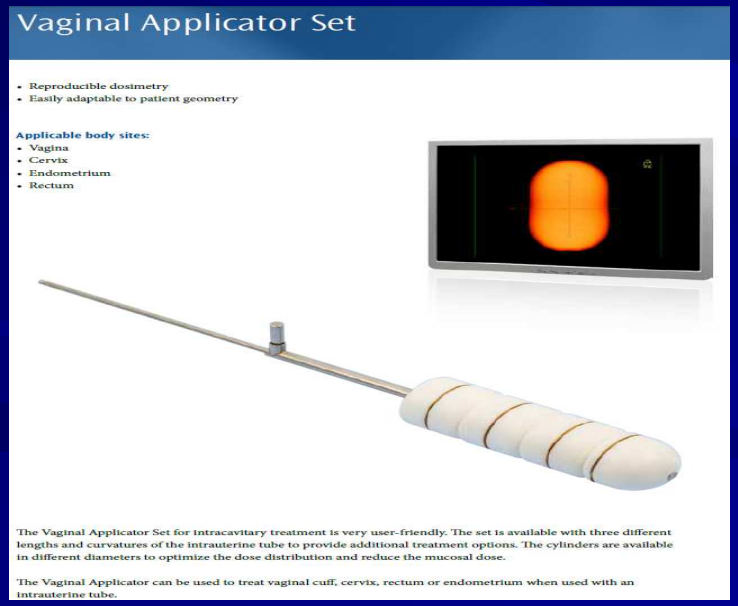
- BRT generally performed after 2-3 weeks ERT to allow moist desquamation resolution and the tumor volume reduction.

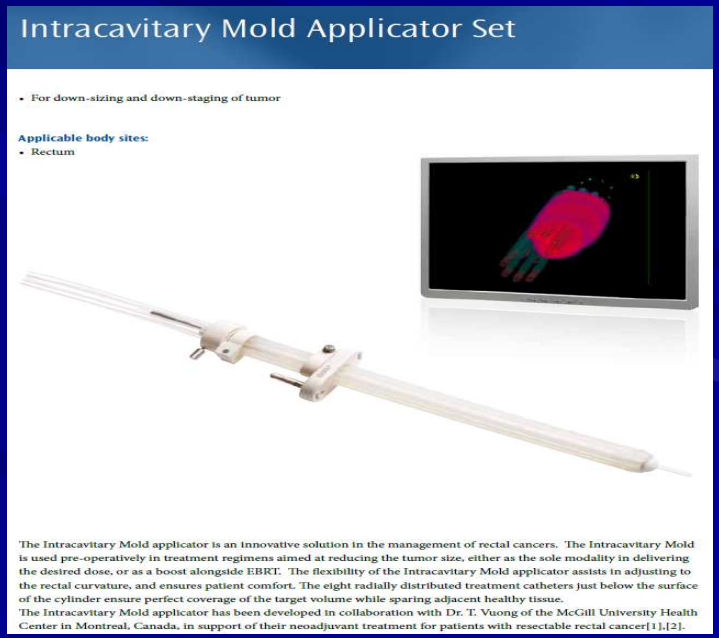
- In anorectal cancer, a number of different approaches are used, depending on the stage and location of the tumor.

- Two different modality of Brachytherapy:
- Endocavitary
- Interstitial

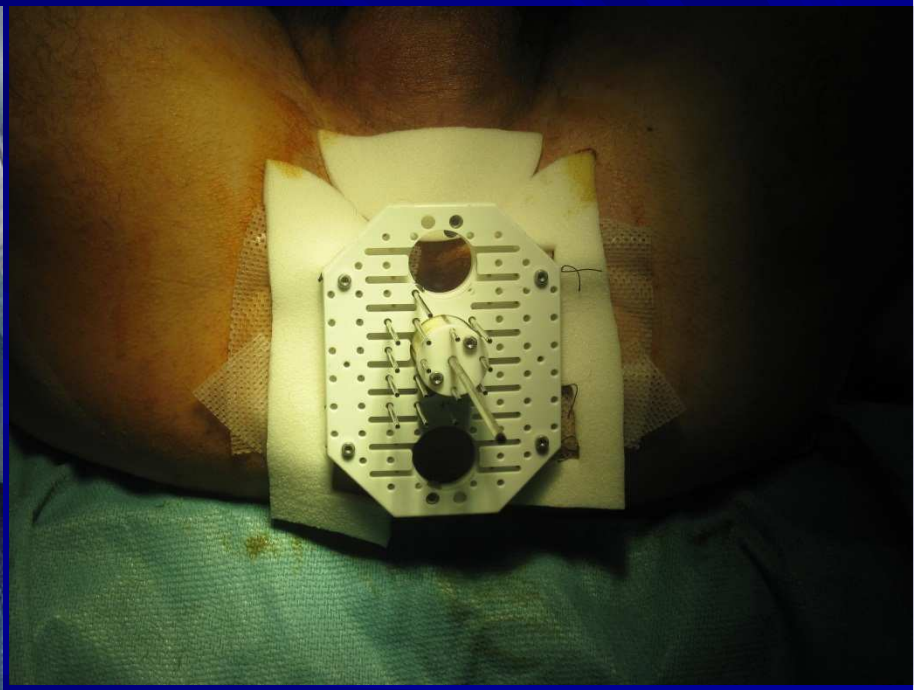
Endocavitary BRT:

