



# Radioterapia stereotassica nel trattamento delle metastasi epatiche



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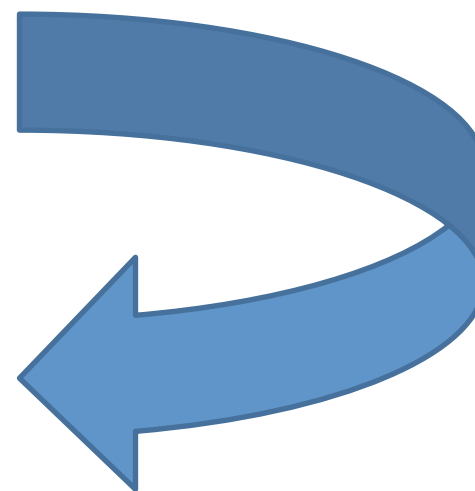
Dott.ssa D. Caivano

Nel 1990 Weichselbaum e Hellman introducono il concetto di malattia OLIGOMETASTATICA.

Terapie locali aggressive



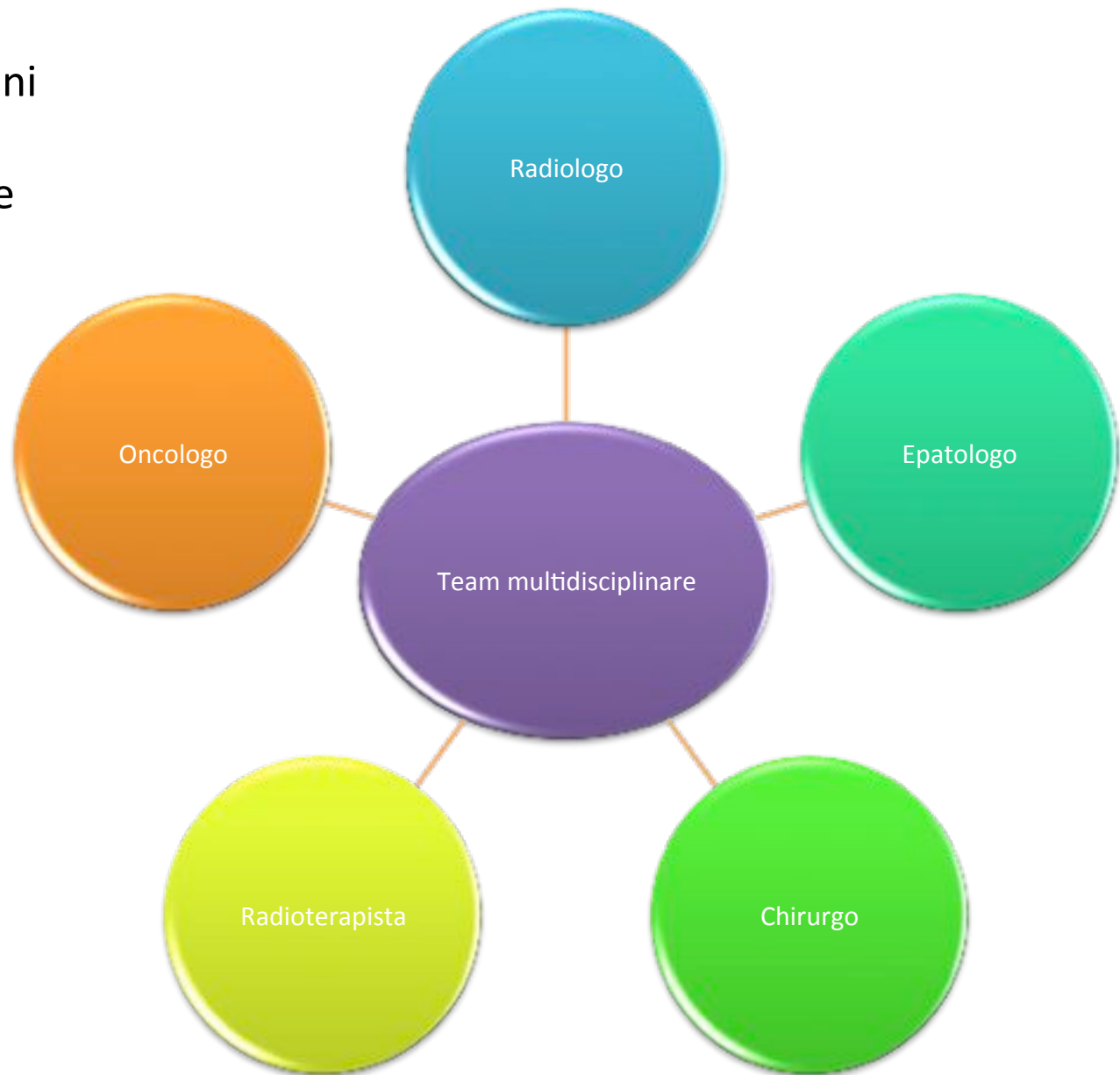
-controllo locale  
-sopravvivenza globale



La terapia non ha più soltanto una finalità PALLIATIVA

*Stereotactic body radiotherapy for oligometastases*  
Alison C Tree, et All. Lancet Oncol 2013; 14: e28–37

Il fegato è uno degli organi  
più frequentemente sede  
di localizzazione  
secondaria di malattia



## CHIRURGIA + TERAPIA SISTEMICA



Ottimi risultati in termini di sopravvivenza globale.

10-20 % dei pazienti sono realmente candidabili alla chirurgia



Cause di inoperabilità :

- stato di diffusione di malattia;
- funzionalità epatica residua;
- numero e localizzazione delle lesioni nel parenchima epatico (distanza <8mm dai grossi vasi e organi).



