RADIOCHIRURGIA E RADIOTERAPIA STEREOTASSICA NELLE METASTASI CEREBRALI IN ACCORDO AI NUOVI INDICI PROGNOSTICI

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INT Fondazione G. Pascale
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ISTITUTO NAZIONALE TUMORI
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Treatment recommendations are based on

- **PATIENT FACTORS**

  age, performance status (PS)

- **TUMOR FACTORS**

  number and size of brain metastases

  tumor type

  extracranial disease activity

- **AVAILABLE TREATMENT OPTIONS**

  access to neurosurgery or stereotactic radiosurgery

PROGNOSTIC SYSTEMS...

Classifications of Recursive Partitioning Analysis **RPA**

	Class 1	Class 2	Class 3
KPS	**≥70**	**≥70**	**<70**
Primary status	Controlled	Uncontrolled	
Age (y)	<65	≥65	
Extra-cranial disease status	Brain only	Brain plus other sites	

Median survival was
7.1 months class I
4.2 months class II
2.3 months class III

GPA GRADED PROGNOSTIC ASSESSMENT

Parameter	GPA Score		
	0	**0.5**	**1.0**
age (yrs)	**>60**	**50–59**	**<50**
KPS score	**<70**	**70–80**	**90–100**
no. of CNS metastases	**>3**	**2–3**	**1**
extracranial metastases	**present**	**NA**	**none**

prognostic index based on 1960 patients treated with WBRT alone, WBRT and radiosensitizers, or WBRT and RSR in the RTOG database, with all patients and data coming from prospective clinical trials.

Brain metastases are a heterogeneous population.....

PROGNOSTIC SYSTEMS...

The GPA was then refined based on a multi institutional analysis of 4259

New diagnosis specific prognostic indices (diagnosis-specific graded prognostic assessment) were defined based only on the statistically significant prognostic factors for each individual diagnosis

Table 3 Diagnosis-specific GPA[15,20,21]

GPA	Significant prognostic factors	GPA scoring criteria

Table 4 Median survivals stratified by diagnosis and diagnosis-specific GPA score for patients with newly diagnosed brain metastases[15,20,21]

Diagnosis	Overall median survival (mo)	Diagnosis-specific GPA			
		GPA: 0-1 Median survival (mo)	GPA: 1.5-2.0 Median survival (mo)	GPA: 2.5-3.0 Median survival (mo)	GPA: 3.5-4.0 Median survival (mo)
NSCLC	7.0	3.0	5.5	9.4	14.8
SCLC	4.9	2.8	4.9	7.7	17.1
Melanoma	6.7	3.4	4.7	8.8	13.2
Renal cell	9.6	3.3	7.3	11.3	14.8
GI	5.4	3.1	4.4	6.9	13.5
Breast	13.8	3.4	7.7	15.1	25.3
Total	7.2	3.1	5.4	9.6	16.7

GI, gastrointestinal; GPA, graded prognostic assessment; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

ECM, extracranial metastases; ER, estrogen receptor; GPA, graded prognostic assessment; Her2, human epidermal growth factor receptor 2; KPS, Karnofsky performance status; #BM, number of brain metastases; NSCLC, non-small cell lung cancer; PR, progesterone receptor; RCC, renal cell carcinoma; SCLC, small cell lung cancer.

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La Nostra Esperienza…

RADIOCHIRURGIA E RADIOTERAPIA STEREOTASSICA NELLE METASTASI CEREBRALI IN ACCORDO AI NUOVI INDICI PROGNOSTICI

SCOPO

Valutare il controllo locale e la sopravvivenza nei pazienti con metastasi cerebrali singole o multiple trattati con radiochirurgia o radioterapia stereotassica in accordo ai nuovi indici prognostici

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La Nostra Esperienza…

MATERIALI E METODI

ELEGIBILITY CRITERIA

Radiosurgery (SRS)

- good performance status KPS >70
- n° of lesions ≤ 4
- limited volume (Ø < 3-4 cm)
- good prognosis (expected survival >6 months)
- controlled extracranial disease

Fractionated stereotactic RT (FSRT)

- If lesion has a Ø > 3 cm (or volume > 14 cc)
- If lesion is near critical structure/s

La Nostra Esperienza…

MATERIALI E METODI

- **Novembre 2012- Marzo 2014: 116 pz (178 lesioni)**

Caratteristiche dei pazienti

	N°	%
Number of patients	116	100%
Gender		
M	64	55%
F	52	45%
Age		
median (y)	62	
range	29-86	
S.D.	11.69	
KPS scale		
<70	4	3%
70-80	12	10%
90-100	100	86%
N° of treated lesions		
1	64	55%
2	25	22%
3	14	12%
>3	13	11%

	N°	%
Extracranial metastatic organs		
0	42	36%
1	44	38%
≥2	30	26%
Primary Site		
NSCLC	50	43%
SCLC	1	1%
Melanoma	18	16%
RCC	4	3%
Breast cancer	23	20%
GI cancer	7	6%
Other	13	11%
Prior WBRT	21	18%
Prior WBRT+boost	4	3%

La Nostra Esperienza…

MATERIALI E METODI

Classificazione dei pazienti in accordo con la Diagnosis-Specific GPA (DS-GPA)