- For superficial lesions
- or palliative intent

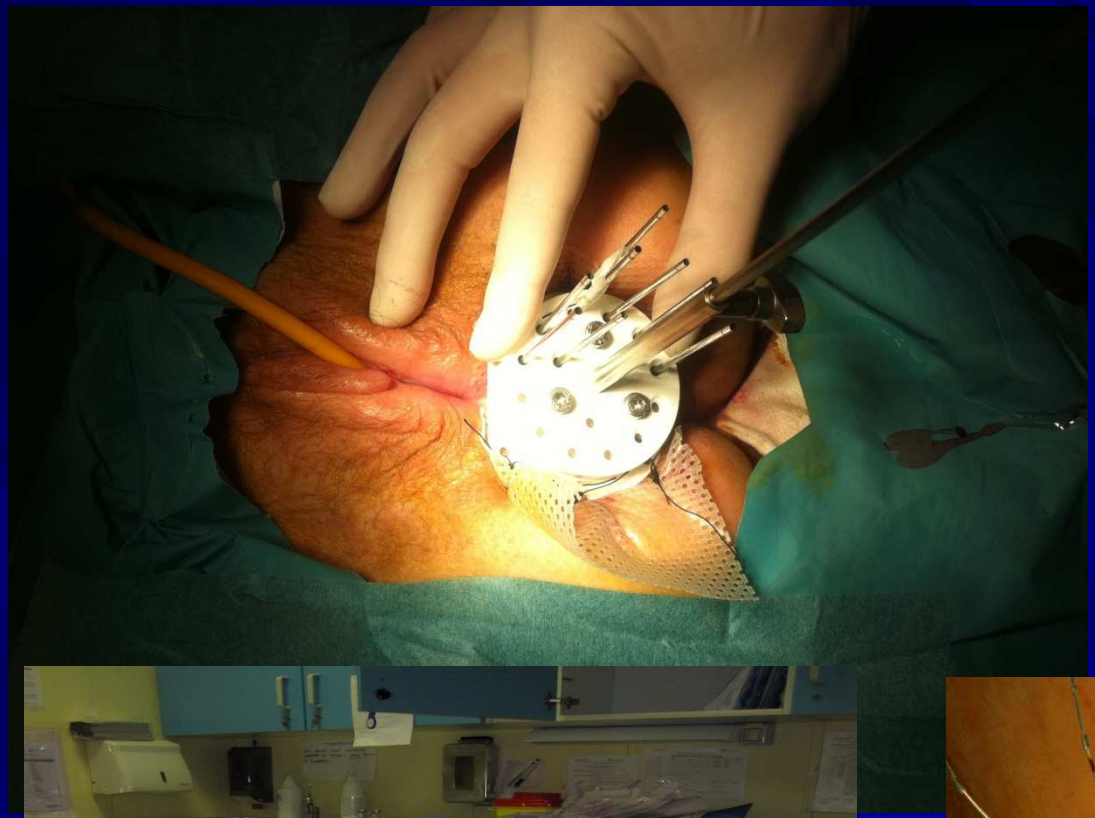




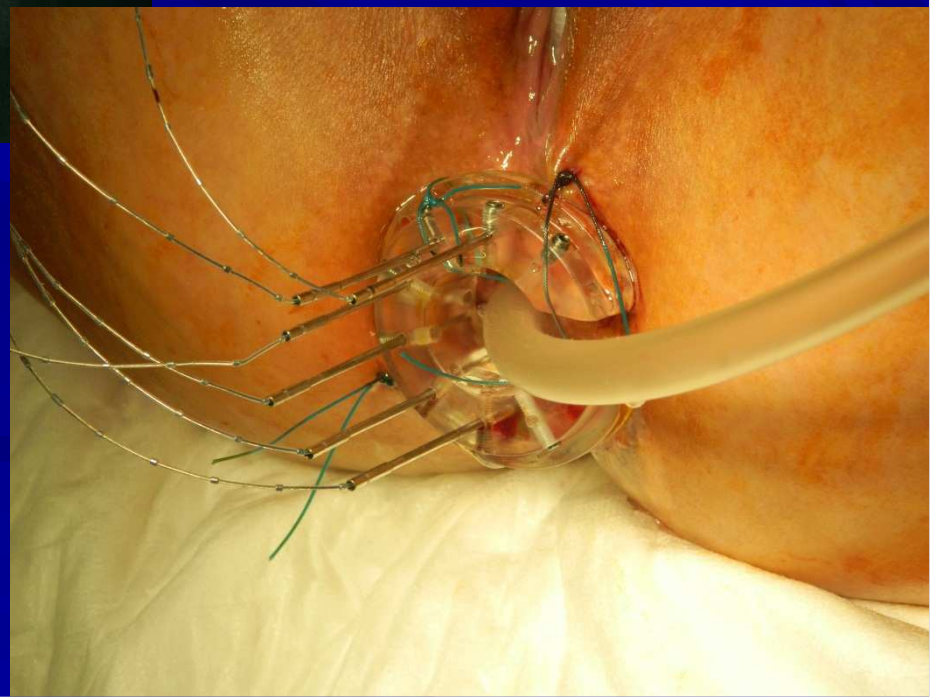
For interstitial BRT are used various types of template