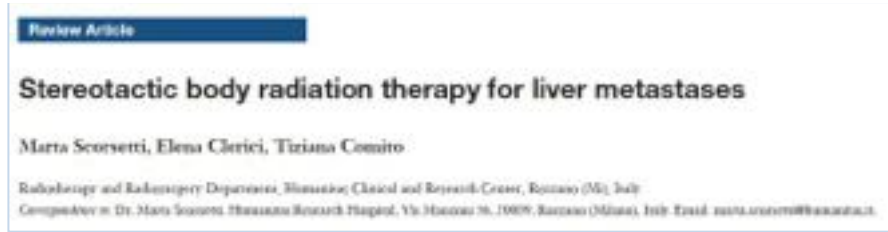
Limiti storici della radioterapia sul  
fegato l'insorgenza della RILD

No RILD:  
Volume: 700mL  
Dose: 15 Gy

TABLE 3: Summary of dose volume constraints for 3-fraction SABR regimen.

Organs at risk	Wulf et al. [15]	Hoyer et al. [24]	Timmerman [30]	Rusthoven et al. [25]	QUANTEC [31]
Liver	$D_{30\%} < 21 \text{ Gy}$ $D_{50\%} < 15 \text{ Gy}$	700 mL < 15 Gy	700 mL < 17 Gy	700 mL < 15 Gy	700 mL $\leq$ 15 Gy $D_{\text{mean}} < 15 \text{ Gy}$
Esophagus	$D_{5 \text{ mL}} < 21 \text{ Gy}$	$D_{1 \text{ mL}} < 21 \text{ Gy}$	$D_{5 \text{ mL}} < 21 \text{ Gy}$ , $D_{\text{max}} < 27 \text{ Gy}$	NA	NA
Stomach	$D_{5 \text{ mL}} < 21 \text{ Gy}$	$D_{1 \text{ mL}} < 21 \text{ Gy}$	$D_{10 \text{ mL}} < 21 \text{ Gy}$ $D_{\text{max}} < 24 \text{ Gy}$	$D_{\text{max}} \leq 30 \text{ Gy}$	$D_{\text{max}} < 30 \text{ Gy}$
Bowel	$D_{5 \text{ mL}} < 21 \text{ Gy}$	$D_{1 \text{ mL}} < 21 \text{ Gy}$	$D_{5 \text{ mL}} < 16 \text{ Gy}$ $D_{\text{max}} < 24 \text{ Gy}$	$D_{\text{max}} \leq 30 \text{ Gy}$	$D_{\text{max}} < 30 \text{ Gy}$
Kidney	NA	Total kidney $D_{35\%} < 15 \text{ Gy}$	Total kidney 200 mL < 14.4 Gy	Total kidney $D_{35\%} < 15 \text{ Gy}$	NA
Spinal cord	NA	$D_{\text{max}} < 18 \text{ Gy}$	$D_{0.25 \text{ mL}} < 18 \text{ Gy}$ $D_{\text{max}} < 22 \text{ Gy}$	$D_{\text{max}} \leq 18 \text{ Gy}$	$D_{\text{max}} \leq 20 \text{ Gy}$
Heart	$D_{5 \text{ mL}} < 21 \text{ Gy}$	$D_{1 \text{ mL}} < 30 \text{ Gy}$	$D_{15 \text{ mL}} < 24 \text{ Gy}$ $D_{\text{max}} < 30 \text{ Gy}$	NA	NA

SABR: stereotactic ablative radiotherapy; QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic; NA: not available;  $D_{x\%}$ : dose to x%;  $D_{x \text{ mL}}$ : dose to x mL;  $D_{\text{max}}$ : maximum point dose;  $D_{\text{mean}}$ : mean dose.



Con l'introduzione della SBRT si sono ottenuti ottimi risultati in termini di :

- controllo locale
- sopravvivenza globale
- tossicità

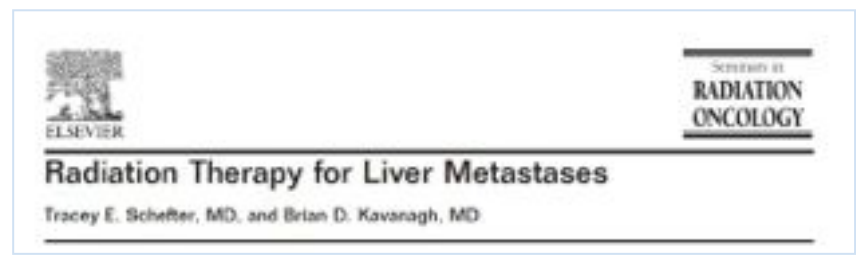
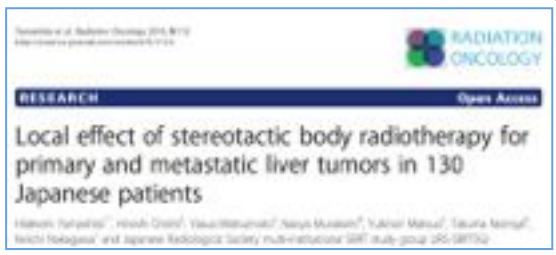
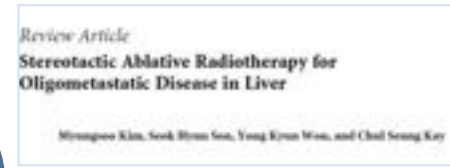


TABLE 1: Results of retrospective trials of SABR for liver metastases.