	DS-GPA				
Primary tumor	**0-1.0**	**1.5-2.0**	**2.5-3.0**	**3.5-4.0**	**N° tot**
NSCLC	3(6%)	24 (48%)	18 (36%)	5 (10%)	50
SCLC	-	-	-	1 (100%)	1
Melanoma	1(5%)	1 (5%)	3 (18%)	13(72%)	18
RCC	-	2 (50%)	2 (50%)	-	4
Breast cancer	1 (5%)	6 (26%)	10 (43%)	6 (26%)	23
GI cancer	3(43%)	1 (14%)	1 (14%)	2 (29%)	7
Other	2 (15%)	4 (31%)	5 (39%)	2 (15%)	13
N pz	10	38	39	29	

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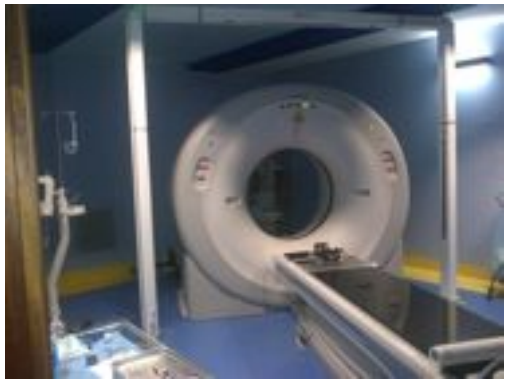
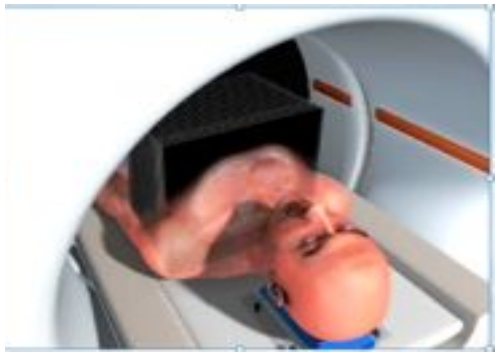
La Nostra Esperienza…

CT/Set-up



Simul-TC con mdc
Slice 1mm



RM T1-T2W con mdc
Slice 1mm

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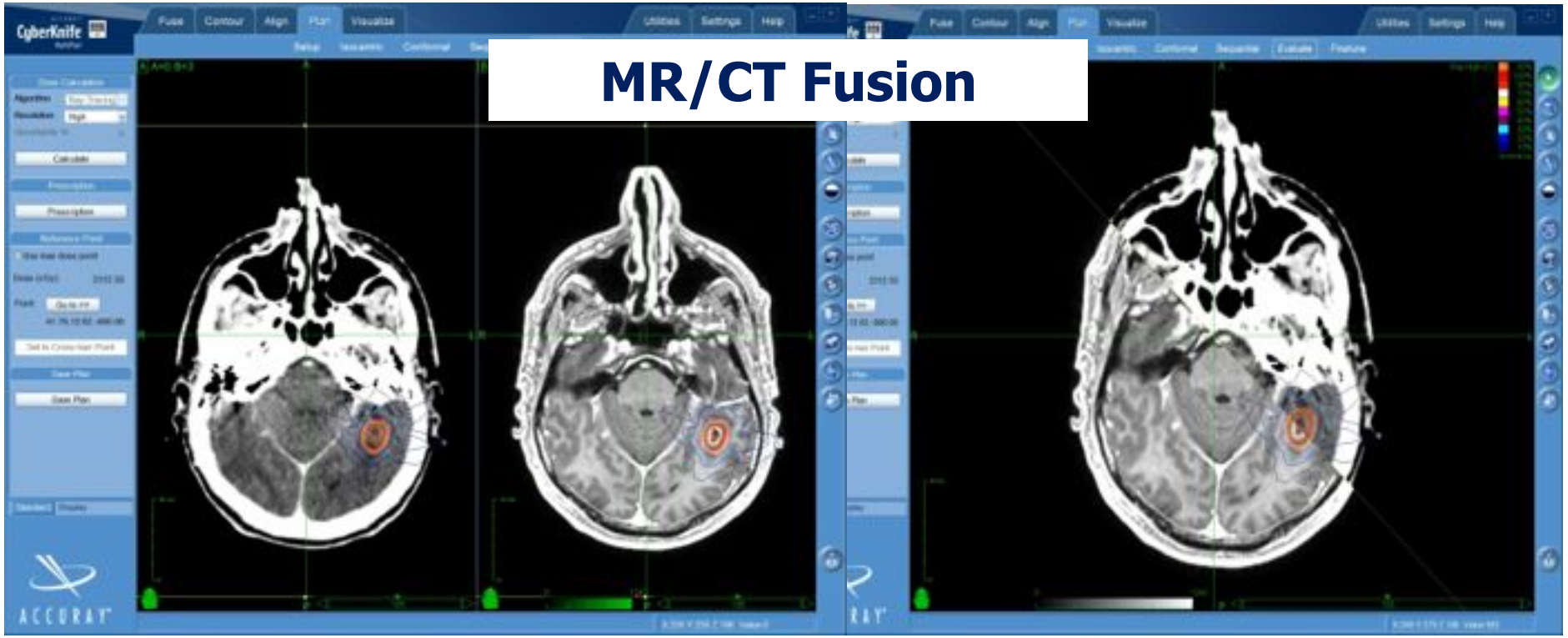
La Nostra Esperienza…

