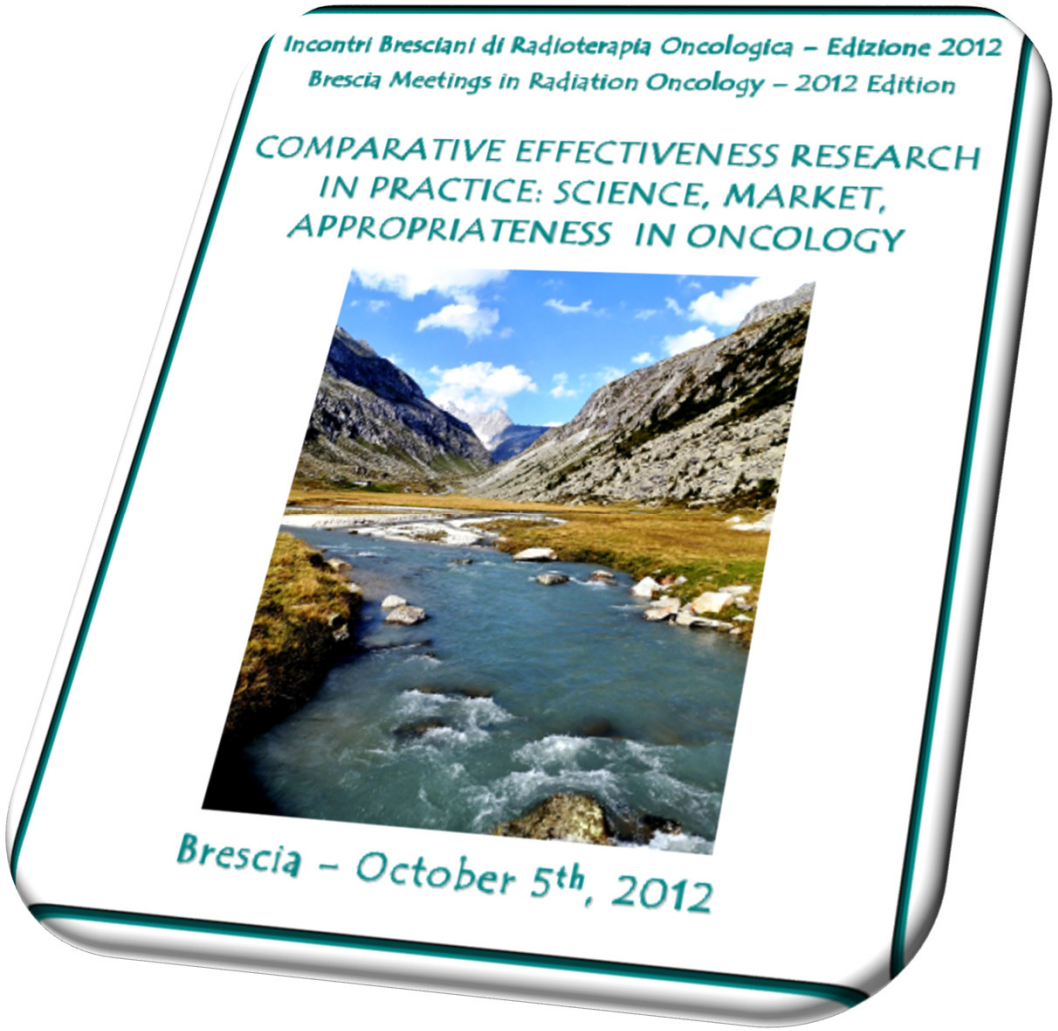


The role of Radiation Oncologist: Hi-tech treatments for liver metastases

Icro Meattini, MD

Radiotherapy-Oncology Unit
AOU Careggi Hospital
Florence University, Italy

Liver Metastases - Background

•The liver is a source of metastases from most common solid malignancies.

•Especially common for GI cancers (portal circulation).

•25% of colorectal cancer (CRC) have liver metastases at diagnosis, another 50% will develop within 5 yrs.

•Although improvements in chemotherapy and targeted therapy have led to improved survival in CRC, systemic treatment rarely eradicate liver metastases.

Schefter TE et al, Semin Radiat Oncol, 2011

Rationale for local therapies in metastatic cancer

1. Anecdotal experience

Low level evidence; e.g. rare tumors with long term disease remission

2. As consolidation

Residual bulky disease with better than expected response to CT (e.g.: breast, lung, colon, prostate)

Timmerman R et al, Ca Cancer J Clin, 2009
Hellman S, J Clin Oncol, 1995

3. Norton-Simon hypothesis

Assumption: effectiveness of typical CT agents is proportional to the growth rate of the tumor.

Rationale: a "debulking" procedure with a potent local therapy would result in:

-a more chemo-sensitive remaining tumor burden

-a less pronounced tumor-induced immunosuppression

Perez and Brady's Principles and Practice of Radiation Oncology 2007

Oligometastases Treatment - Rationale

•Cancer metastases were thought to represent an incurable state.

•Some patients with "oligo" or isolated site of metastases can be potentially cured with local therapy usually combined with effective systemic therapy.

Hellman et al, JCO, 1995

•The classic model of oligometastases in which local therapy can lead to a cure is in metastatic CRC patients (less clear for other tumors).

•For favorable group of CRC (<5cm, long DFS interval, low CEA, negative margins), resection series have yielded 5-yrs survival rate between 50-60%.

Shah et al, J Am Coll Surg, 2007

•Many patients are not suitable for resection because of medical or surgical reasons.

Schefter TE et al, Semin Radiat Oncol, 2011

Liver Metastases - Radiotherapy

•Initially RT for liver metastases was viewed exclusively as a palliative treatment.