Study	Patients	Lesions	Tumor volume or size (median)	Type of mets	Dose	Median FU	LC	OS	Toxicity
Blomgren et al. (1995) [14]	14	17	3–260 mL	CRC (11) Anal canal (1) Kidney (1) Ovarian (1)	7.7–45 Gy (1–4 fx)	9.6 mo	NR 50% response rate	NR	2 cases of hemorrhagic gastritis
Wulf et al. (2006) [15]	44 (39 liver mets)	51	9–355 mL	CRC (23) Breast (11) Ovarian (4) Other (13)	30–37.5 Gy (3 fx) 26 Gy (1 fx)	2 yr	1-yr LC, 92%, 2-yr LC, 66%	1-yr OS, 72% 2-yr OS, 32%	No grade 2–4 toxicity
Katz et al. (2007) [16]	69	174	0.6–12.5 cm (2.7 cm)	CRC (20) Breast (16) Pancreas (9) Lung (5) Other (19)	30–55 Gy (5–15 fx)	14.5 mo	10-mo LC, 76%, 20-mo LC, 57%	Median survival, 14.5 mo, 6-mo OS, 46%, 12-mo OS, 24%	No grade 3/4 toxicity
van der Pool et al. (2010) [17]	20	31	0.7–6.2 cm (2.3 cm)	All CRC	30–37.5 Gy (3 fx)	26 mo	1-yr LC, 100%, 2-yr LC, 74%	Median survival, 34 mo, 1-yr OS, 100%, 2-yr OS, 83%	2 grade 3 late liver enzyme changes, 1 grade 2 rib fracture
Chang et al. (2011) [18]	65	102	0.6–3088 mL (30.1 mL)	All CRC	22–60 Gy (1–6 fx)	14.4 mo	1-yr LC, 62%, 2-yr LC, 45%	1-yr OS, 72%, 2-yr OS, 38%	2 grade 3 gastritis, 2 grade 3 elevated liver enzymes.
Vautravers-Dewas et al. (2011) [19]	42	62	0.7–10 cm (3.4 cm)		40 Gy (4 fx) 45 Gy (3 fx)	14.3 mo	2-yr LC, 86%	2-yr OS, 48%	
Lanciano et al. (2012) [20]	30 (23 liver mets)	41	2.29–316 mL (60.9 mL)	CRC (15) Breast (3) Esophagus (1) GIST (1) Pancreas (1) NSCLC (2)	36–60 Gy (3 fx) 50 Gy (5 fx)	22 mo	1-yr LC, 92%, 2-yr LC, 56%	1-yr OS, 73%, 2-yr OS, 31%	No grade 3/4 toxicity
Habermehl et al. (2013) [21]	90	138	11–333 mL (62 mL)	CRC (70) Breast (27) Pancreas (11) Ovarian (7) Lung (6) Others (16), by site	10–30 Gy (1 fx)	21.7 mo	87%, 69%, and 59% after 6, 12, and 18 mo	Median OS 24.3 mo; local PFS was 87%, 70%, and 59% after 6, 12, and 18 mo, respectively	No RILD

SABR: stereotactic ablative radiotherapy; LC: local control; OS: overall survival; CRC: colorectal cancer; GIST: gastrointestinal stromal tumor; NSCLC: non-small cell lung cancer; NR: not reported; fx: fractions; RILD: radiation-induced liver disease.

TABLE 2: Results of prospective trials of SABR for liver metastases.

Study	Design	Patients	Lesions	Tumor volume or size (median)	Type of mets	Dose	Median FU	LC	OS	Toxicity
Herfarth et al. (2001) [22]	Phase I/II	33	56	NR by patient	NR by patient (only by lesion)	Dose escalation, 14–26 Gy (1 fx)	18 mo	18-mo LC, 67%	1-yr OS, 72%	No significant toxicity reported
Méndez Romero et al., (2006) [23]	Phase I/II (HCC and mets)	25 (17 liver mets)	34	1.1–322 mL (22.2 mL)	CRC (14) Lung (1) Breast (1) Carcinoid (1)	30–375 Gy (3 fx)	12.9 mo	1-yr LC, 100%; 2-yr LC, and 86%	1-yr OS, 85%; 2-yr OS, 62%	2 transient grade 3 elevated liver enzymes.
Hoyer et al. (2006) [24]	Phase II (CRC oligometas)	64 (44 liver mets)	NR	1–8.8 cm (3.5 cm)	CRC (44)	45 Gy (3 fx)	4.3 yr	2-yr LC, 79% (by tumor) and 64% (by patient)	2-yr OS, 38%	1 liver failure, 2 severe late GI toxicities
Rusthoven et al. (2009) [25]	Phase I/II	47	63	0.75–97.98 mL (14.93 mL)	CRC (15) Lung (10) Breast (4) Ovarian (3) Esophageal (3) HCC (2) Other (10)	Dose escalation, 36–60 Gy (3 fx)	16 mo	1-yr LC, 95%; 2-yr LC, 92%	Median survival, 20.5 mo, 2-yr OS, 30%	No RILD 1 grade 3 soft tissue toxicity
Lee et al. (2009) [26]	Phase I/II	68	140	1.2–3,090 mL (75.9 mL)	CRC (40) Breast (12) Gallbladder (4) Lung (2) Anal canal (2) Melanoma (2) Other (6)	Individualized dose, 27.7–60 Gy (6 fx)	10.8 mo	1-yr LC, 71%	Median survival, 18 mo	No RILD 10% grade 3/4 acute toxicity, no grade 3/4 late toxicity
Ambrosino et al. (2009) [27]	Prospective cohort	27	1–3 lesions for each patient	20–165 mL (69 mL)	CRC (11) Other (16)	25–60 Gy (3 fx)	13 mo	Crude LC rate 74%		No serious toxicity
Rule et al. (2011) [28]	Phase I	27	37	NR		Dose escalation, 30 Gy (3 fx), 50 Gy (3 fx), 60 Gy (5 fx)	20 mo	24-mo LC: (30 Gy) 56%; (50 Gy) 89%; (60 Gy) 100		No serious toxicity
Scorsetti et al. (2013) [29]	Phase II	61	76	1.8–134.3 mL (18.6 mL)	CRC (29) Breast (11) GY (7) Other (14)	75 Gy (3 fx)	12 mo	12-mo LC 94%	Median survival, 19 mo 12-mo OS, 83.5%; 18-mo OS, 65%	No RILD

SABR: stereotactic ablative radiotherapy; LC: local control; OS: overall survival; CRC: colorectal cancer; HCC: hepatocellular carcinoma; GY: gynecological; NR: not reported; fx: fractions; RILD: radiation-induced liver disease.