Contouring



MR/CT Fusion

VOLUMES

GTV: tumor

CTV = GTV

PTV: is CTV plus 2 mm margin

OARs

Lens	Optic chiasm	
Optic nerve	Eyes	
Whole brain	Brain stem	
Spinal cord	choclea	Skin

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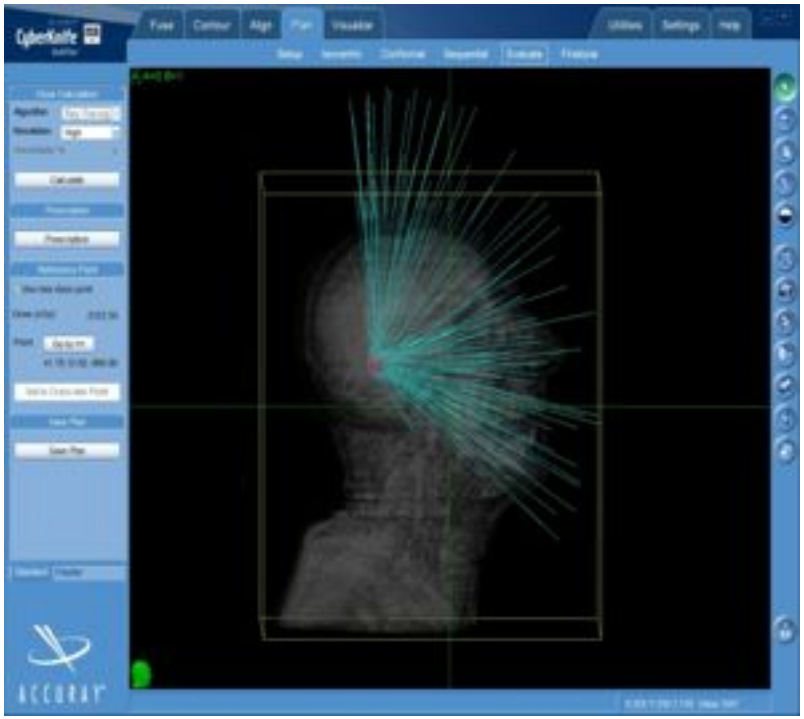
La Nostra Esperienza…

Planning



- 72% frazione singola (range10-24 Gy)
- 3% due frazioni (range 18-21 Gy)
- 23% tre frazioni (range 18-24Gy)
- 2% con cinque frazioni (range 20-25Gy)

La dose è stata prescritta all'isodose dell'80%

Volume 18, Number 4 October 2008

Seminars in RADIATION ONCOLOGY

ELSEVIER

CONSTRAINTS

An Overview of Hypofractionation and Introduction to This Issue of *Seminars in Radiation Oncology*

Table 2 Mostly Unvalidated Normal Tissue Dose Constraints for SBRT

SINGLE-FRACTION TREATMENT

Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Optic pathway	<0.2	8	10	Neuritis
Cochlea			12	Hearing loss
Brainstem	<1	10	15	Cranial neuropathy
Spinal cord	<0.25	10	14	Myelitis
	<1.2	7		
Cauda equina	<5	14	16	Neuritis
Sacral plexus	<3	14.4	16	Neuropathy
Esophagus*	<5	14.5	19	Stenosis/fistula
Ipsilateral brachial plexus	<3	14.4	16	Neuropathy
Heart/pericardium	<15	16	22	Pericarditis
Great vessels	<10	31	37	Aneurysm
Trachea and ipsilateral bronchus*	<4	8.8	22	Stenosis/fistula
Skin	<10	14.4	16	Ulceration
Stomach	<10	13	16	Ulceration/fistula
Duodenum*	<5	8.8	16	Ulceration
Jejunum/ileum*	<5	9.8	19	Enteritis/obstruction
Colon*	<20	11	22	Colitis/fistula
Rectum*	<20	11	22	Proctitis/fistula
Bladder wall	<15	8.7	22	Cystitis/fistula
Penile bulb	<3	14	34	Impotence
Femoral heads (right and left)	<10	14		Necrosis
Renal hilum/vascular trunk	<2/3 volume	10.6		Malignant hypertension

Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	7	Basic lung function
Lung (right and left)	1,000	7.4	Pneumonitis
Liver	700		
Renal cortex (right and left)	200		

THREE-FRACTION TREATMENT

Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Optic pathway	<0.2	15 (5 Gy/fx)	19.5 (6.5 Gy/fx)	Neuritis
Cochlea			20 (6.67 Gy/fx)	Hearing loss
Brainstem	<1	18 (6 Gy/fx)	23 (7.67 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25	18 (6 Gy/fx)	22 (7.33 Gy/fx)	Myelitis
	<1.2	11.1 (3.7 Gy/fx)		
Cauda equina	<5	21.9 (7.3 Gy/fx)	24 (8 Gy/fx)	Neuritis
Sacral plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Esophagus*	<5	21 (7 Gy/fx)	27 (9 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Neuropathy
Heart/pericardium	<15	24 (8 Gy/fx)	30 (10 Gy/fx)	Pericarditis
Great vessels	<10	39 (13 Gy/fx)	45 (15 Gy/fx)	Aneurysm
Trachea and ipsilateral bronchus*	<4	15 (5 Gy/fx)	30 (10 Gy/fx)	Stenosis/fistula
Skin	<10	22.5 (7.5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Stomach	<10	21 (7 Gy/fx)	24 (8 Gy/fx)	Ulceration/fistula
Duodenum*	<5	15 (5 Gy/fx)	24 (8 Gy/fx)	Ulceration
Jejunum/ileum*	<5	16.2 (5.4 Gy/fx)	27 (9 Gy/fx)	Enteritis/obstruction
Colon*	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Colitis/fistula
Rectum*	<20	20.4 (6.8 Gy/fx)	30 (10 Gy/fx)	Proctitis/fistula
Bladder wall	<15	15 (5 Gy/fx)	30 (10 Gy/fx)	Cystitis/fistula
Penile bulb	<3	21.9 (7.3 Gy/fx)	42 (14 Gy/fx)	Impotence
Femoral heads (right and left)	<10	21.9 (7.3 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	18.6 (6.2 Gy/fx)		Malignant hypertension

Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	10.5 (3.5 Gy/fx)	Basic lung function
Lung (right and left)	1,000	11.4 (3.8 Gy/fx)	Pneumonitis
Liver	700	17.1 (5.7 Gy/fx)	Basic liver function
Renal cortex (right and left)	200	14.4 (4.8 Gy/fx)	Basic renal function

FIVE-FRACTION TREATMENT

Serial Tissue	Volume (mL)	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Optic pathway	<0.2	20 (4 Gy/fx)	25 (5 Gy/fx)	Neuritis
Cochlea			27.5 (5.5 Gy/fx)	Hearing loss
Brainstem	<1	26 (5.2 Gy/fx)	31 (6.2 Gy/fx)	Cranial neuropathy
Spinal cord	<0.25	22.5 (4.5 Gy/fx)	30 (6 Gy/fx)	Myelitis
	<1.2	13.5 (2.7 Gy/fx)		
Cauda equina	<5	30 (6 Gy/fx)	34 (6.4 Gy/fx)	Neuritis
Sacral plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Esophagus*	<5	27.5 (5.5 Gy/fx)	35 (7 Gy/fx)	Stenosis/fistula
Ipsilateral brachial plexus	<3	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Neuropathy
Heart/pericardium	<15	32 (6.4 Gy/fx)	38 (7.6 Gy/fx)	Pericarditis
Great vessels	<10	47 (9.4 Gy/fx)	53 (10.6 Gy/fx)	Aneurysm
Trachea and ipsilateral bronchus*	<4	18 (3.6 Gy/fx)	38 (7.6 Gy/fx)	Stenosis/fistula
Skin	<10	30 (6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Stomach	<10	28 (5.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration/fistula
Duodenum*	<5	18 (3.6 Gy/fx)	32 (6.4 Gy/fx)	Ulceration
Jejunum/ileum*	<5	19.5 (3.9 Gy/fx)	35 (7 Gy/fx)	enteritis/obstruction
Colon*	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	colitis/fistula
Rectum*	<20	25 (5 Gy/fx)	38 (7.6 Gy/fx)	proctitis/fistula
Bladder wall	<15	18.3 (3.65 Gy/fx)	38 (7.6 Gy/fx)	cystitis/fistula
Penile bulb	<3	30 (6 Gy/fx)	50 (10 Gy/fx)	Impotence
Femoral heads (right and left)	<10	30 (6 Gy/fx)		Necrosis
Renal hilum/vascular trunk	<2/3 volume	23 (4.6 Gy/fx)		Malignant hypertension

Parallel Tissue	Critical Volume (mL)	Critical Volume Dose Max (Gy)	Endpoint (≥Grade 3)
Lung (right and left)	1,500	12.5 (2.5 Gy/fx)	Basic lung function
Lung (right and left)	1000	13.5 (2.7 Gy/fx)	Pneumonitis
Liver	700	21 (4.2 Gy/fx)	Basic liver function
Renal cortex (right and left)	200	17.5 (3.5 Gy/fx)	Basic renal function

*Avoid circumferential irradiation.

CONSTRAINTS

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Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy

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Complications of Treatment

Stereotactic radiosurgery and hypofractionated stereotactic radiotherapy: Normal tissue dose constraints of the central nervous system