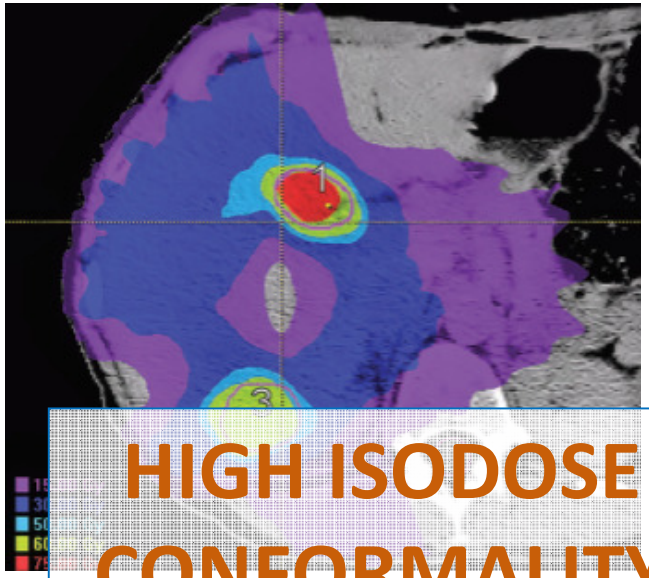
•The dose-limiting toxicity from whole-liver RT is radiation-induced liver disease (classic RILD).

•Target movement/Multiple healthy tissue near the target.

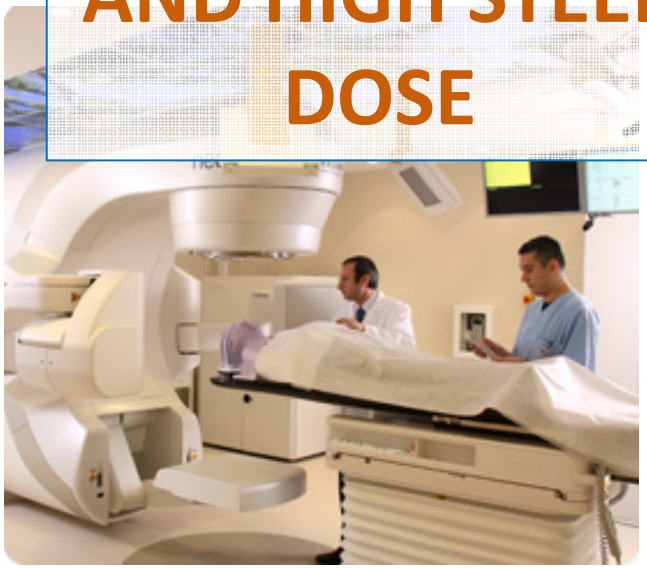
•Advent of 3dCRT planning and delivery technology→ partial liver irradiation→higher dose delivered safely.

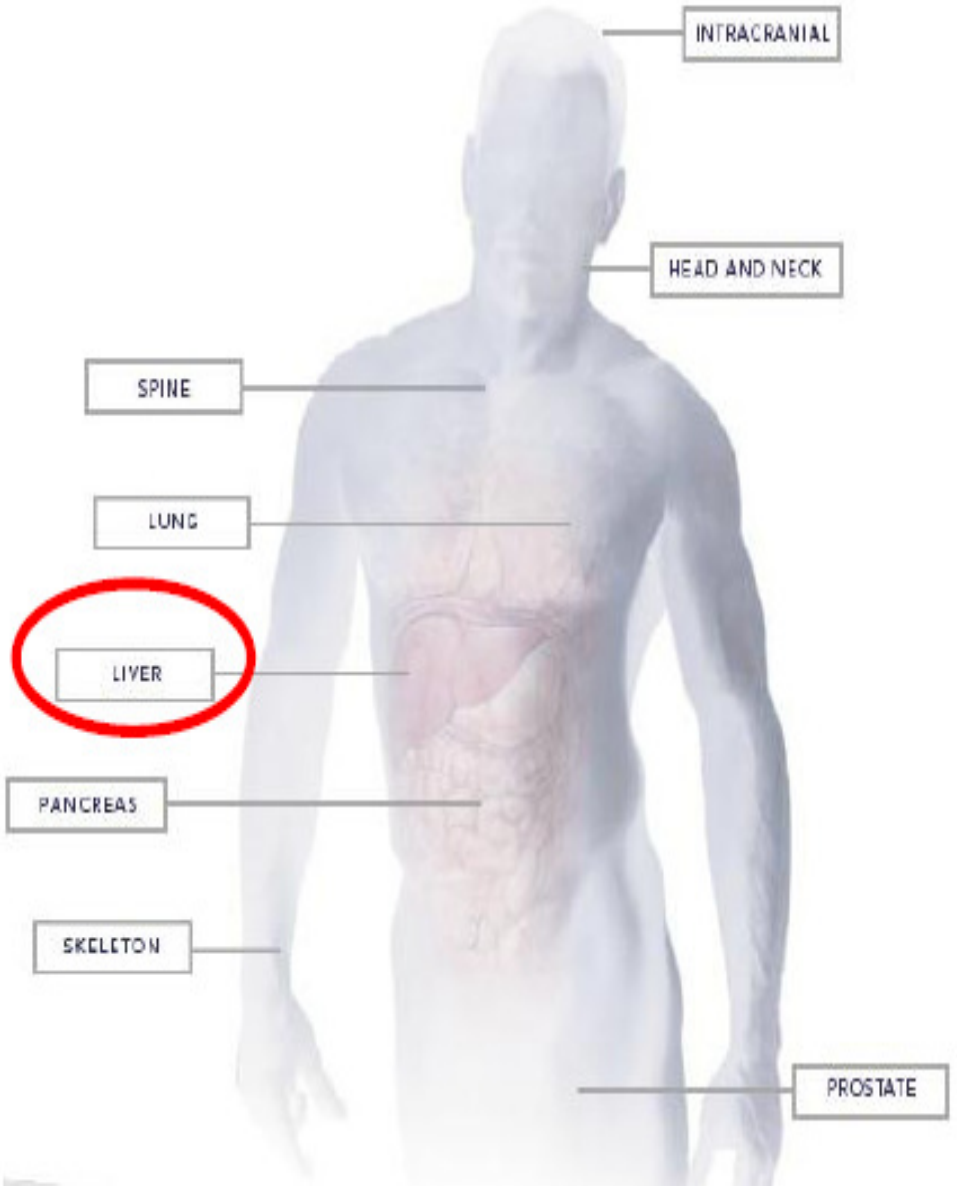
•The application of SBRT has allowed even more intensive tumor dose escalation in a hypofractionated schedule.

