HUMANITAS
CANCER CENTER

Farmaci innovativi
e ipofrazionamento

PALACONGRESSI DI RIMINI
30 settembre, 1-2 ottobre 2016

# Phase II trial on SBRT for unresectable Liver Metastases: Long-term outcomes and prognostic factors of survival

*Comito T, Franzese C, Clerici E, Tozzi A, Iftode C, Navarria P, D'Agostino G, De Rose F, Franceschini D, Ascolese AM, Di Brina L, Scorsetti M.*

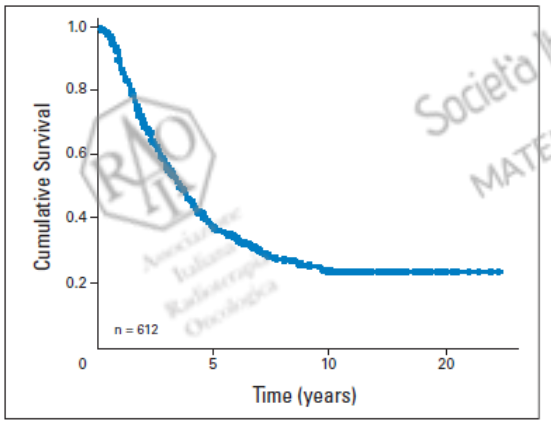
**TIZIANA COMITO M.D.**
**Radioterapia e Radiochirurgia. Humanitas Clinical and Research Center**
***tiziana.comito@humanitas.it***

# Background

- The liver is a common site of metastases for gastrointestinal, lung and breast cancers

- In colorectal cancer 30% to 70% of patients will develop liver metastases, often isolated or associated with limited metastatic foci of disease.

- **Surgical resection** of CRC liver metastases improves overall survival




- 1 year OS : 90-95%
- 5-year OS : 30-60%
- median OS of 3-3.5 years

**Only 10-60% of patients were suitable for surgical resection**





Adam, De Gramont. The Oncologist, 2012
Kemeny N. et al, Oncology 2006

# Background

- **Radiofrequency ablation (RFA)** is the most valid alternative to surgery**:**

  - local control rates of 90-98%
  - 1, 2 and 5-year survival rates of 87%-70% and 34%,
  - median overall survival of 25 months

- **RFA Limits:**
  - lesions higher than 3 cm of diameter
  - lesions located in proximity of major blood vessels, main biliary tract, gallbladder or just beneath the diaphragm



**Liver metastases treatment:**
**is there an alternative?**



Kemeny N. et al, Oncology 2006
Shen A et al, J Gastroenterol Hepatol. 2013

# Liver metastases treatment: the role of SBRT

**Table 1 Prospective clinical trials in the literature studying stereotactic ablative radiotherapy in liver metastases and their results**