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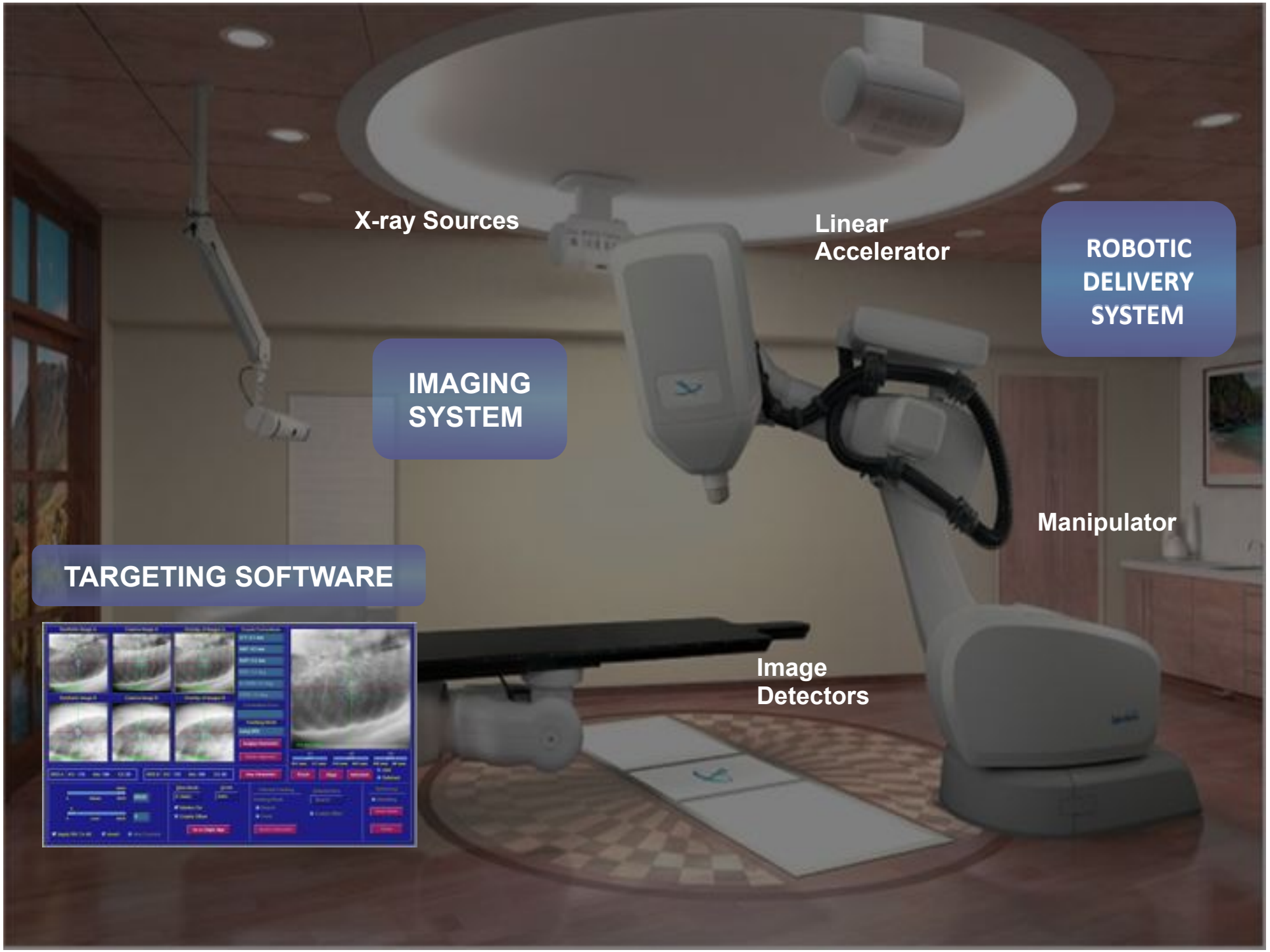
Table 2
Summary of central nervous system dose expected to yield acceptable toxicity outcomes after single fraction SRS.

Structure	Outcome	Constraint
Brain parenchyma[a]	Necrosis	Tissue V12 <5–10 ml Tissue V10 <10 ml
Brainstem	Necrosis or neurologic deficits	<10–12 Gy maximum
Optic nerve/optic chiasm	Vision loss, anopsia, decreased visual acuity	<10–12 Gy maximum
Carotid artery	Occlusion	<20–23 Gy maximum
Acoustic neuroma	Symptomatic cranial nerve V and/or VII neuropathy	<12–13 Gy at tumor margin
	Hearing preservation	<12–13 Gy at tumor margin
Modiolus of cochlea	Hearing preservation	<4–5 Gy maximum
Cochlea	Hearing preservation	<6 Gy maximum
Spinal cord (RTOG 06-31)	Symptomatic myelopathy	0.35 ml <10 Gy[b] 0.035 ml <14 Gy[b]
Cauda equina (RTOG 06-31)	Symptomatic neuritis	<16 Gy maximum[b] 5 ml <14 Gy[b]
Spinal cord (conservative)	Symptomatic myelopathy	<8–10 Gy maximum
Thecal sac (conservative)	Symptomatic myelopathy	<10–14 Gy maximum


X-ray Sources
Linear Accelerator
ROBOTIC DELIVERY SYSTEM
IMAGING SYSTEM
Manipulator
TARGETING SOFTWARE
Image Detectors

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La Nostra Esperienza…

Delivery

Skull Tracking System

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La Nostra Esperienza...

RISULTATI

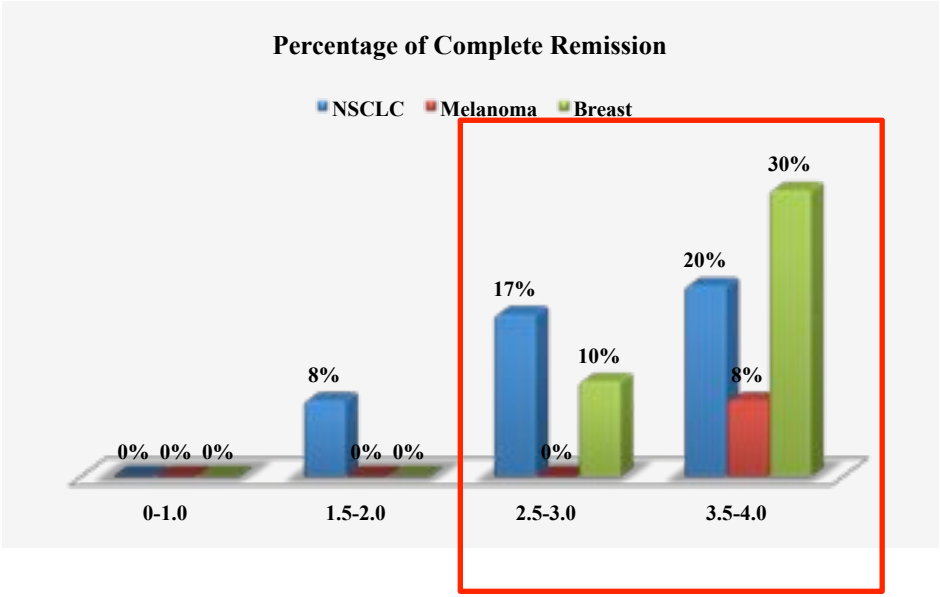
Overall median survival and local tumor control rate stratified by diagnosis and diagnosis-specific GPA score