Schefter TE et al, Semin Radiat Oncol, 2011



HIGH ISODOSE CONFORMALITY AND HIGH STEEP DOSE





Irradiation of liver disease - Requirements

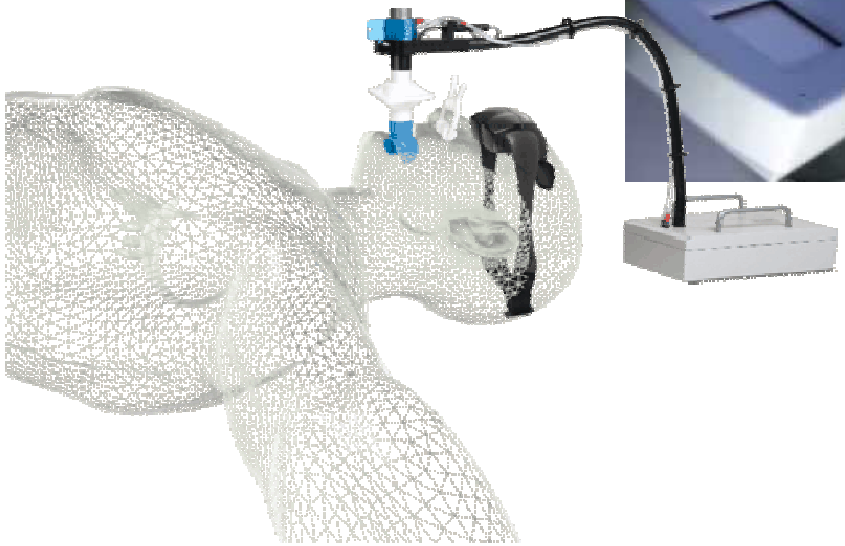
1) Optimize dose distribution

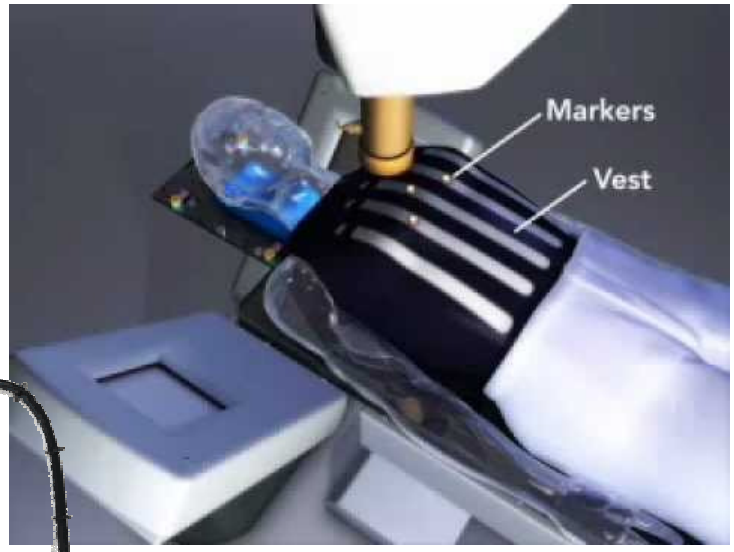
2) Reduce irradiated volume

-Gating

-Abdominal compression

-Tracking





Irradiation of liver disease - Requirements

3) Respect dose constraints

Organ at risk	Wulf *et al.* (36)	Rusthoven *et al.* (37)	Hoyer RAS–Trial (www.cirro.dk)	RTOG 0236 SBRT lung (www.rtog.org)	QUANTEC (48)
Liver (CTV excluded)	30% <21 Gy* 50% <15 Gy*	700 mL < 15 Gy	700 mL < 15 Gy	NA	700 mL ≤15 Gy D_{mean} < 15 Gy
Stomach	$D_{5\ mL}$ <21 Gy	D_{max} ≤30 Gy	$D_{1\ mL}$ <21 Gy	NA	D_{max} <30 Gy ($D_{5\ mL}$ <22.5 Gy)
Bowel	$D_{5\ mL}$ <21 Gy	D_{max} ≤30 Gy	$D_{1\ mL}$ <21 Gy	NA	D_{max} <30 Gy
Esophagus	$D_{5\ mL}$ <21 Gy	NA	$D_{1\ mL}$ <21 Gy	D_{max} ≤27 Gy	NA
Kidney	NA	Total kidney $D_{35\%}$ <15 Gy	Total kidney $D_{35\%}$ <15 Gy	NA	NA
Spinal cord	NA	D_{max} ≤18 Gy	D_{max} <18 Gy	D_{max} ≤18 Gy	D_{max} ≤20 Gy
Heart	$D_{5\ mL}$ <21 Gy	NA	$D_{1\ mL}$ <30 Gy	D_{max} ≤30 Gy	NA

Abbreviations: SBRT = stereotactic body radiotherapy; RTOG = Radiation Therapy Oncology Group; CTV = clinical target volume; NA = not available; Dx % = dose to x%; Dx mL = dose to x mL; D_{max} = maximum dose.
* Liver including clinical target volume.

Constraints proposed for 3-fraction SBRT schedule

Hoyer M et al, IJROBP, 2012

Hi-tech treatments for liver metastases

IMRT delivered with MLC

•Segmental IMRT (step-and-shoot)