| Ref. | Design | No of patients | Tumor size | SABR dose | Toxicity | Outcomes |
|---|---|---|---|---|---|---|
| Scorsetti *et al*[15] | Phase II (preliminary report) | 61 (76 tumors) | 1.8-134.3 $cm^3$ (mean 18.6 $cm^3$) | 75 Gy in 3 fractions | No case of RILD. Twenty-six percent had grade 2 transaminase increase (normalised in 3 mo). Grade 2 fatigue in 65% patients, one grade 3 chest wall pain which regressed within 1 year. | 1-yr LC94, 22-mo LC 90.6% |
| Goodman *et al*[16] | Phase I (HCC and liver mets) | 26 (19 liver mets) | 0.8-146.6 mL (median, 32.6 mL) | Dose escalation, 18-30 Gy (1 fr) | No dose-limiting toxicity<br>4 cases of Grade 2 late toxicity (2 GI, 2 soft tissue/rib) | 1-yr local failure, 3%<br>2-yr OS, 49% (mets only) |
| Ambrosino *et al*[17] | Prospective cohort | 27 | 20-165 mL (median, 69 mL) | 25-60 Gy (3 fr) | No serious toxicity | Crude LC rate 74% |
| Lee *et al*[18] | Phase I - II | 68 | 1.2-3090 mL (median, 75.9 mL) | Individualized dose, 27.7-60 Gy (6 fr) | No RILD, 10% Grade 3/4 acute toxicity<br>No Grade 3/4 late toxicity | 1-yr LC, 71% Median survival, 17.6 mo |
| Rusthoven *et al*[19] | Phase I - II | 47 | 0.75-97.98 mL (median, 14.93 mL) | Dose escalation, 36-60 Gy (3 fr) | No RILD, Late Grade ¾ < 2% | 1-yr LC, 95%<br>2-yr LC, 92%<br>Median survival, 20.5 mo |
| Høyer *et al*[10] | Phase II (CRC oligomets) | 64 (44 liver mets) | 1-8.8 cm (median, 3.5 cm) | 45 Gy (3 fr) | One liver failure, two severe late GI Toxicities | 2-yr LC, 79% (by tumor) and 64% (by patient) |
| Méndez Romero *et al*[20] | Phase I - II (HCC and mets) | 25 (17 liver mets) | 1.1-322 mL (median, 22.2 mL) | 30-37.5 Gy (3 fr) | Two Grade 3 liver toxicities | 2-yr LC, 86%<br>2-yr OS, 62% |
| Herfarth *et al*[21] | Phase I - II | 35 | 1-132 mL (median, 10 mL) | Dose escalation, 14-26 Gy (1 fr) | No significant toxicity reported | 1-yr LC, 71%<br>18-mo LC, 67%<br>1-yr OS, 72% |





*Nair et al, WJR 2014*

# Phase II study: inclusion criteria and end points


**Is Stereotactic Body Radiation Therapy an Attractive Option for Unresectable Liver Metastases? A Preliminary Report From a Phase 2 Trial**

Marta Scorsetti, MD,* Stefano Arcangeli, MD,* Angelo Tozzi, MD,* Tiziana Comito, MD,* Filippo Alongi, MD,* Pierina Navarria, MD,* Pietro Mancosu, MSc,* Giacomo Reggiori, MSc,* Antonella Fogliata, MSc,† Guido Torzilli, MD,† Stefano Tomatis, MSc,* and Luca Cozzi, PhD‡

*MAIN INCLUSION CRITERIA:*

- Unresectable liver metastases
- Maximum tumor diameter < 6cm
- ≤ 3 discrete lesions

*END POINTS:*

Primary: in-field local control

Secondary: toxicity and overall survival

# Phase II study: Median follow-up: 2.3 years

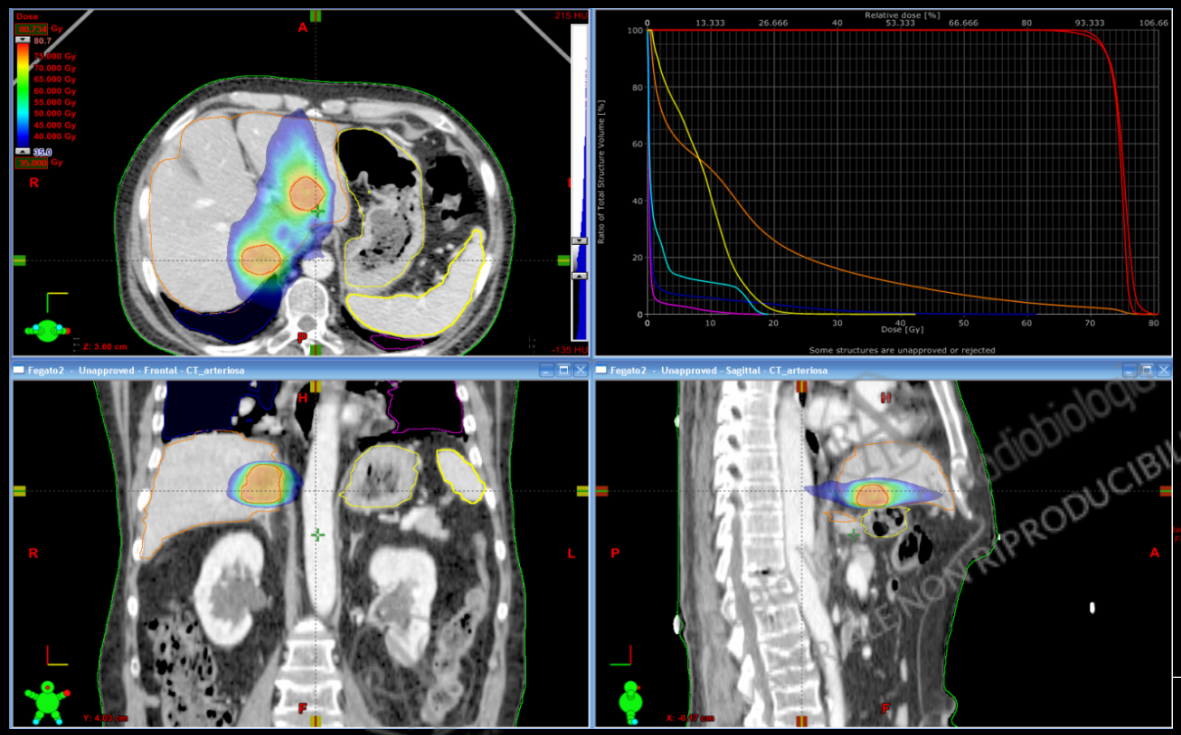
**Table 1** Baseline patient and treatment characteristics