Diagnosis	OS median (mo)	Local Tumor Control Rate							N°
		CR	PR	SD	PD	(n-e)	no FU	death	tot
NSCLC									
0-1.0	2	0	0	1(33%)	0	2(66%)	0	0	3
1.5-2.0	4(2-17)	2(8%)	5(21%)	3(13%)	3(12%)	4(16%)	3(12%)	4(16%)	24
2.5-3.0	5(2-17)	3(17%)	2(11%)	1(5%)	4(22%)	0	3(17%)	5(28%)	18
3.5-4.0	5(2-10)	1(20%)	1(20%)	0	3(60%)	0	0	0	5
Melanoma									
0-1.0	3	0	0	0	0	0	0	1(100%)	1
1.5-2.0	5	0	0	0	1(100%)	0	0	0	1
2.5-3.0	11(6-14)	0	1(33%)	0	1(33%)	0	0	1(33%)	3
3.5-4.0	3.5(2-5)	1(8%)	3(23%)	0	3(23%)	5(38%)	0	1(8%)	13
Breast									
0-1.0		0	0	0	0	0	1(100%)	0	1
1.5-2.0	2.5(1-4)	0	1(17%)	1(17%)	0	0	0	4(66%)	6
2.5-3.0	8(4-12)	1(10%)	2(20%)	2(20%)	2(20%)	1(10%)	2(20%)	0	10
3.5-4.0	7(3-12)	2(30%)	0	3(50%)	1(20%)	0	0	0	6

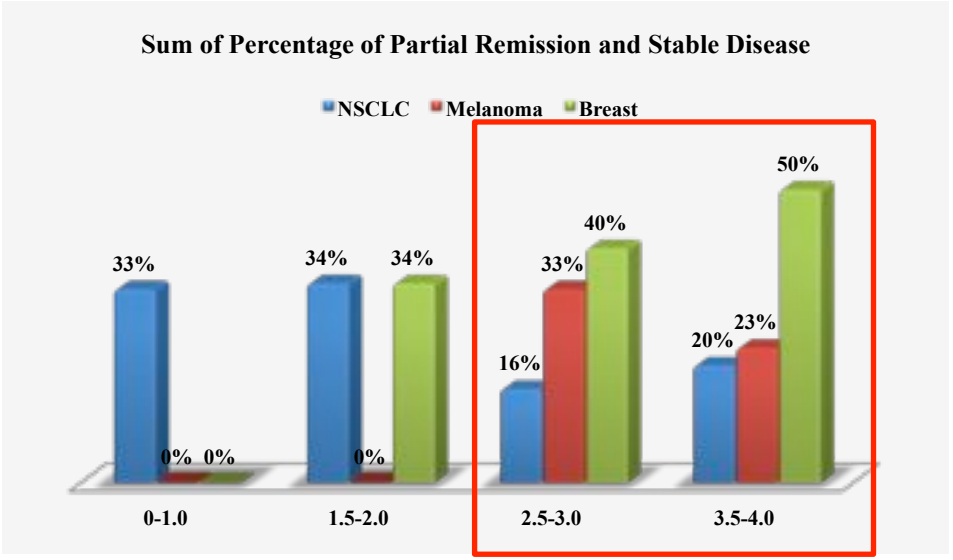
La Nostra Esperienza…

RISULTATI

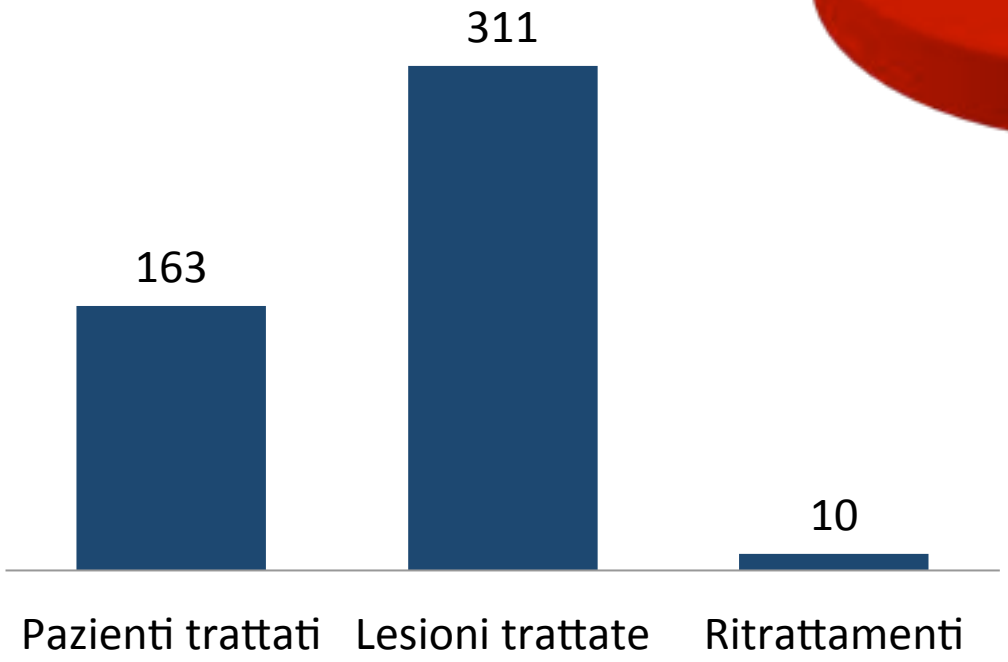
Percentage of complete remission (CR) in NSCLC, Melanoma and Breast Stratified by DS-GPA