-**Gantry** does **not move** during irradiation

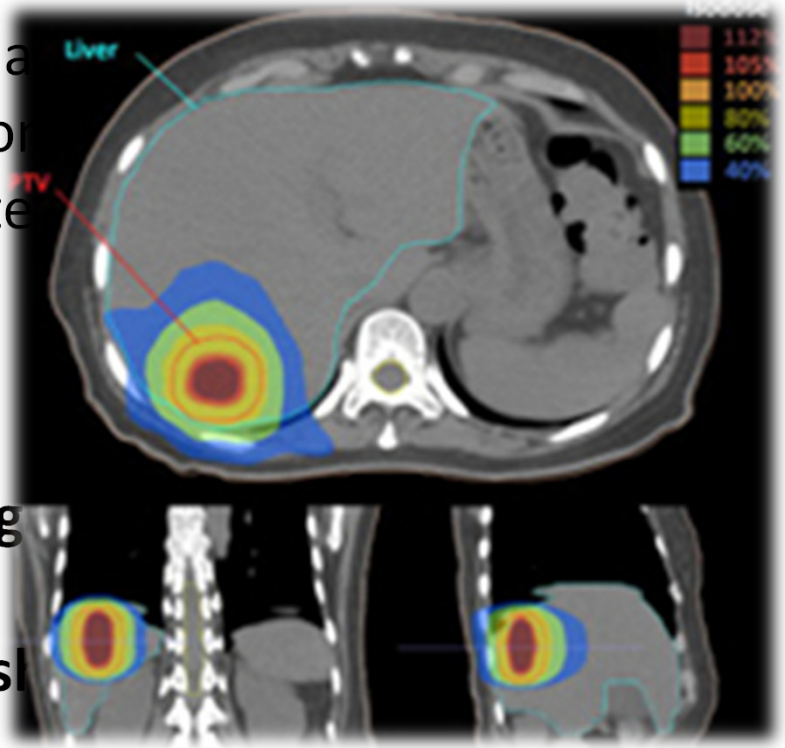
-Each collimator shape is a subfield (segment)

•Dynamic IMRT (sliding window)

-**Collimator** shape **changes** during irradia

-**Gantry** does **not move** during irradiatio

-Leaf positions, speed, MU and dose rate



VMAT

-One or more gantry arcs

-**Continuously varying beam aperture, g**

-Maximize benefit of IMRT

-Widest range of beam orientations in **s**

Hi-tech treatments for liver metastases

TomoTherapy

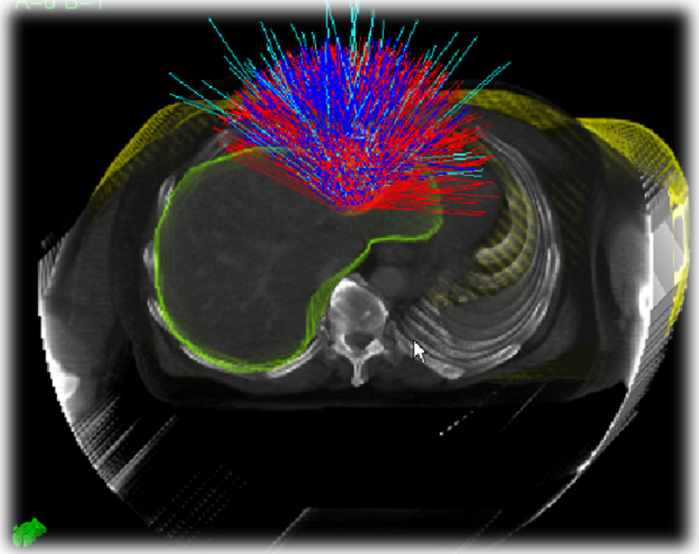
-Geometry of a helical CT scanner

-6 MV linear accelerator in a slip ring gantry

-Beam passes through a primary collimator and is further collimated into a fan-beam shape-ring

-Gantry continuously rotates during treatment

-The patient is continuously translated through the rotating beam plane



CyberKnife

-Compact LINAC in a robotic arm

-6 degrees of freedom

-Image guided system (intrafraction imaging)

-Non coplanar geometry

-Use of fiducials

-Tracking movement system

Hi-tech treatments for liver metastases

	Imaging before fraction	Automatic Positioning	Non-coplanar beams	Intra-fraction imaging	Intensity modulation	Motion management
Linac + IGRT+ abdominal compression	Y	Y/N	Y (limited)	N	Y	Gating (CT-based)
Tomotherapy	Y	Y	N	N	Y	-
CyberKnife	Y	Y	Y	Y	N	Real Time Tracking

Adapted by Mirabel X, Oral Communication at ESTRO 31, Barcelona

SBRT: retrospective studies

STUDY	PATIENTS	LESIONS	RT DOSE	OUTCOME
Blomgren et al, 1995	14	17	7.7/45 Gy in 1/4 fr	**50% RR**
Wulf et al, 2006	39	51	30/37.5 Gy in 3 fr 26 Gy in 1fr	**1-year: 92%** **2-year: 66%**
Katz et al, 2007	69	174	30/55 Gy in 3-15 fr	**2-year: 57%**
Van der Pool et al, 2010	20 (only CRC)	31	30/37.5 Gy in 3 fr	**2-year: 74%**
Vautravers-Dewas et al, 2011	42 (CK)	62	40 Gy in 4 fr 45 Gy in 3 fr	**2-year: 86%**

SBRT: prospective studies

STUDY	PATIENTS	LESIONS	RT DOSE	OUTCOME
Herfarth et al, 2004 *Phase I/II*	35	51	14/26 Gy in 1 fr	**18 months:** **67%**
Mendez et al, 2006 *Phase I/II*	17	34	30/37.5 Gy in 3 fr	**2-year: 86%**
Hoyer et al, 2006 *Phase II*	44 (only CRC)	NA	45 Gy in 3 fr	**2-year: 79%**
Lee et al, 2009 *Phase I/II*	68	140	28/60 Gy in 6 fr	**1-year: 71%**
Rusthoven et al, 2009 *Phase I/II*	47	63	36/60 Gy In 3 fr	**2-year: 92%**
Goodman et al, 2010 *Phase I*	19	33	18/30 Gy in 1 fr	**1-year: 77%**
Rule et al, 2011 *Phase I*	26	35	30 Gy in 3fx 50 Gy in 5fx 60 Gy in 3fx	**2-year: 56%** **2-year: 89%** **2-year: 100%**

SBRT: prospective studies

STUDY	PATIENTS	LESIONS	RT DOSE	OUTCOME
Herfarth et al, 2004 *Phase I/II*	35	51	14/26 Gy in 1 fr	**18 months:** **67%**
Mendez et al, 2006 *Phase I/II*	17	34	30/37.5 Gy in 3 fr	**2-year: 86%**
Hoyer et al, 2006 *Phase II*	44 (only CRC)	NA	45 Gy in 3 fr	**2-year: 79%**
Lee et al, 2009 *Phase I/II*	68	140	28/60 Gy in 6 fr	**1-year: 71%**
Rusthoven et al, 2009 *Phase I/II*	47	63	36/60 Gy In 3 fr	**2-year: 92%**
Goodman et al, 2010 *Phase I*	19	33	18/30 Gy in 1 fr	**1-year: 77%**
Rule et al, 2011 *Phase I*	26	35	30 Gy in 3fx 50 Gy in 5fx 60 Gy in 3fx	**2-year: 56%** **2-year: 89%** **2-year: 100%**