Courtesy Dr. Galuppi




microSelectron HDR



Anal cancer BRT

- The procedure requires anesthesia, usually spinal.
Insertion of 1-2 landmarks of Ag to locate the residual tumor or the scar
- Using the template, needle placement along submucosal course, must be controlled with finger.
Treatment planning according to the Paris system
- (parallel needles, equally spaced, to 1-1.5 cm)

Anal cancer BRT

- T1-2: 5 charged needles 5-7 cm
- T3: 6-7 needles loaded 7-8 cm

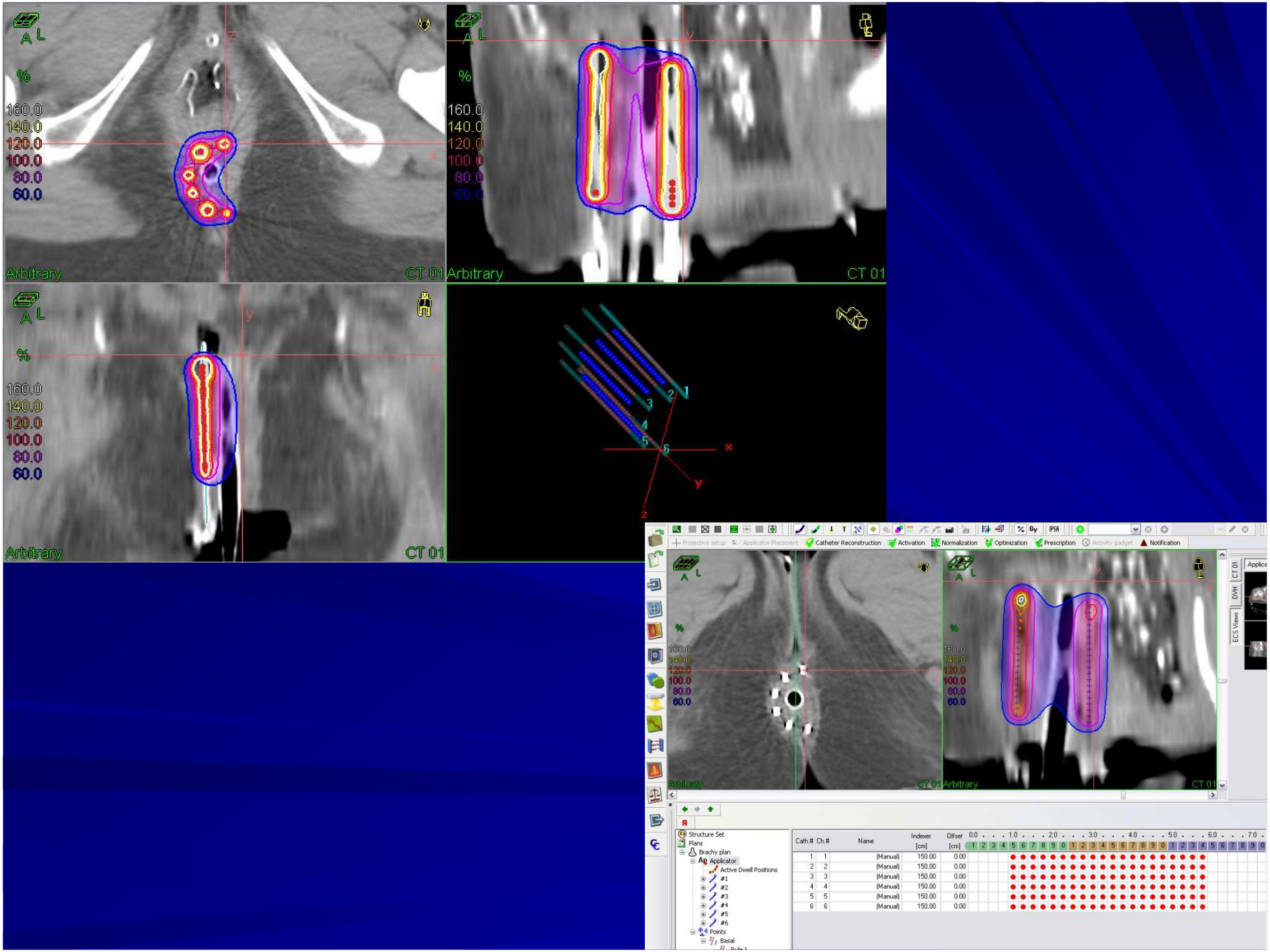
Anal cancer BRT

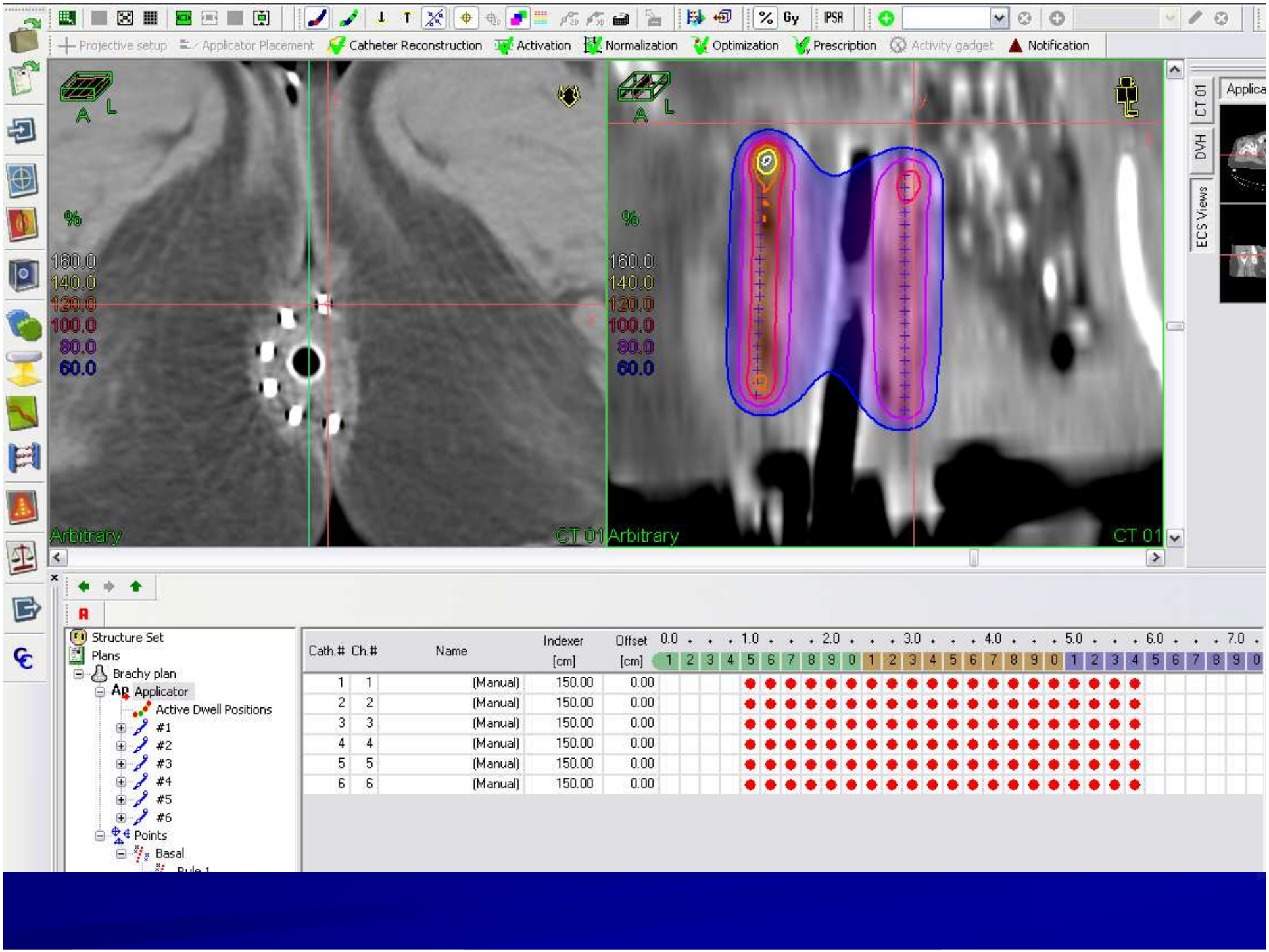
- In case of treatment of recto-vaginal septum, vaginal packing to avoid the anterior wall of the vagina