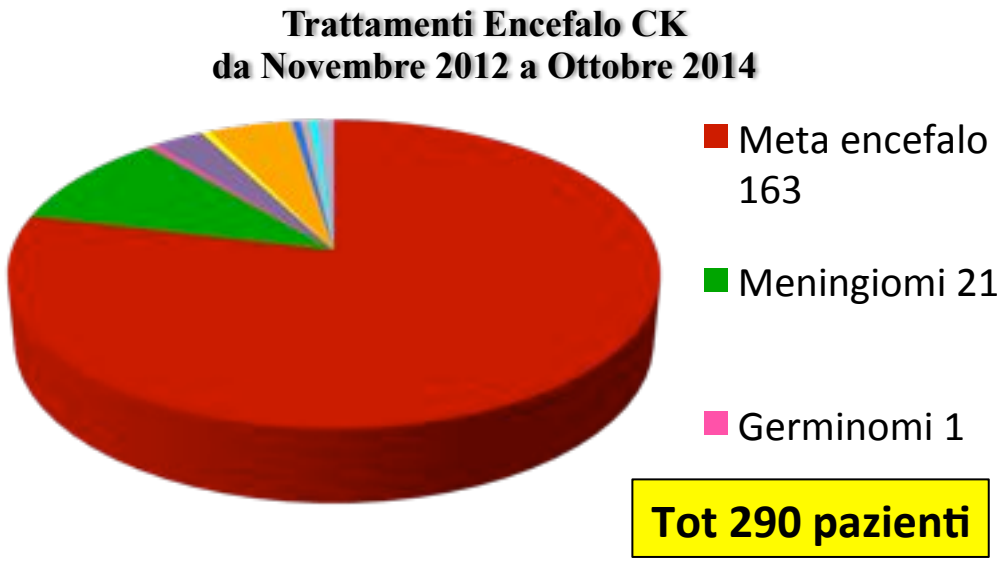


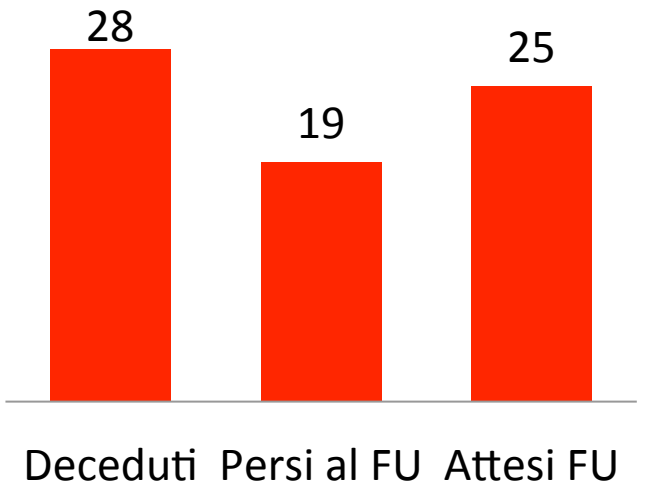
Sum of percentage of partial remission (PR) and stable disease (SD) in NSCLC, Melanoma and Breast Stratified by DS-GPA