SBRT and liver metastases - EBM

- **Significant heterogeneity** concerning:
- Patients election (CRC vs other tumors)
- Tumor volumes
- Total dose; dose per fraction; dosimetric planning criteria

- **Difficult interpretation of results**:
- Heavily pretreated patients
- Limited life expectancy
- Difficult to compare outcome with other local modalities

- **Local control: favorable**
- 1-year: 70% - 100% 2-years: 60% - 90%
- Results mainly dependent on tumor volume and RT dose

Hoyer M et al, IJROBP, 2012

SBRT: toxicity

- ≥ G3 toxicity: **uncommon**
  - Rare: gastrointestinal and soft tissue/bone complications
  - Radiation induced liver disease (RILD): very low risk

- Critical volume model:
  - Up to 80% of the liver can be safely removed in a patient with adequate liver function
  - Minimum volume of 700 mL or 35% of normal liver should remain uninjured by SBRT
  - Mandatory: at least 700 mL of normal liver (entire liver minus cumulative GTV) have to receive less than 15 Gy.

Shefter TE et al, IJROBP, 2005

SBRT: Italian phase I/II study

- *Prospective, phase I/II study of SBRT not amenable to surgery.*
  - KPS>70; adequate liver function
  - ≤ 3 hepatic lesions; maximum diameter 6 cm

- *Treatment procedures:*
  - 4DCT/gating procedures allowed
  - **Dose prescription: 75 Gy in 3 fractions with PTV covered by the 67% isodose**

- *Dose constraints:*
  - ≥ 700 cc of healthy liver should receive ≤ 15 Gy
  - Spinal chord Dmax: < 18 Gy
  - Kidneys V15: ≤ 35%
  - Stomach and duodenum Dmax: < 21 Gy
  - Rib cage V30: < 30 cc

Scorsetti M et al, Radiat Oncol, 2012

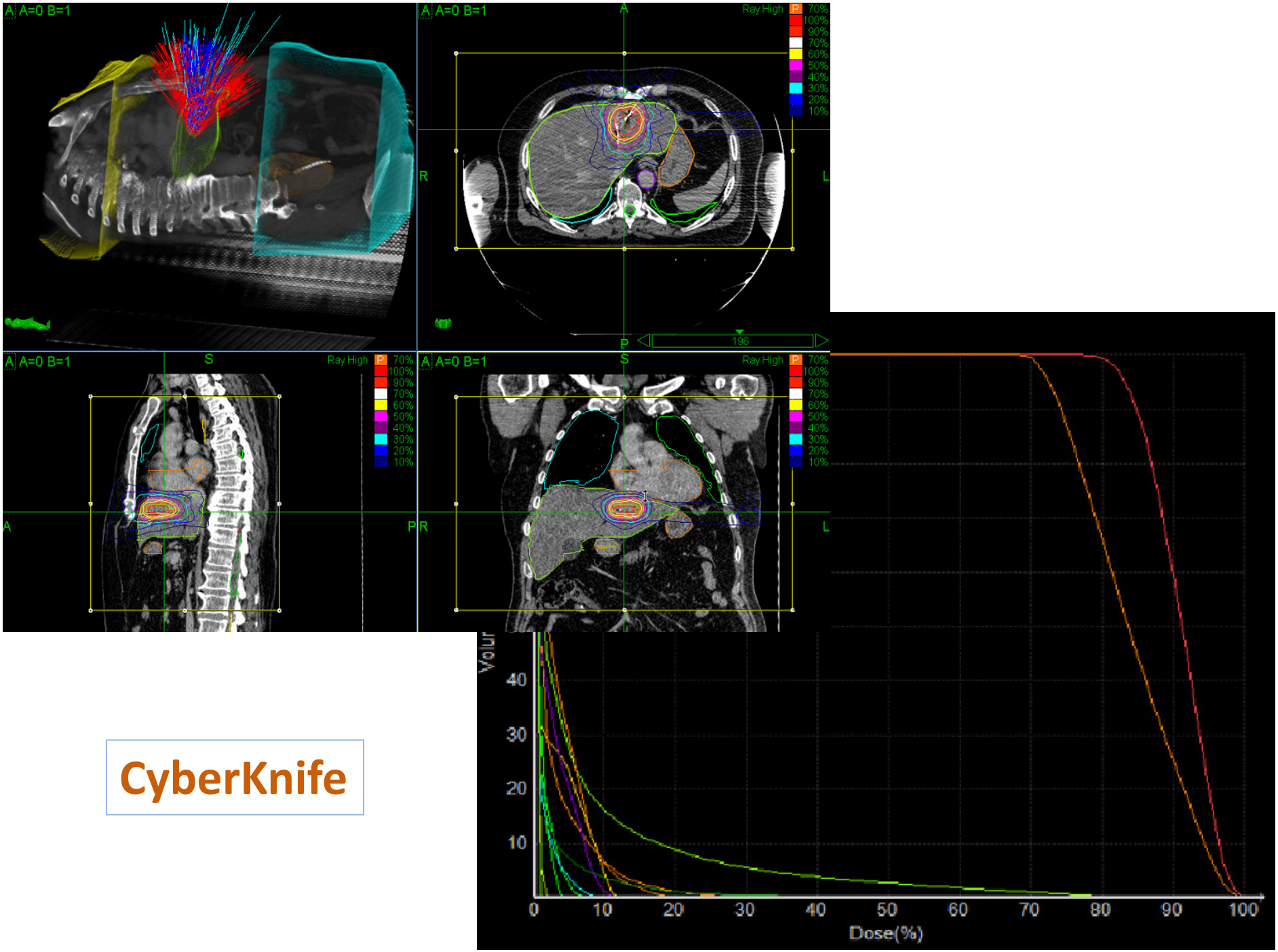
SBRT: future direction

- RAS – trial:
  - RDM trial of RFA VS SBRT for colorectal liver metastases
  - Primary endpoint: local progression free survival at 3 years
  - Max 1-4 liver metastases; diameter maximum of 4 cm
  - Expected end accrual (300 pts): December 2012