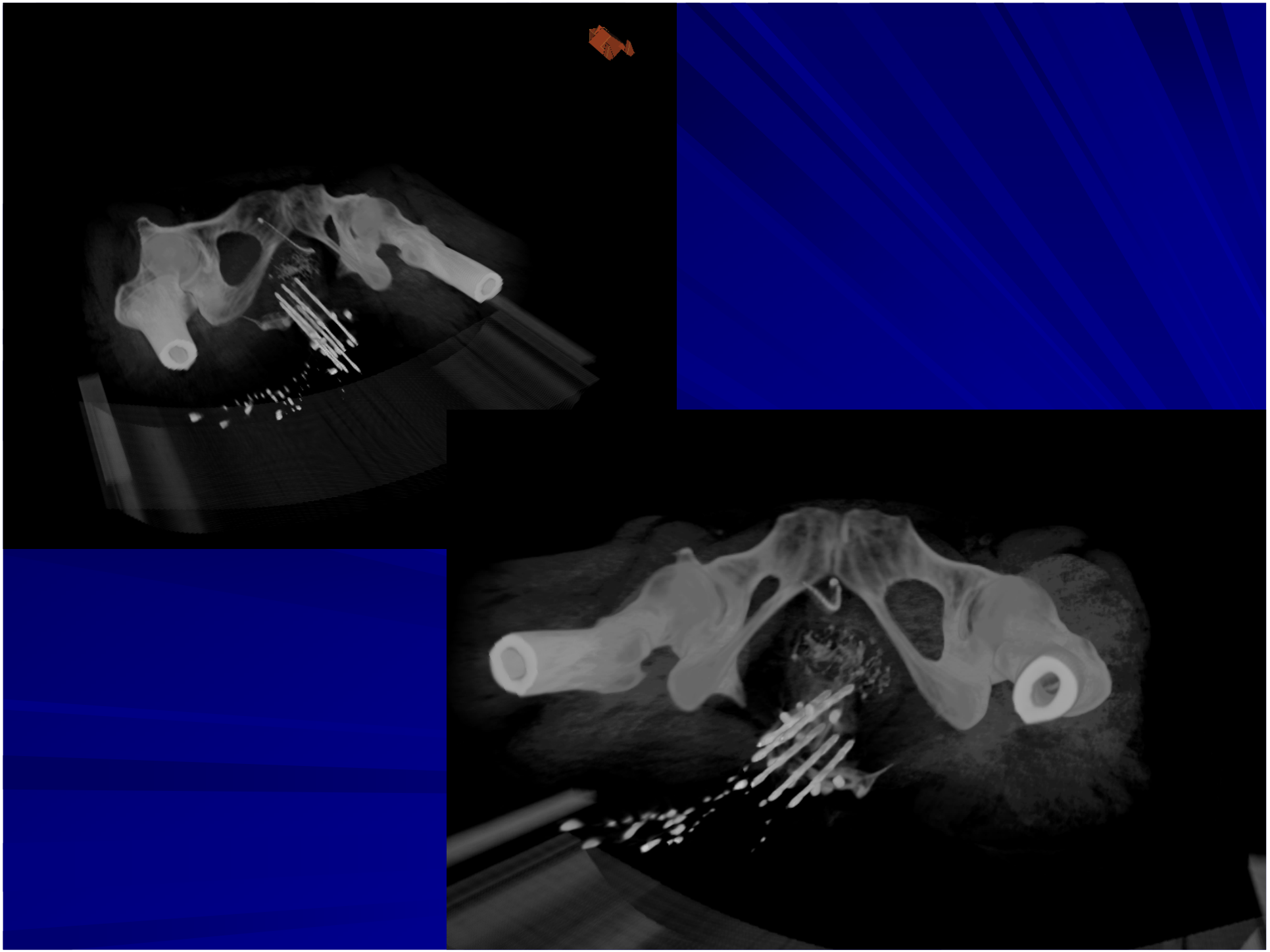
ADVANTAGES

- - High dose in a small volume
  - High dose gradient
  - Maximum sparing of organs at risk
  - Decreased late toxicity (necrosis, incontinence)

- -Reduced treatment time


A L
%
160.0
140.0
120.0
100.0
80.0
60.0
Arbitrary
CT 01
Projective setup
Applicator Placement
Catheter Reconstruction
Activation
Normalization
Optimization
Prescription
Activity gadget
Notification
Structure Set
Plans
Brachy plan
Applicator
Active Dwell Positions
#1
#2
#3
#4
#5
#6
Points
Basal
Cath.# Ch.# Name Indexer [cm] Offset [cm]
1 1 [Manual] 150.00 0.00
2 2 [Manual] 150.00 0.00
3 3 [Manual] 150.00 0.00
4 4 [Manual] 150.00 0.00
5 5 [Manual] 150.00 0.00
6 6 [Manual] 150.00 0.00
CT 01
DVH
ECS Views


Projective setup
Applicator Placement
Catheter Reconstruction
Activation
Normalization
Optimization
Prescription
Activity gadget
Notification
IPSA
Gy
%
160.0
140.0
120.0
100.0
80.0
60.0
Arbitrary
CT 01
DVH
ECS Views
Structure Set
Plans
Brachy plan
Applicator
Active Dwell Positions
#1
#2
#3
#4
#5
#6
Points
Basal
Cath.#
Ch.#
Name
Indexer [cm]
Offset [cm]
(Manual)
150.00
0.00



CONCLUSIONI1

- E una ottima tecnica che consente un buon controllo locale (80-90%)
- Ottimo impatto sulla QoL (conservazione sfinterica)
- Non è indicata per neoplasie che coinvolgono l’intera circonferenza dello sfintere

Esperienza IGRT Ferrara

- Dal 2008 al 2011 sono stati trattati con tecnica IGRT 8 pazienti (6 F 2 M)

- Età 35-88 (64)