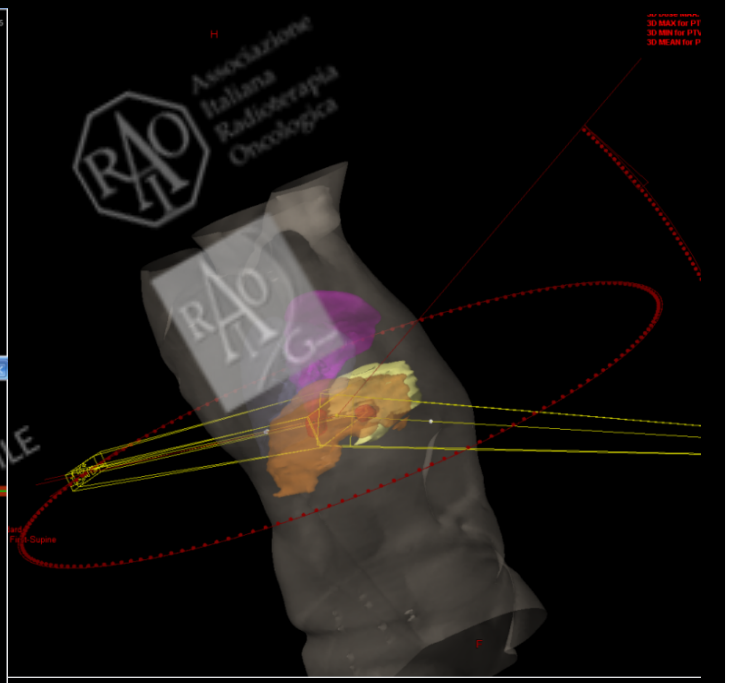
| Characteristic | n | % |
|---|---|---|
| No. of patients | 61 | |
| Male | 26 | 42.6 |
| Female | 35 | 57.4 |
| Median age, y | 65 | - |
| Range | 39-87 | |
| No. of liver lesions | | |
| 1 | 48 | 78.7 |
| 2 | 11 | 18.0 |
| 3 | 2 | 3.3 |
| Primary | | |
| Colorectal | 29 | 47.5 |
| Breast | 11 | 18.0 |
| Gynecological | 7 | 11.5 |
| Other | 14 | 22.9 |
| Time since diagnosis, mo | | |
| ≤12 | 35 | 57.4 |
| >12 | 26 | 42.6 |
| No. of prior systemic treatment regimens | | |
| 0 | 10 | 16.4 |
| 1 | 15 | 24.6 |
| 2 | 13 | 21.3 |
| 3 | 14 | 22.9 |
| ≥4 | 9 | 14.7 |
| Presence of stable extrahepatic disease | | |
| Yes | 21 | 34.4 |
| No | 40 | 65.6 |
| Prior liver-directed therapy | | |
| Yes | 28 | 45.9 |
| Surgery | 21 | 75 |
| RFA | 2 | 7 |
| Both | 5 | 19 |
| No | 33 | 54.1 |