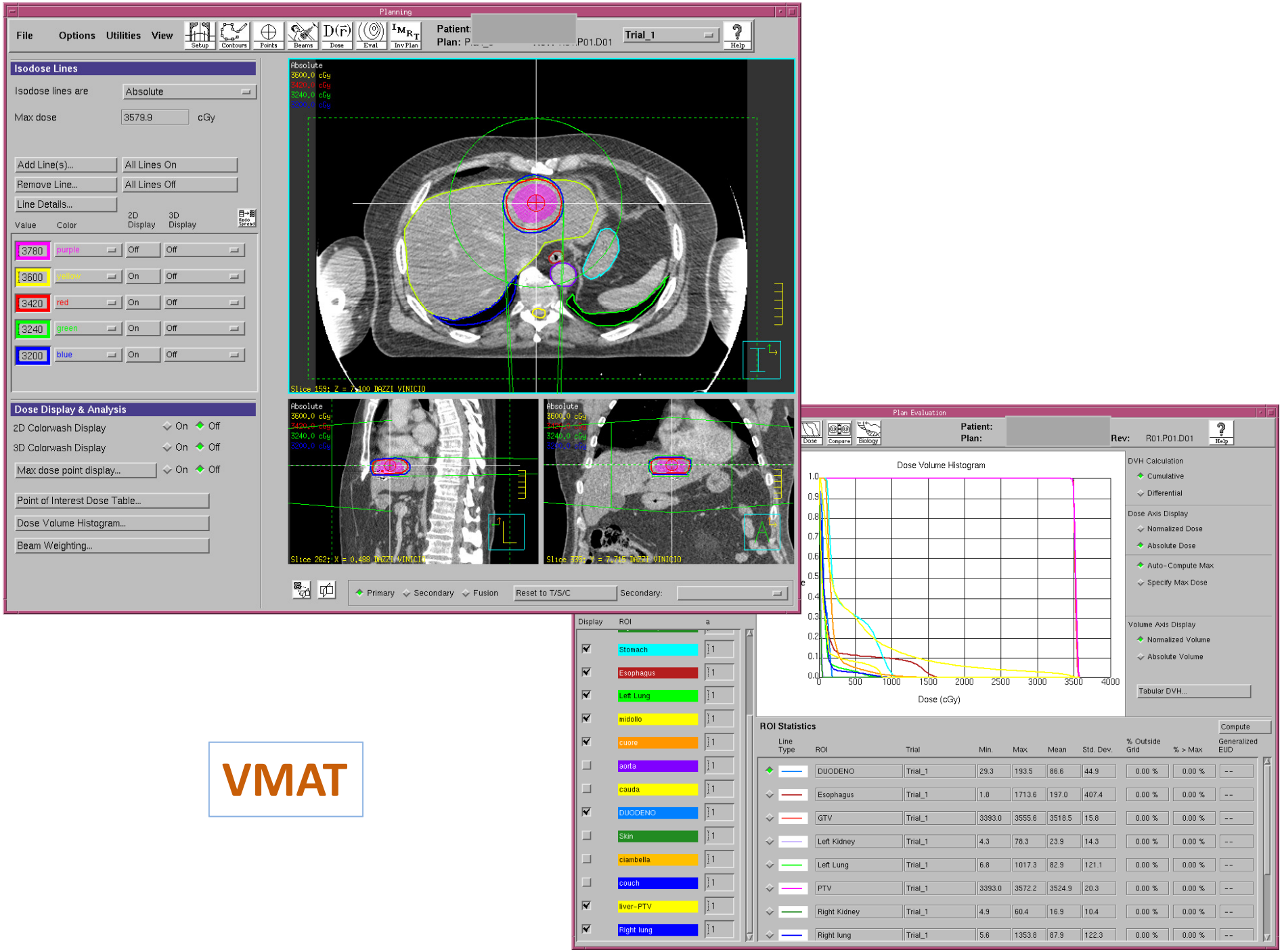
http://clinicaltrials.gov/ct2/show/NCT01233544

- SLIM – trial:
  - Sorafenib + RT for liver metastases (phase I/II study)
  - Primary endpoint: MTD of sorafenib + RT; acute toxicity
  - Secondary endpoints: late toxicity, local control, OS
  - Study completion date (44 pts): January 2013