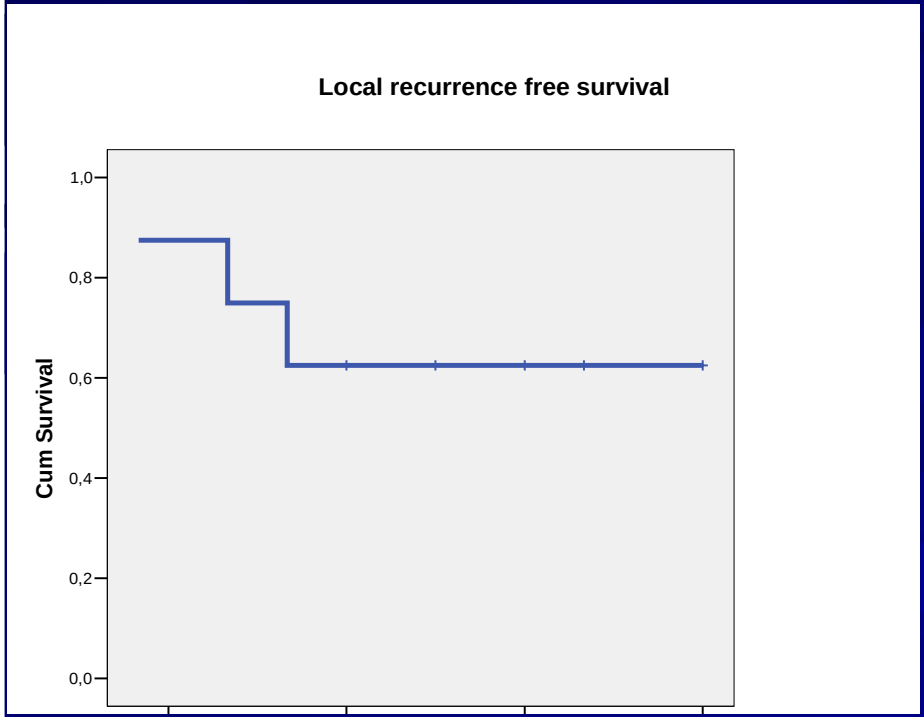
- Staging

cT2 cN0	1
cT3 cN0	3
cT3 cN2	1
cT4 cN1	1
cT4 cN2	1
cT3 cN0	1

- Dose

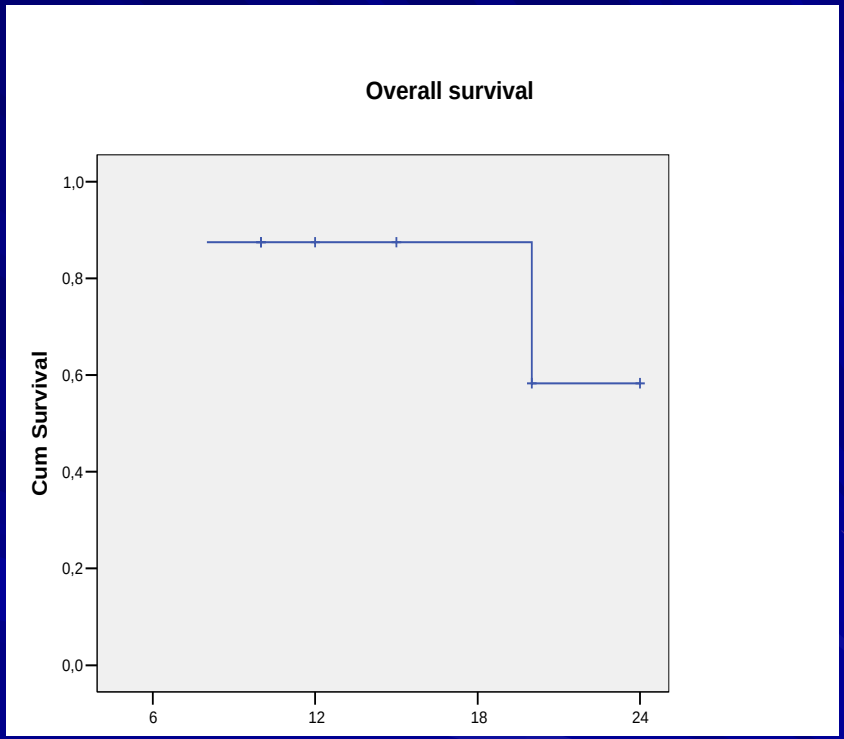
  45-46 Gy sulla pelvi e boost tra 10 e 21 Gy