# Phase II study: dose prescription

| Treatment | No. of lesions | % |
|---|---|---|
| Lesion diameter (mm) | | |
| ≤30 mm | 45 | 59.2 |
| >30 mm | 31 | 40.8 |
| CTV volume ($cm^3$) | | |
| Mean ± SD | 18.6 ± 22.7 | |
| Range | 1.8-134.3 | |
| PTV volume ($cm^3$) | | |
| Mean | 54.9 ± 41.998 | |
| Range | 7.7-209.4 | |
| Dose prescription (per lesion) | | |
| Full dose (75 Gy) | 62 | 82 |
| 90% (67.5 Gy) | 6 | 8 |
| 80% (60 Gy) | 4 | 5 |
| 70% (52.5 Gy) | 4 | 5 |

# Phase II study: dose distribution



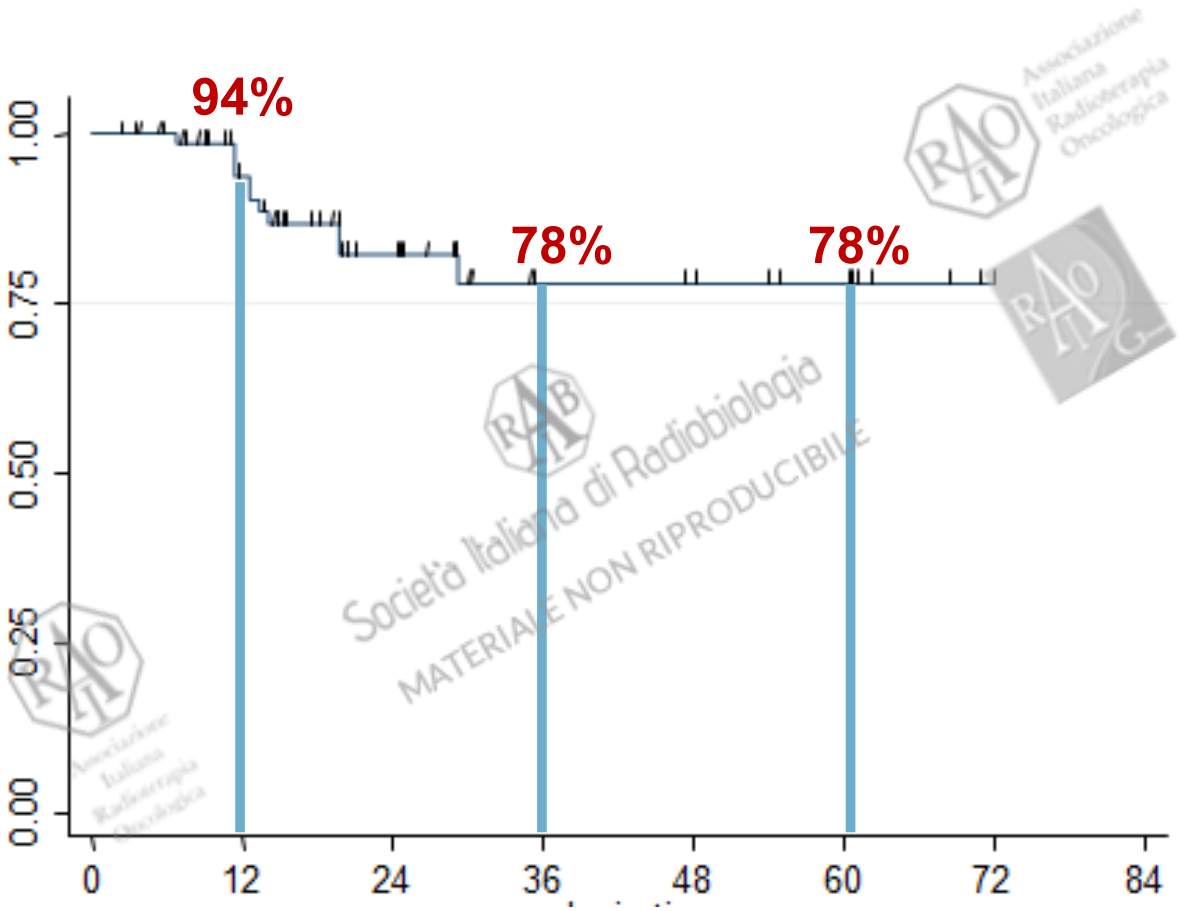


PTV1&PTV2: V95%=99.5%
Spinal cord: Max dose=17.3 Gy
Stomach: Max=21.0Gy, Mean=9.5 Gy