# Obiettivi dello studio:

- Controllo locale;
- Tossicità acuta e tardiva secondo scala RTOG.

PS < 2

N° lesioni epatiche  $\leq 3$

Pazienti non elegibili a chirurgia o ad altri trattamenti locali

Localizzazione della lesione (distanza da organi e grossi vasi  $> 8\text{mm}$ )

Funzionalità epatica residua: volume epatico sano  $\geq$  a  $700\text{ cm}^3$

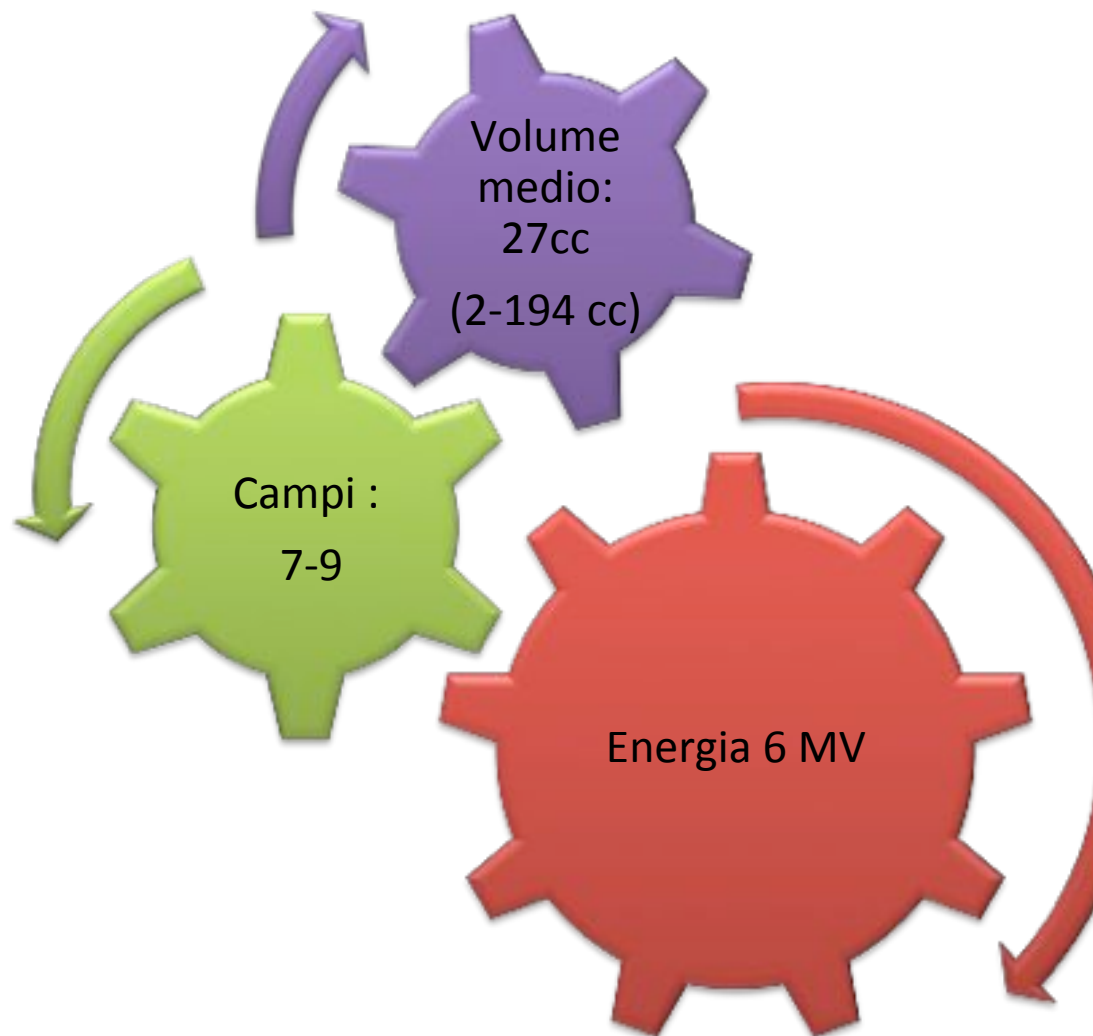
No. totale di pazienti	23 (dal 2007al 2014)	
No. totale di lesioni	34	
Età (anni)		
mediana	71	
range	46-83	
Pazienti sottoposti a chemioterapia		
si	22	96%
no	1	4%
Volume della lesione(cm3)		
Volume medio	27	
range	2-194	
PS		
0	12	52%
1	11	48%