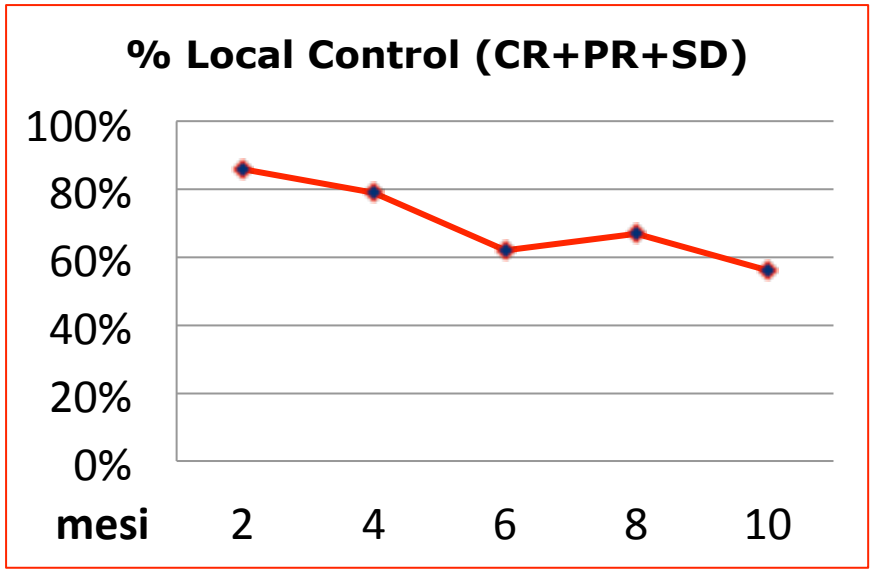


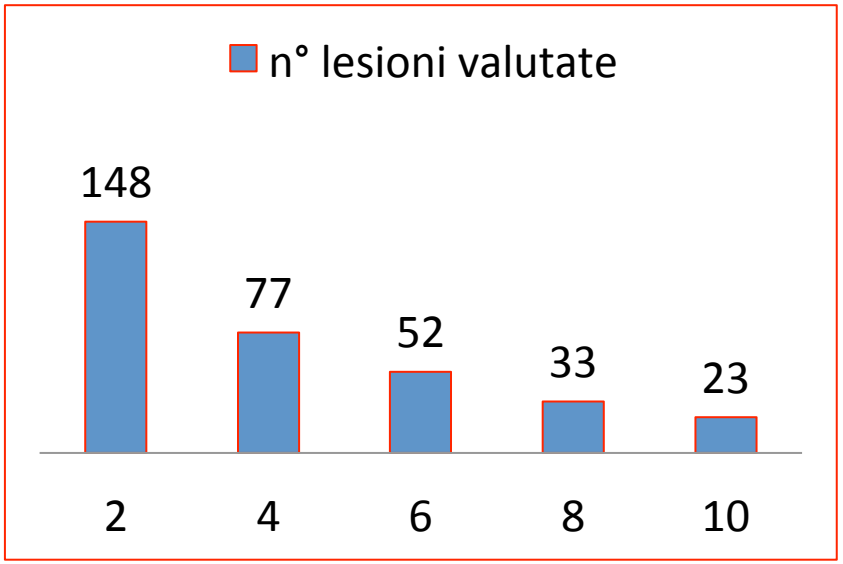
Ad oggi…..

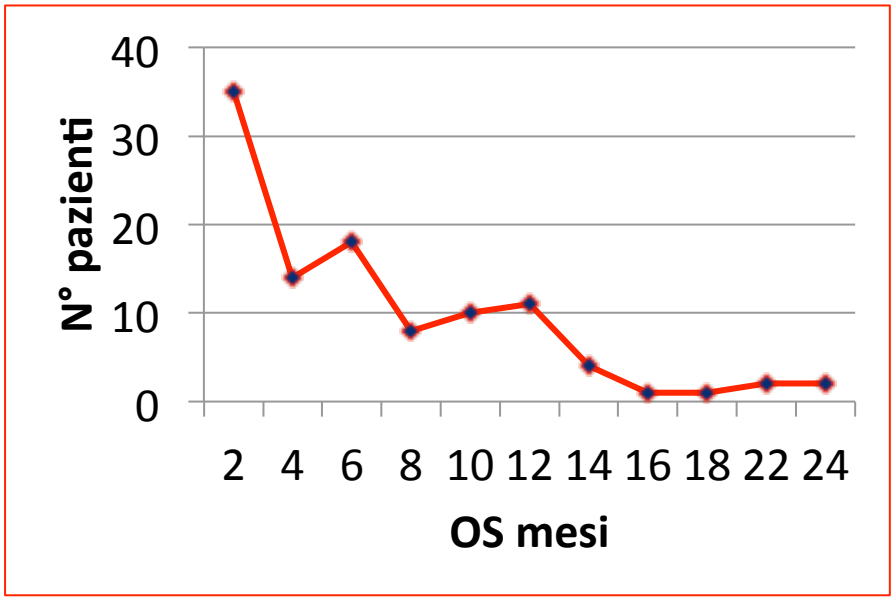

311
163
10
Pazienti trattati
Lesioni trattate
Ritrattamenti


Trattamenti Encefalo CK
da Novembre 2012 a Ottobre 2014
Meta encefalo 163
Meningiomi 21
Germinomi 1
Tot 290 pazienti


28
19
25
Deceduti
Persi al FU
Attesi FU


% Local Control (CR+PR+SD)
100%
80%
60%
40%
20%
0%
mesi
2
4
6
8
10


n° lesioni valutate
148
77
52
33
23
2
4
6
8
10


N° pazienti
40
30
20
10
0
2 4 6 8 10 12 14 16 18 22 24
OS mesi

La Nostra Esperienza…

CONCLUSIONI

- **Un buon controllo locale (CR, PR E SD) nelle classi a miglior prognosi sembrerebbe confermare il prezioso contributo della DS-GPA nella corretta selezione dei pazienti con BMs, specialmente se si utilizzano tecnologie avanzate come il Cyberknife**

- **L'Overall Survival sembrerebbe essere in linea con quella di altri studi monoistituzionali essendo influenzata da un follow-up troppo breve**

- **È necessario un più lungo FU per capire se il trattamento radiochirugico/ stereotassico delle BMs nei pazienti con buona prognosi può migliorare oltre che il controllo locale anche la sopravvivenza e offrire ai pazienti una miglior qualità di vita ritardando i possibili disturbi cognitivi legati al WBRT**

Grazie per l'attenzione