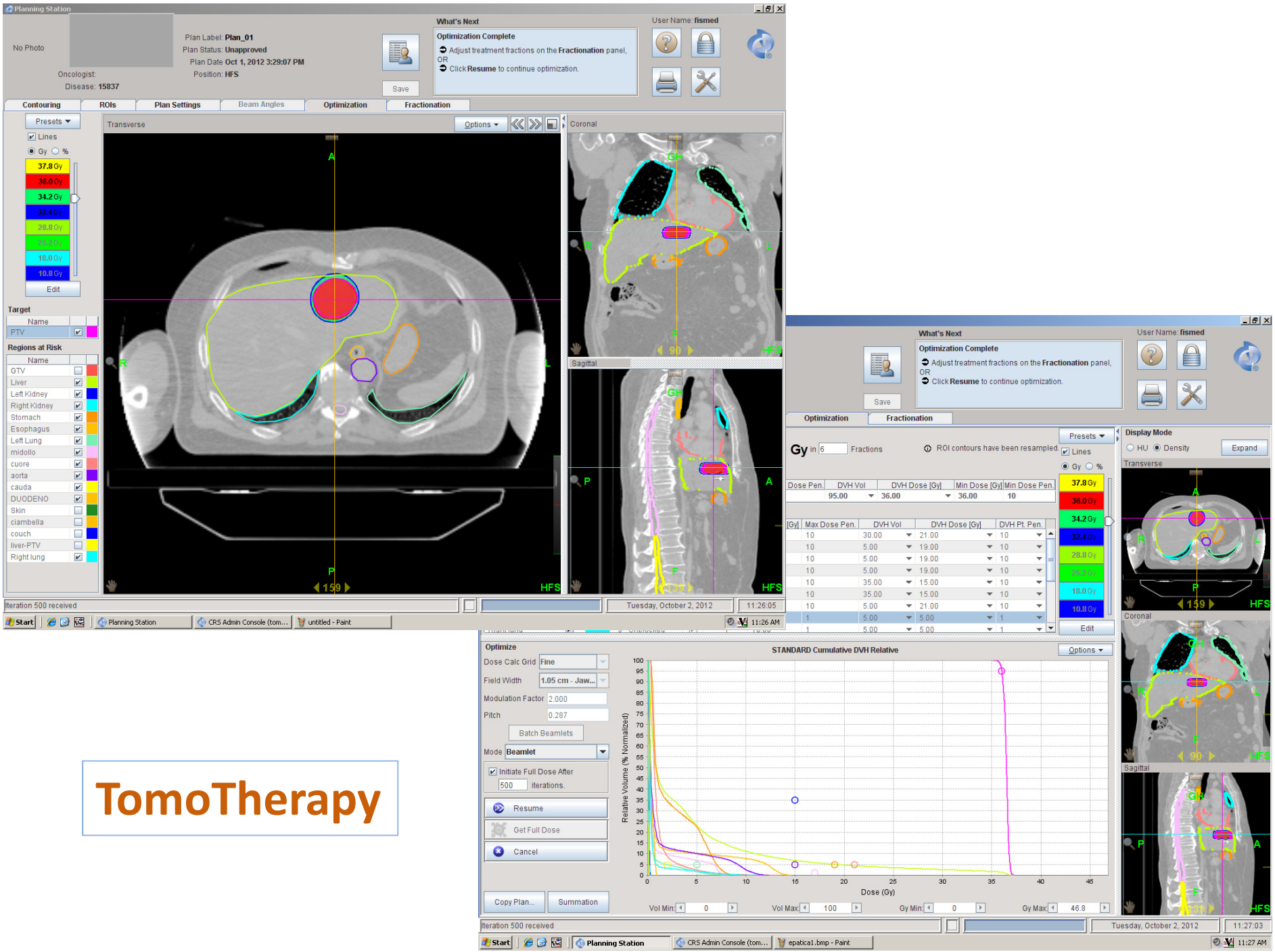
http://clinicaltrials.gov/ct2/show/NCT00892424


A=0 B=1
Ray High
70%
100%
90%
70%
60%
50%
40%
30%
20%
10%
R
L
A
P
S
196
Volur
40
30
20
10
0
10
20
30
40
50
60
70
80
90
100
Dose(%)