**Frazionamenti:**

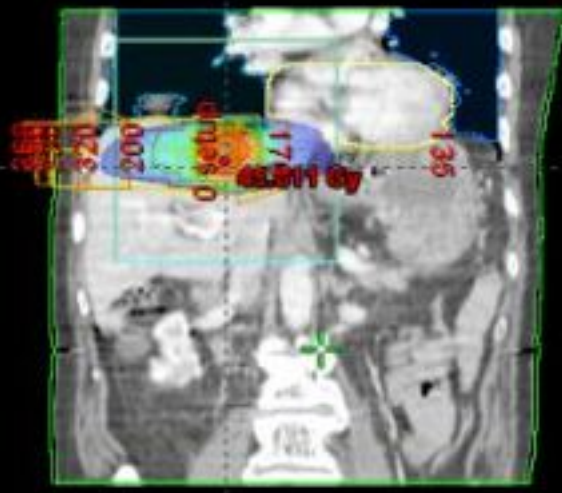
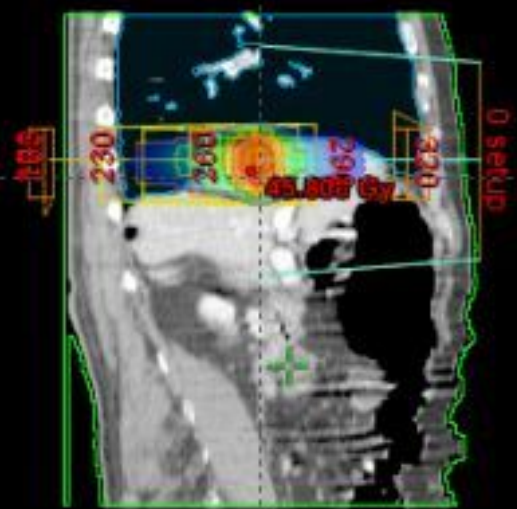
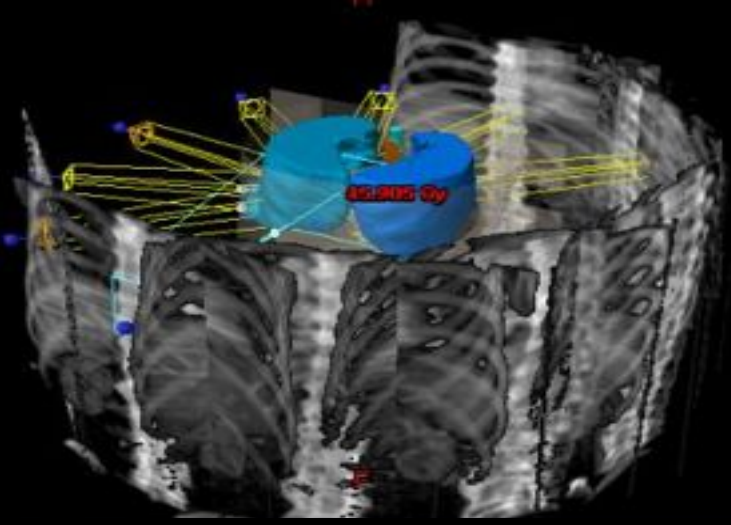
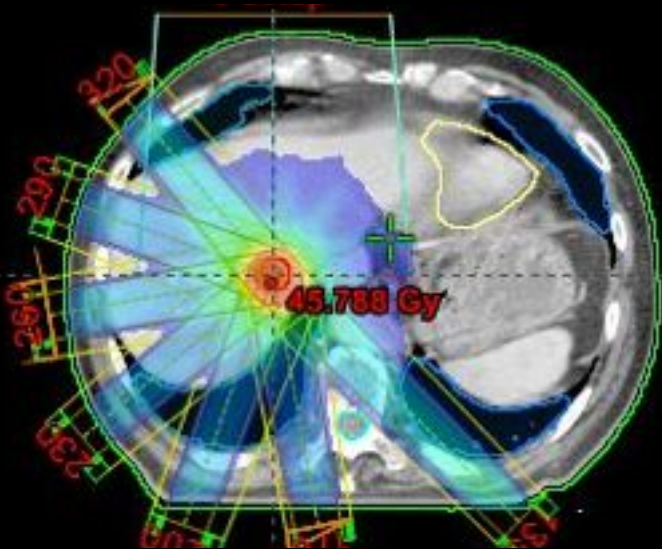
- 13 paz: 30 Gy in unica frazione
- 17 paz: 23 Gy in unica frazione
- 4 paz: 45 Gy in 3 frazioni

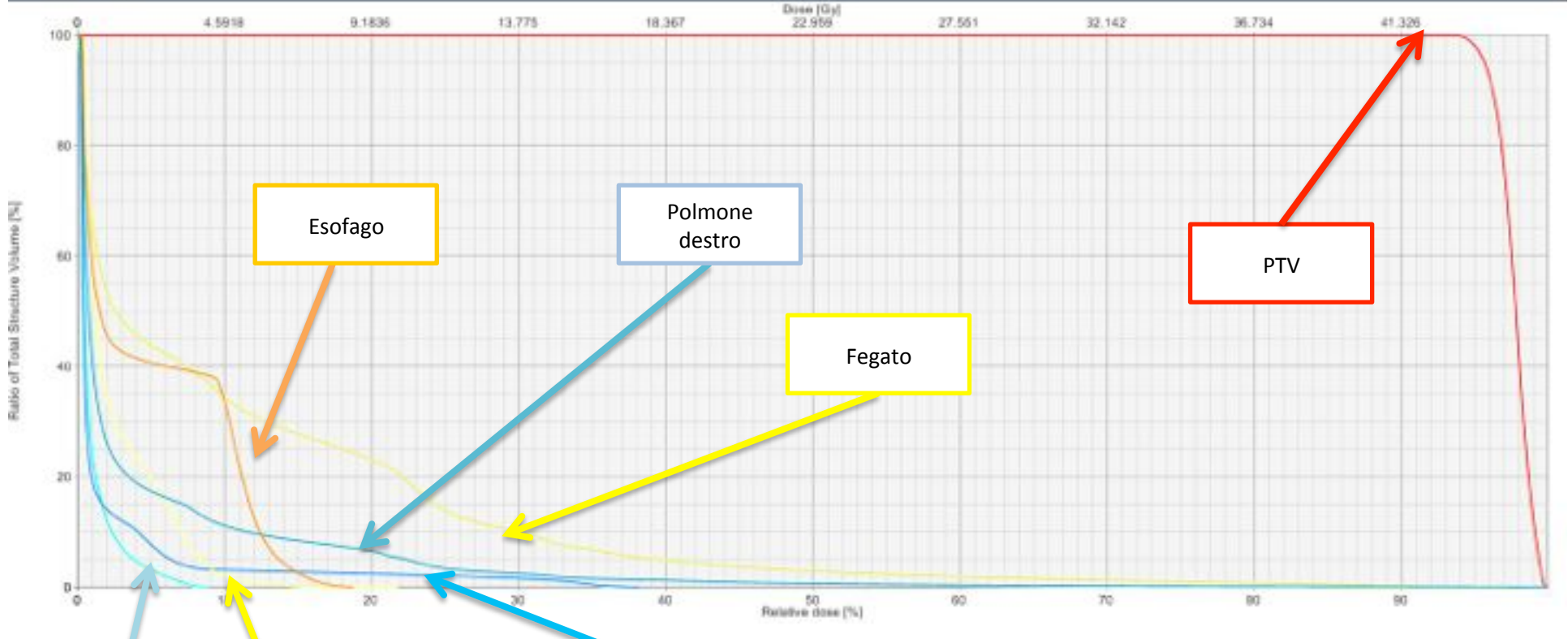
La dose ed il tipo di frazionamento dipendono da:

- dimensioni della lesione;
- vicinanza degli organi a rischio → riduzione di tossicità (sec. RTOG).