Liver: Mean=15.5 Gy, D15Gyfree=2811cc

1 isocentre, 3 arcs
Jaw tracking

MU:3216+3527+563
BOT: 174s(80+82+14s)

# Long term results: Local control






**Median LC = 1.7 years**

# Long term results: Local control

**1 - year LC = 94%**
**3 – years LC = 78%**
**5 – years LC = 78%**



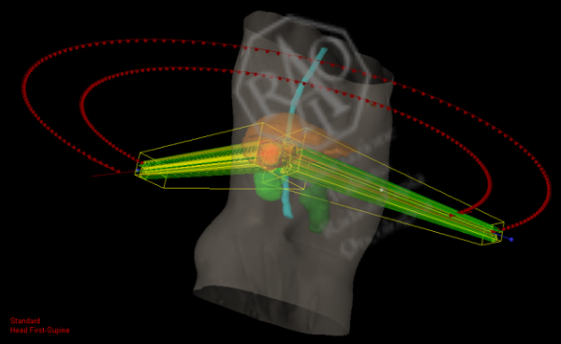
- **No correlation between LC and lesion size**
- **No correlation between LC and hystologies**

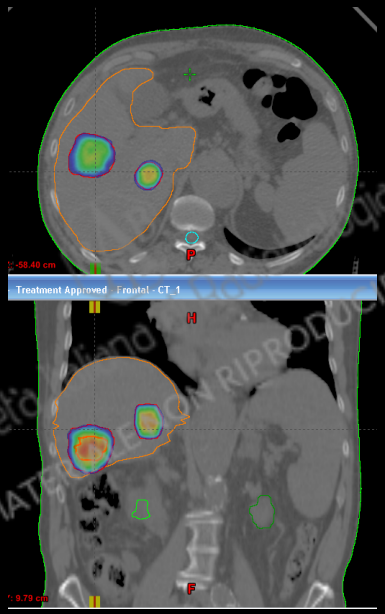
# Long term results: Local control

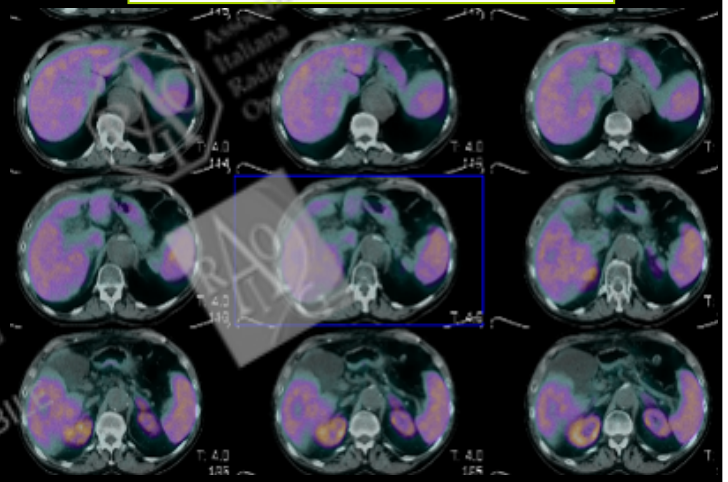
PET before

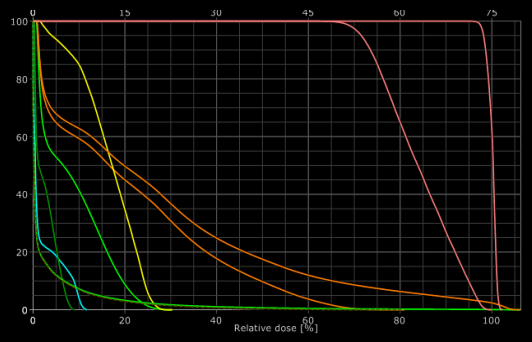
RapidArc
1 isocentre
2 arcs
Jaw tracking