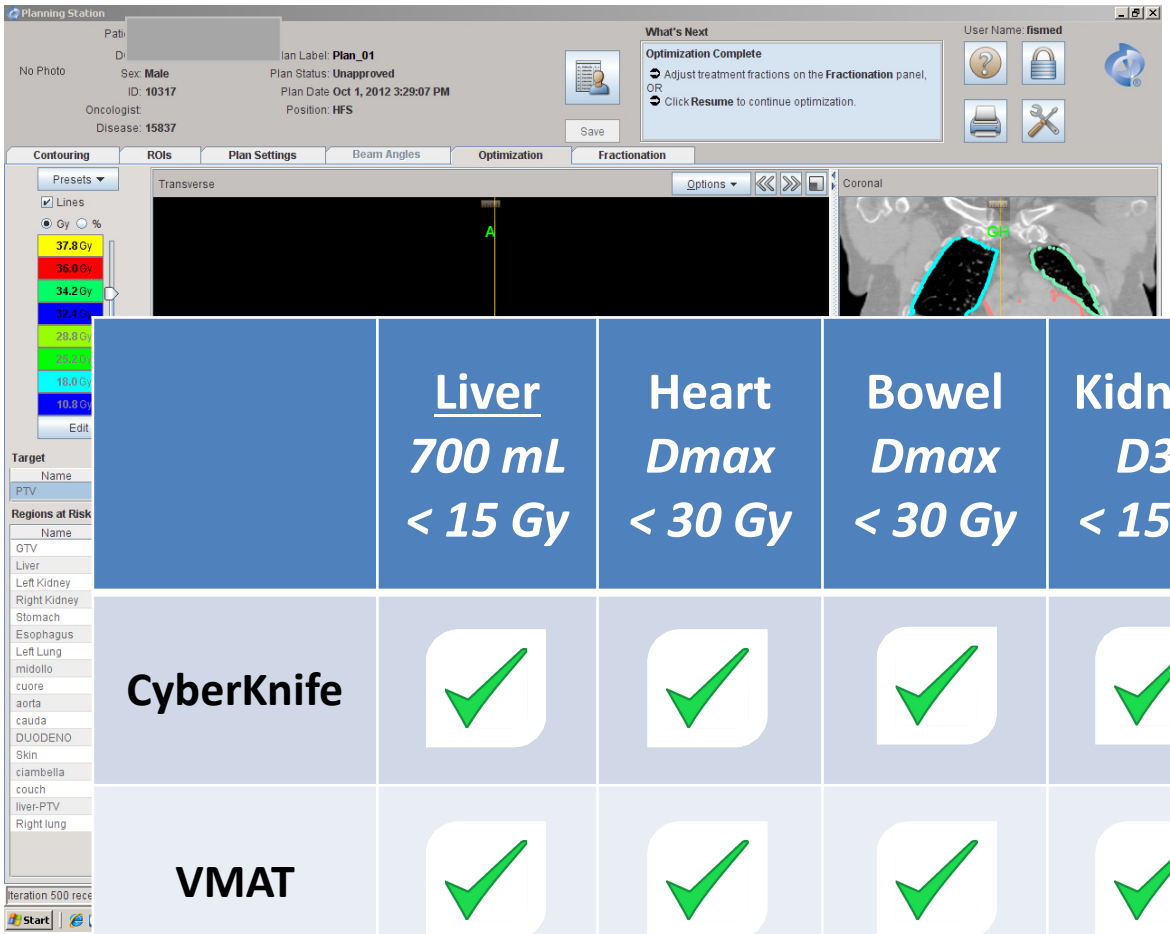
CyberKnife


Planning
File
Options
Utilities
View
Setup
Contours
Points
Beams
Dose
Eval
Inv Plan
Patient:
Plan:
Trial_1
Help
Isodose Lines
Isodose lines are
Absolute
Max dose
3579.9
cGy
Add Line(s)...
All Lines On
Remove Line...
All Lines Off
Line Details...
Value
Color
2D Display
3D Display
3780
purple
3600
yellow
3420
red
3240
green
3200
blue
Dose Display & Analysis
2D Colorwash Display
3D Colorwash Display
Max dose point display...
Point of Interest Dose Table...
Dose Volume Histogram...
Beam Weighting...
Primary
Secondary
Fusion
Reset to T/S/C
Secondary:
Plan Evaluation
Dose
Compare
Biology
Rev:
R01.P01.D01
Dose Volume Histogram
Dose (cGy)
DVH Calculation
Cumulative
Differential
Dose Axis Display
Normalized Dose
Absolute Dose
Auto-Compute Max
Specify Max Dose
Volume Axis Display
Normalized Volume
Absolute Volume
Tabular DVH...
ROI Statistics
Compute
Line Type
ROI
Trial
Min.
Max.
Mean
Std. Dev.
% Outside Grid
% > Max
Generalized EUD
DUODENO
Esophagus
GTV
Left Kidney
Left Lung
PTV
Right Kidney
Right lung
Display
Stomach
Esophagus
Left Lung
midollo
cuore
aorta
cauda
DUODENO
Skin
ciambella
couch
liver-PTV
Right lung

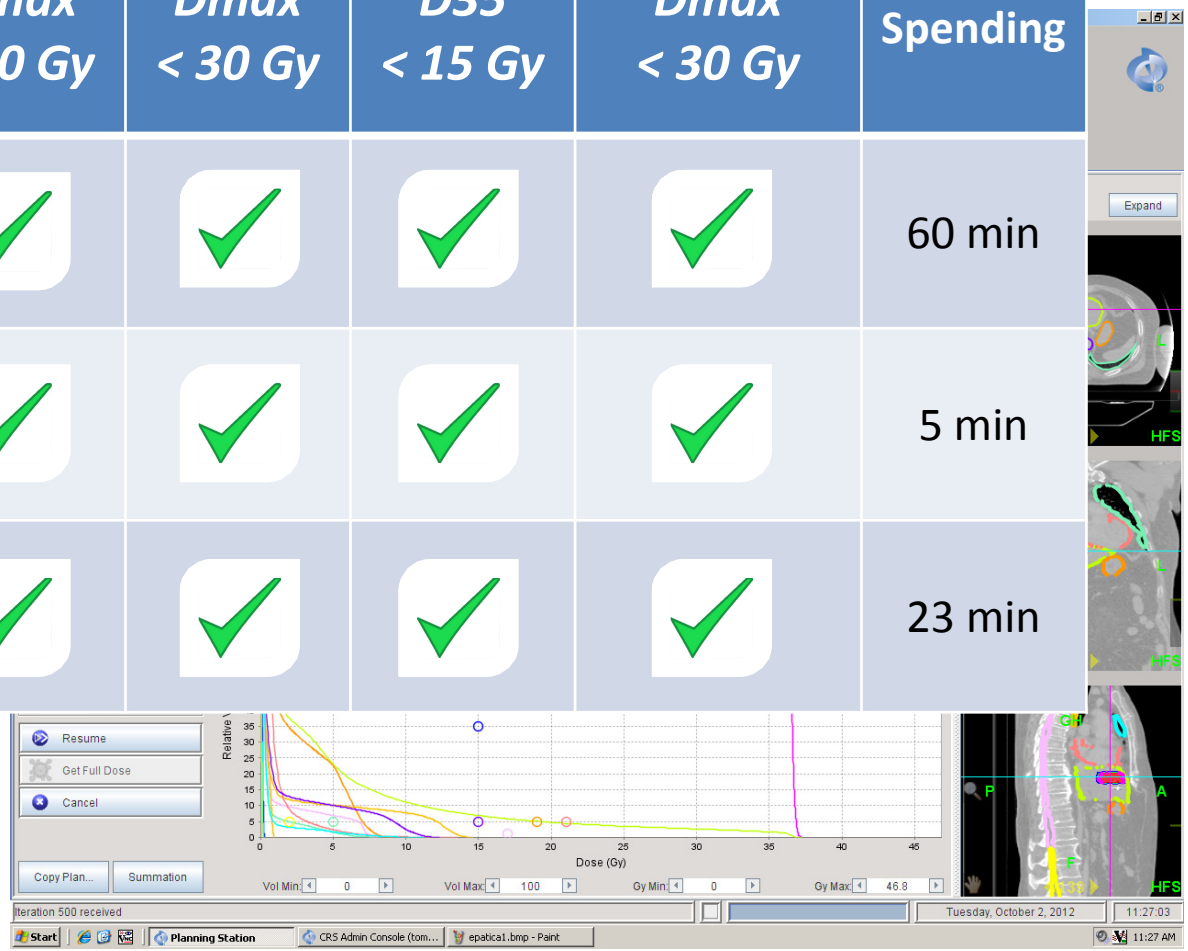
VMAT



TomoTherapy



	Liver *700 mL < 15 Gy*	Heart *Dmax < 30 Gy*	Bowel *Dmax < 30 Gy*	Kidneys *D35 < 15 Gy*	Stomach *Dmax < 30 Gy*	Time Spending
CyberKnife	✓	✓	✓	✓	✓	60 min
VMAT	✓	✓	✓	✓	✓	5 min
TomoTher	✓	✓	✓	✓	✓	23 min



Conclusions

•Until recently, the liver was difficult to treat in routine with RT.

•Technologies development→ new treatment approach

-Highly effective doses are deliverable to liver metastases

-With effective protection for healthy tissue

•Hi-technologies represent just a more refined tool in the hands of Clinical Oncologist.

Conclusions

•Appropriate: suitable for a particular person, condition, occasion, or place.

•The optimal combination of systemic and local therapies is yet to be determined.

•Future studies will hopefully include patients with improved prognosis who are more likely to benefit from ablation of their liver metastases (appropriateness).

•Studies with favorable patients are necessary to better determine the late toxicity profile and long-term local control in well defined patient populations.

Thanks for your attention…