La valutazione sul controllo locale e sulla sopravvivenza libera da progressione di malattia è effettuata basandosi sui criteri RECIST 1.1





Midollo spinale

Cuore

Esophago

Polmone destro

Fegato

Polmone sinistro

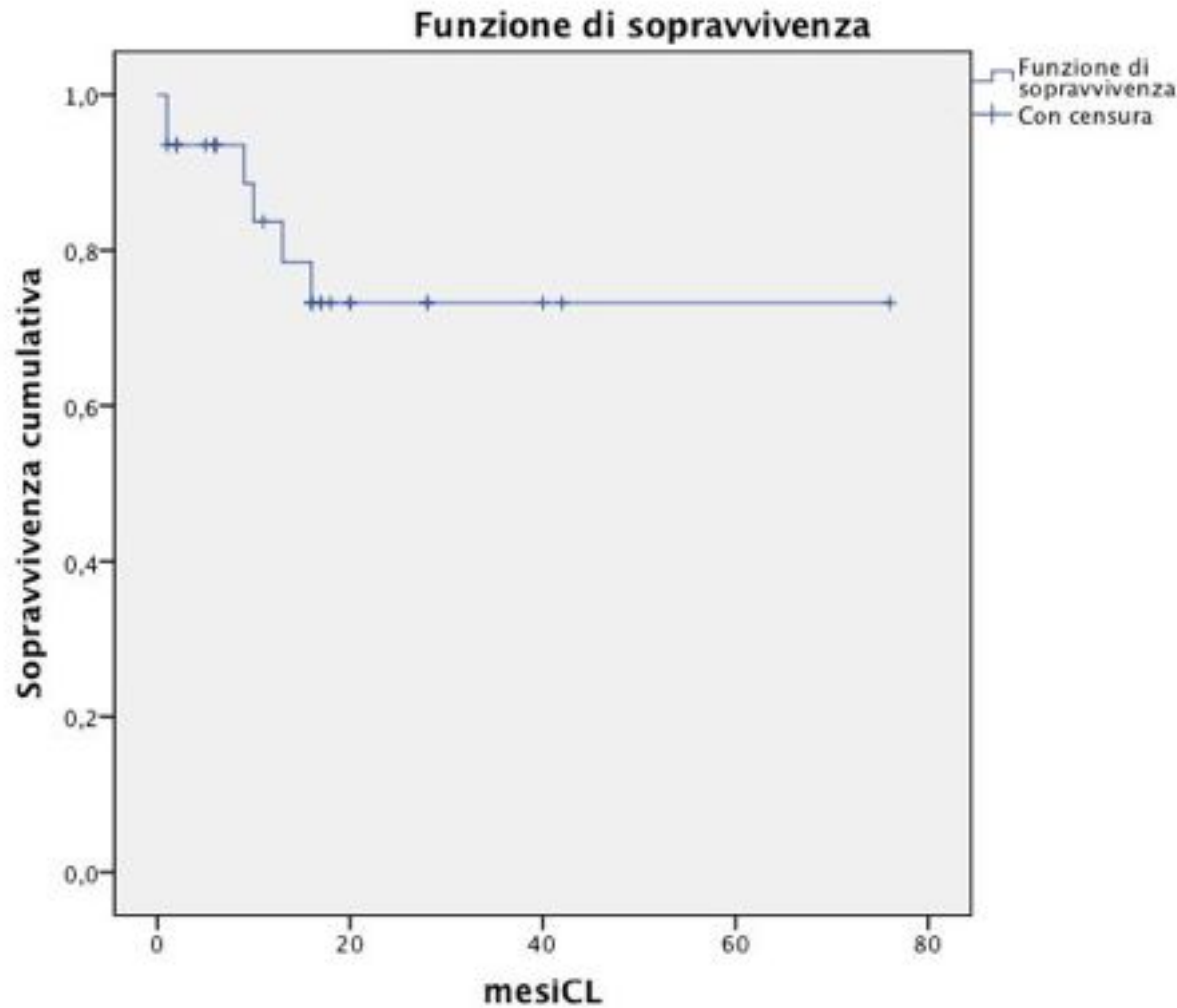
PTV

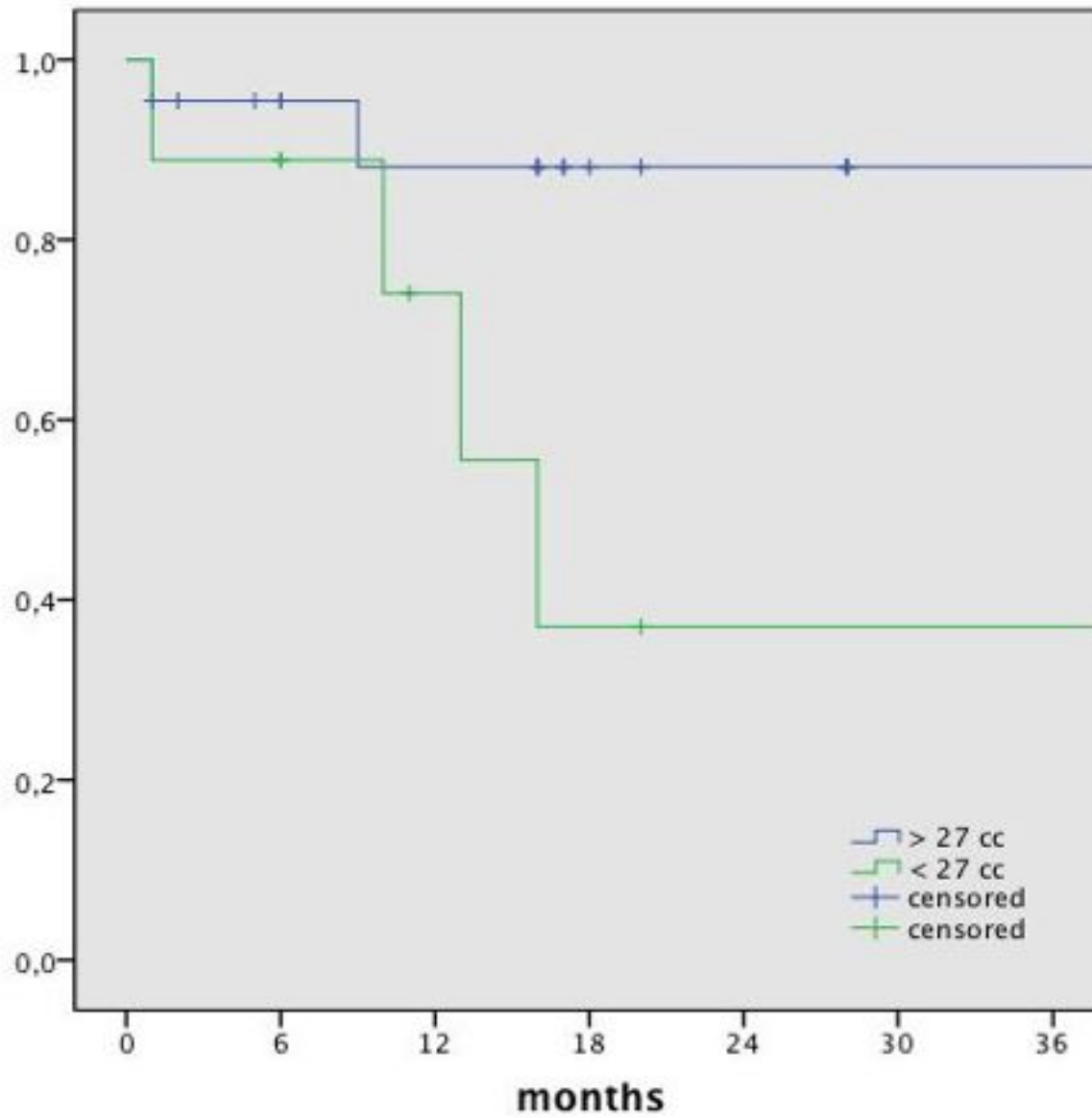
# RISULTATI:

## CONTROLLO LOCALE

-1 anno → 94%

-2anni → 74 %

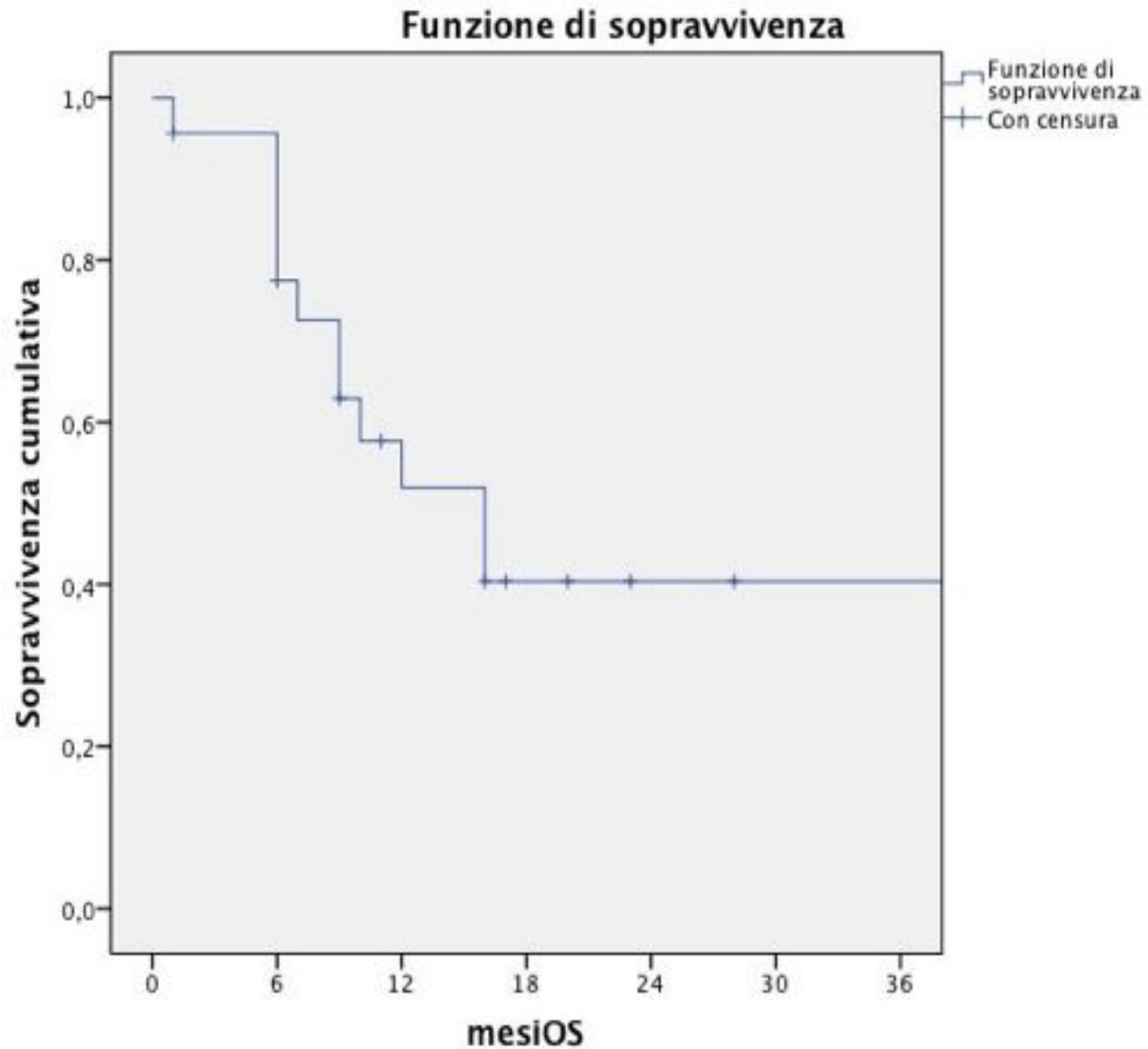




Log-rank test  
P=0.033



## OVERALL SURVIVAL



1 anno → 58%

2 anni → 41%

Mediana di sopravvivenza



16 mesi

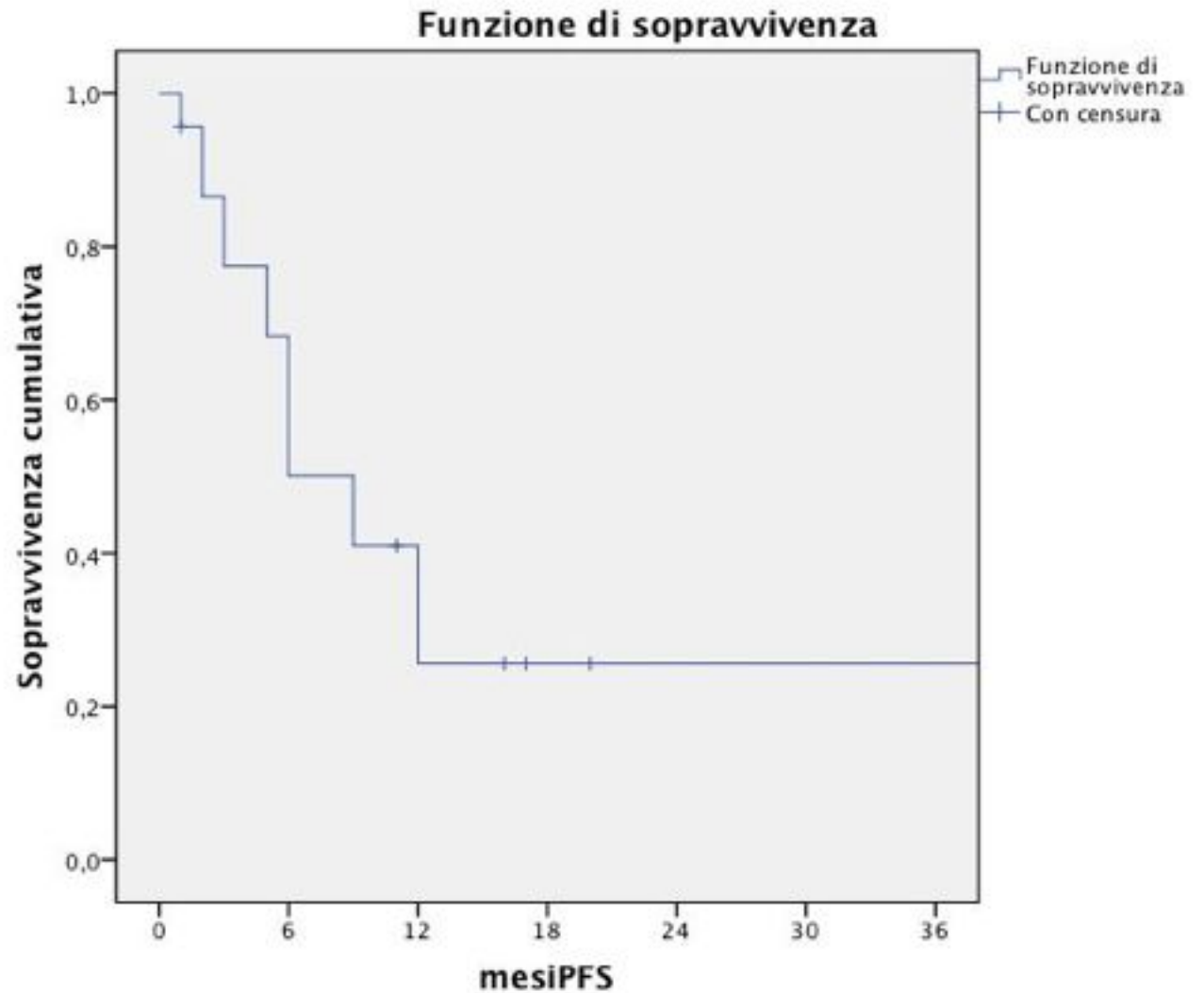
# SOPRAVVIVENZA LIBERA DA PROGRESSIONE DI MALATTIA

1 anno → 51%  
2 anni → 26 %

Mediana PFS



9 mesi



# RISULTATI

- Tossicità acuta:
  - G-I G1 in 1/23 paz
  - G-I G2 in 1/23 paz
- Tossicità tardiva:
  - G-I G1 in 3/23 paz

# CONCLUSIONI:

In conclusione la radioterapia stereotassica nel trattamento delle metastasi epatiche presenta dei vantaggi:

- carattere non invasivo del trattamento;
- breve durata del trattamento;
- buoni risultati in termini di controllo locale;
- effetti secondari limitati.

GRAZIE PER L'ATTENZIONE



Associazione  
Italiana  
Radioterapia  
Oncologica