13 Mesi di FU medio

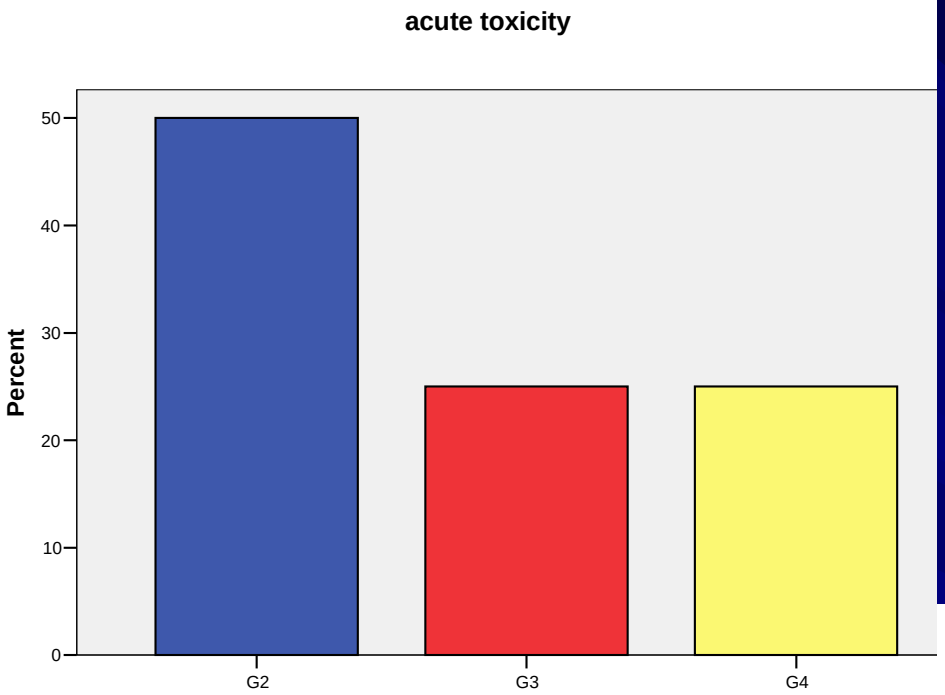


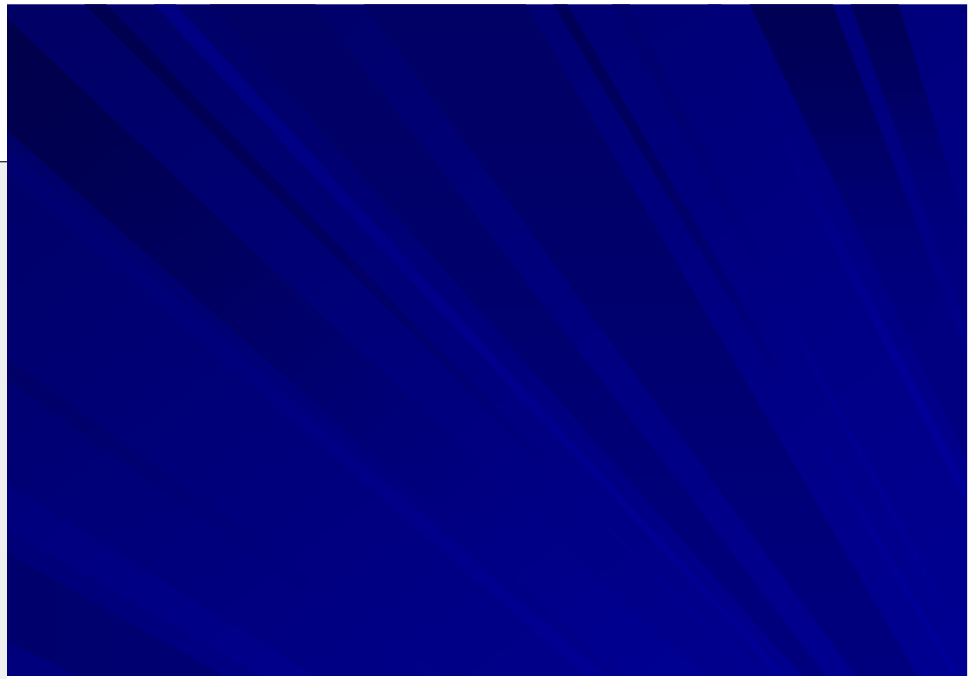
LRFS a 1 anno = 62.5%

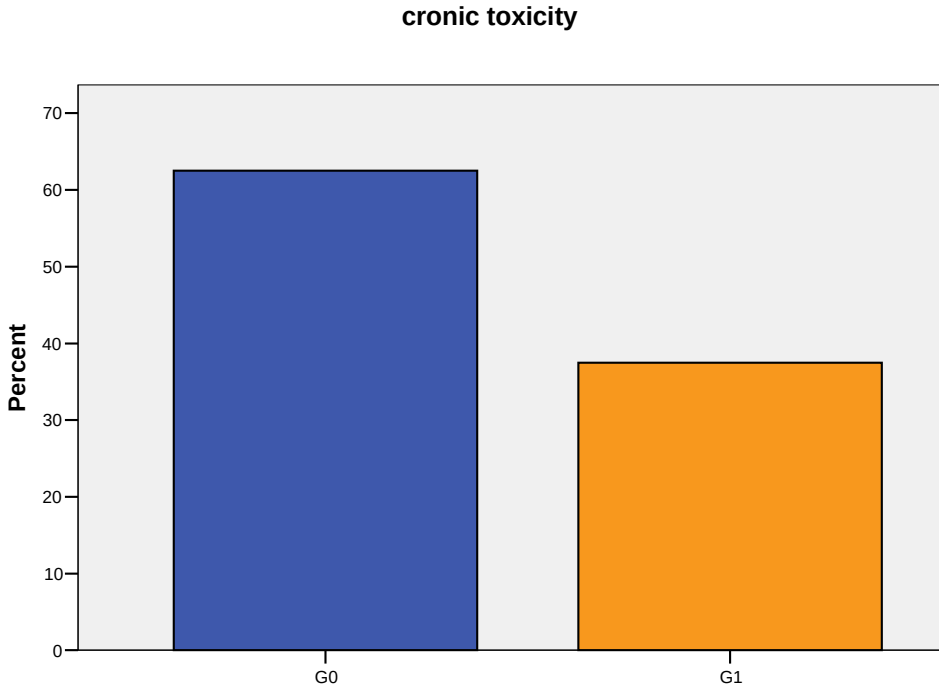
3 recurrences

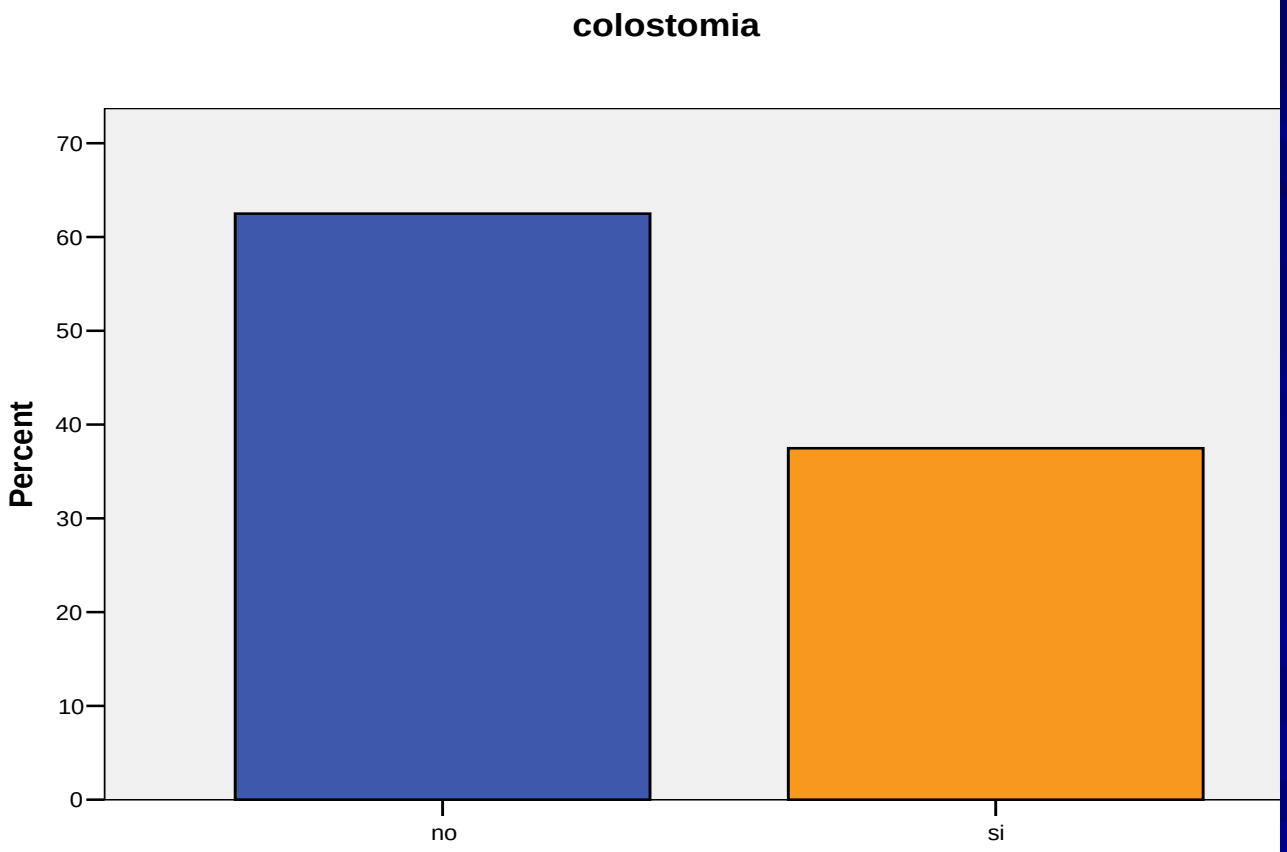


1 anno Os 87.5%
2 anni OS 58.3%


acute toxicity
Percent
50
40
30
20
10
0
G2
G3
G4




cronic toxicity
Percent
70
60
50
40
30
20
10
0
G0
G1



2 colostomie per recurrence

CONCLUSIONI 2

- Approccio multidisciplinare
- Il trattamento di scelta in prima istanza è RT-CT con MITo ad eccezione di piccole lesioni G1 del margine R-
- E’ fortemente raccomandato l’utilizzo di tecniche IMRT