PET after 6 months



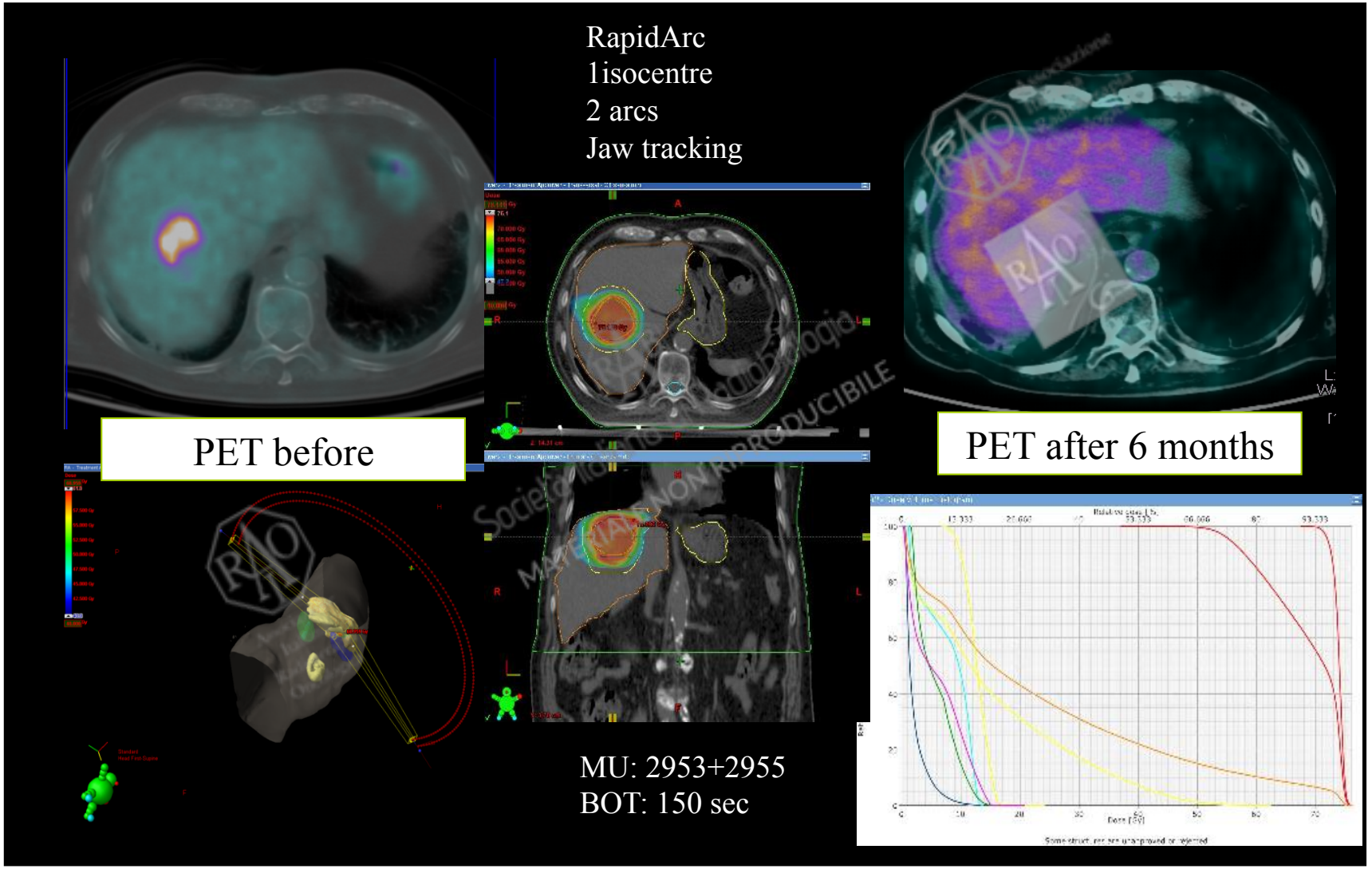


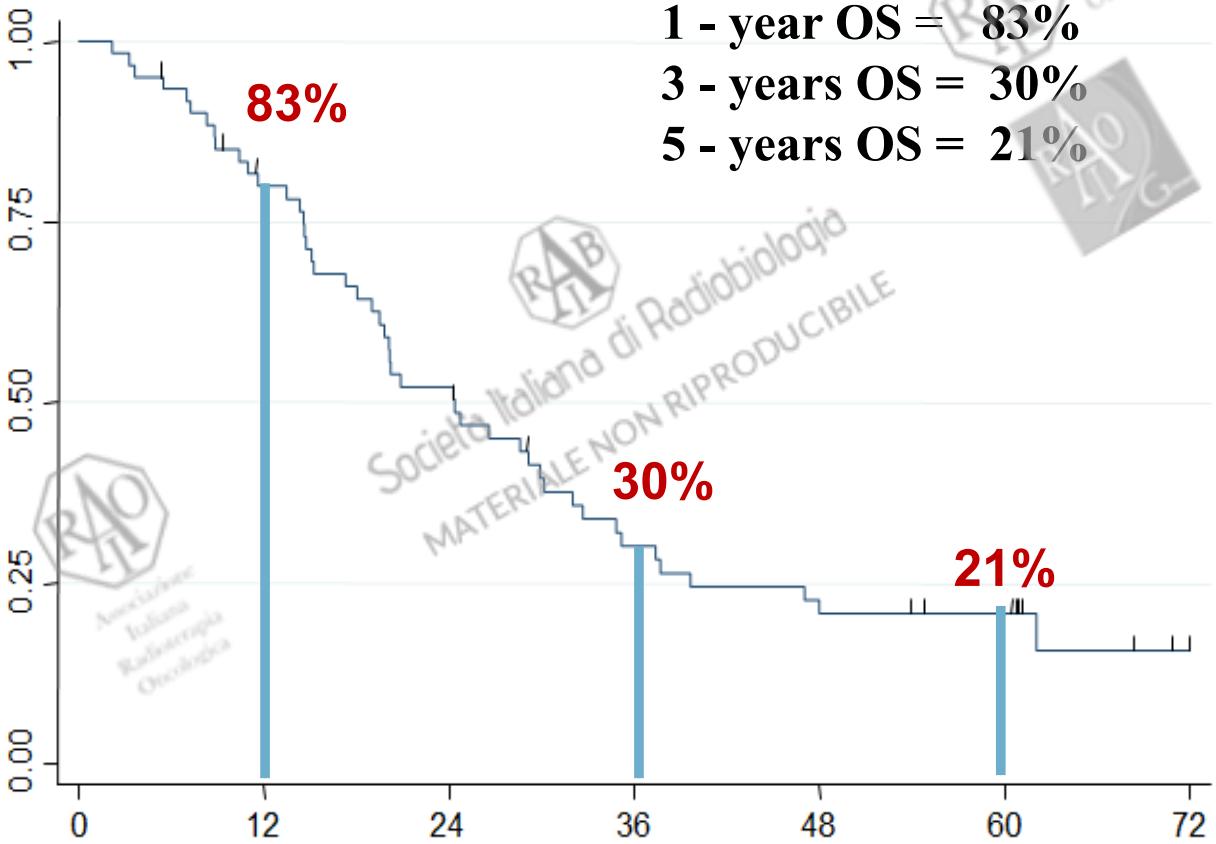



MU:3174+3004
BOT:170s

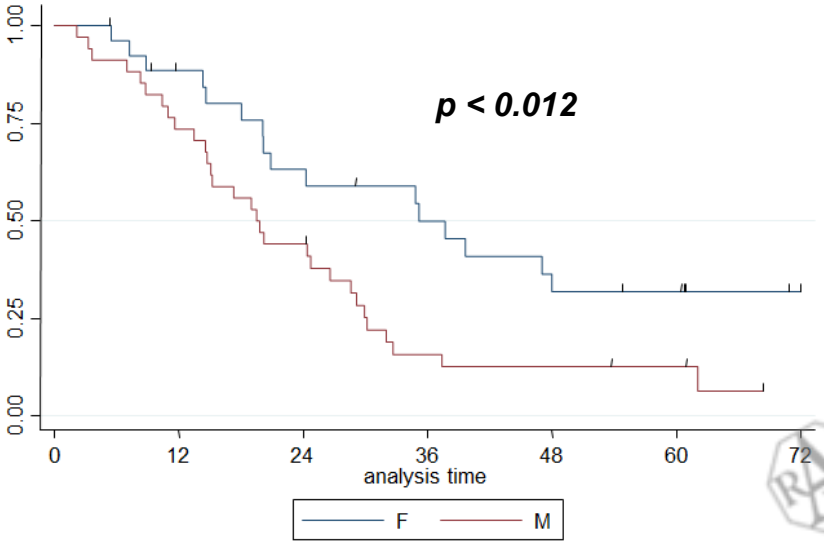
# Long term results: Local control



# Median OS from SBRT was 2.3 years

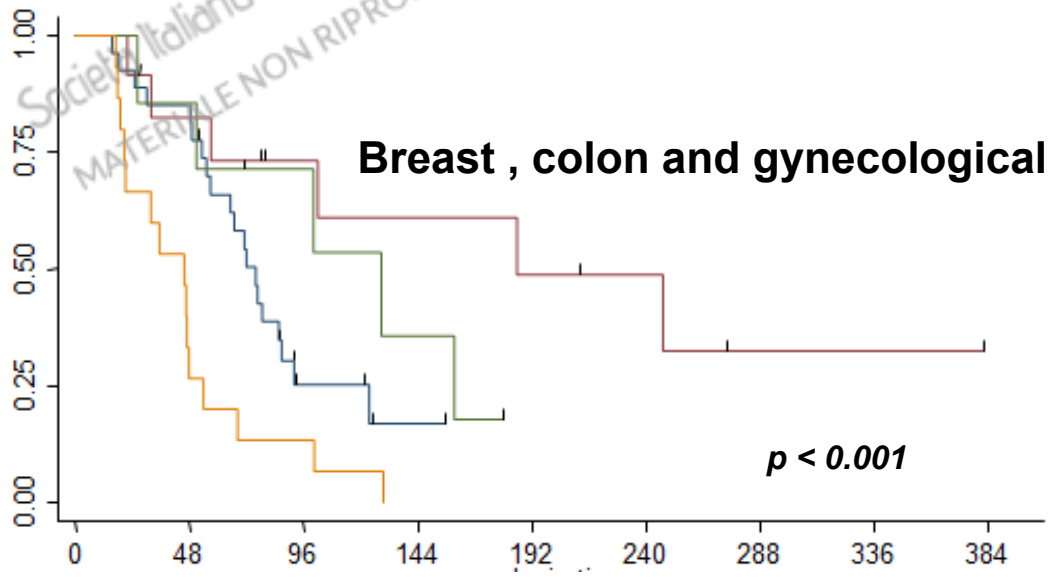


# Prognostic factors affecting survival




Multivariate analysis showed two independent positive prognostic factors affecting survival:

- female sex
- primary tumour




**Breast , colon and gynecological cancer**

# Toxicity

**ACUTE and LATE TOXICITY:**

**No G3-G4 or G5 toxicity observed**

**No RILD**

# Conclusions

**Long-term results of this Phase II study suggest the efficacy and safety of SBRT for unresectable liver metastases also at 5 years of follow-up.**

**Selection of cases with positive prognostic factors may improve long-term survival of these oligometastastic patients and may confirm the role of SBRT as an effective alternative local therapy for liver metastases.**

# Thank you!



**“We can not solve our problems with the same level of thinking that created them”**

**A. Einstein**