



# CyberKnife radiosurgery for single and multiple cerebral metastases - experiences of the Maria Skłodowska-Curie Memorial Cancer Center

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# Stereotactic radiosurgery or neurosurgery?

- ✓ 76 patients; 38 CyberKnife radiosurgery, 38 - surgery
- ✓ Similar baseline characteristics

	CyberKnife	surgery
1-year overall survival	53.5%	30.5%
1-year local control	50.8%	31.3%
1-year intracranial control	50.8%	27.7%

- ✓ OS associated with age, performance status and Graded Prognostic Assessment (GPA)

# Single dose versus fractionated stereotactic radiotherapy for brain metastases

	SRS	FSRT	p
Gender	39/19	16/24	<0.01
Median age	60	53	NS
KPS $\geq 70$ / $<70$	55/3	35/5	NS
No. of extracranial metastatic organs 0/1/ $\geq 2$	36/10/12	11/8/21	<0.01
RPA class	20/35/3	8/27/5	NS
GPA score	10/40/8	7/29/4	NS
New/recurrent metastasis	42/16	22/18	NS
No. of treated lesions 1/2/ $\geq 3$	43/9/6	34/3/3	NS
Previous WBRT (0/1)	16/12	24/16	0.04
Previous surgery (0/1)	48/10	36/4	NS

# Single dose versus fractionated stereotactic radiotherapy for brain metastases

- ✓ Median OS – 7 months
- ✓ SRS – median OS = 6 months
- ✓ FSRT – median OS = 8 months  $P=0.89$
- ✓ OS @ 6 months 53%, OS @ 12 months 34%
- ✓ SRS: OS @ 6 months 48%, OS @ 12 months 36%
- ✓ FSRT: OS @ 6 months 60%, OS @ 12 months 31%
- ✓ KPS  $\geq 70$ , controlled primary site, no extracranial metastases, lower RPA class, higher GPA score, single lesion in brain and no WBRT significant in univariate analysis
- ✓ Only the number of extracranial metastatic organs significant in multivariate analysis

# Fractionated stereotactic radiotherapy for brain metastases – the dose

- ✓ Three fractions – tumors > 2.5 cm but < 4 cm in diameter
- ✓ Five fractions – tumors larger than 4 cm
- ✓ Stepwise dose escalation

Steps	3 fractions	5 fractions
I stage	18-22 (6-7.3/fx) Gy	21-25 (4.2-5/fx) Gy
II stage	22-27 (7.3-9/fx) Gy	25-31 (5-6.2/fx) Gy
III stage – target level	27-30 (9-10/fx) Gy	31-35 (6.2-7/fx) Gy

# Fractionated stereotactic radiotherapy for brain metastases – the dose

- ✓ 54 patients, 61 large ( $\geq 2.5$  cm) metastases (102 metastases in total)
- ✓ No previous craniotomy
- ✓ No prior cranial irradiation
- ✓ Karnofsky performance status  $\geq 40$
- ✓ PTV = contrast-enhancing lesion + 2 mm
- ✓ At least five patients in each dose level
- ✓ Patients followed-up for at least 6 months to assess toxicity
- ✓ Dose escalation after assessment of dose-limiting toxicity
- ✓ FSRT delivered daily
- ✓ Accompanying smaller lesions treated with a single dose of 13-20 Gy

# Fractionated stereotactic radiotherapy for brain metastases – the dose

Volume	Number of lesions treated with FSRT		
	Level I	Level II	Level III
8-15 cm <sup>3</sup>	6	11	11
15-33 cm <sup>3</sup>	0	9	11
Over 33 cm <sup>3</sup>	3	6	4

## Fractionated stereotactic radiotherapy for brain metastases – the dose

- ✓ Median OS – 6 months
- ✓ OS @ 6 months: 52%, OS @ 12 months: 31%
- ✓ 43/50 died from extracranial disease progression
- ✓ Only the presence of extracranial disease associated with worse prognosis (HR: 2.91, 95% CI: 1.39-6.07)
- ✓ Local tumor control 84% @ 6 months and 78% @ 12 months (all mets)
- ✓ One-year local tumor control rates: **66%, 65%, and 68%** for **level I, II, and III**, respectively
- ✓ At the first evaluation after 1-3 months 41 large mets showed PR, 9 - SD, and 11 – PD of 61 treated
- ✓ LC significantly worse for the largest lesions ( $> 33 \text{ cm}^3$ )



# Purpose of the study

- ✓ Evaluation of outcome after single fraction and hypofractionated CyberKnife radiosurgery for brain metastases
- ✓ Comparison of outcomes in patients with single and multiple metastases
- ✓ Evaluation of usefulness of scoring indices and the dose and volume effects

## Material - patients

	All	SRS	FSRT	p
Gender	M-37/F-50	M-18/F-19	M-19/F-31	NS
Median age (range)	60 (30-84)	57 (30-82)	61 (30-84)	NS
KPS >70/≤70	77/10	34/3	44/6	NS
BSBM*	27/48/9/3	9/24/3/1	18/24/6/2	NS
RPA class	57/29/0	28/9/0	30/20/0	NS
GPA score**	7/44/21/15	4/22/6/5	3/22/15/10	NS
WBRT (0/1)	24/63 (72.4%)	7/30 (81%)	17/33 (66%)	NS
Surgery (0/1)	62/25 (28.7%)	22/15 (40%)	40/10 (20%)	0.02

\* Basic Score for Brain Metastases

\*\* Graded Prognostic Assessment: GPA I: 0-1, GPA II: 1.5-2.5, GPA III: 3, GPA IV: 3.5-4

## Material - patients

	All	Single lesion	Multiple metastases	p
Gender	M-37/F-50	M-24/F-24	M-13/F-26	NS
Median age (range)	60 (30-84)	62 (30-84)	56 (30-71)	NS
KPS >70/≤70	77/10	43/5	35/4	NS
BSBM*	27/48/9/3	16/28/2/2	11/20/7/1	NS
RPA class	57/29/0	27/21/0	31/8/0	0.02
GPA score**	7/44/21/15	0/24/14/10	7/20/7/5	NS
WBRT (0/1)	24/63 (72.4%)	21/27 (56%)	3/36 (92%)	0.0002
Surgery (0/1)	62/25 (28.7%)	39/9 (19%)	24/15 (38%)	0.04

\* Basic Score for Brain Metastases

\*\* Graded Prognostic Assessment: GPA I: 0-1, GPA II: 1.5-2.5, GPA III: 3, GPA IV: 3.5-4

# Material - patients

	Single fraction		FSRT		Total	
Primary site	No	%	No	%	No	%
Lung	13	35.1	17	34	30	34.5
Breast	7	18.9	18	36	25	28.7
Kidney	3	8.1	5	10	8	9.2
Melanoma	1	2.7	4	8	5	5.7
Colon and rectum	5	13.5	1	2	6	6.8
Unknown primary	3	8.1	0	0	3	3.4
Uterus	2	5.4	0	0	2	2.3
Other*	3	8.1	5	10	8	9.2
Total	37	42.5	50	57.5	87	100

\*laryngeal cancer, bladder cancer, seminoma, penile cancer, small intestine sarcoma, thyroid cancer, lymphoma, gastric cancer

# Material - patients

	Single fraction		FSRT		Total	
Number of lesions	No	%	No	%	No	%
1	20	54	28	56	48	55
2	8	21	10	20	18	21
≥3 (3-9)	9	25	12	24	21	24
Total Fraction doses:	37		50		87	

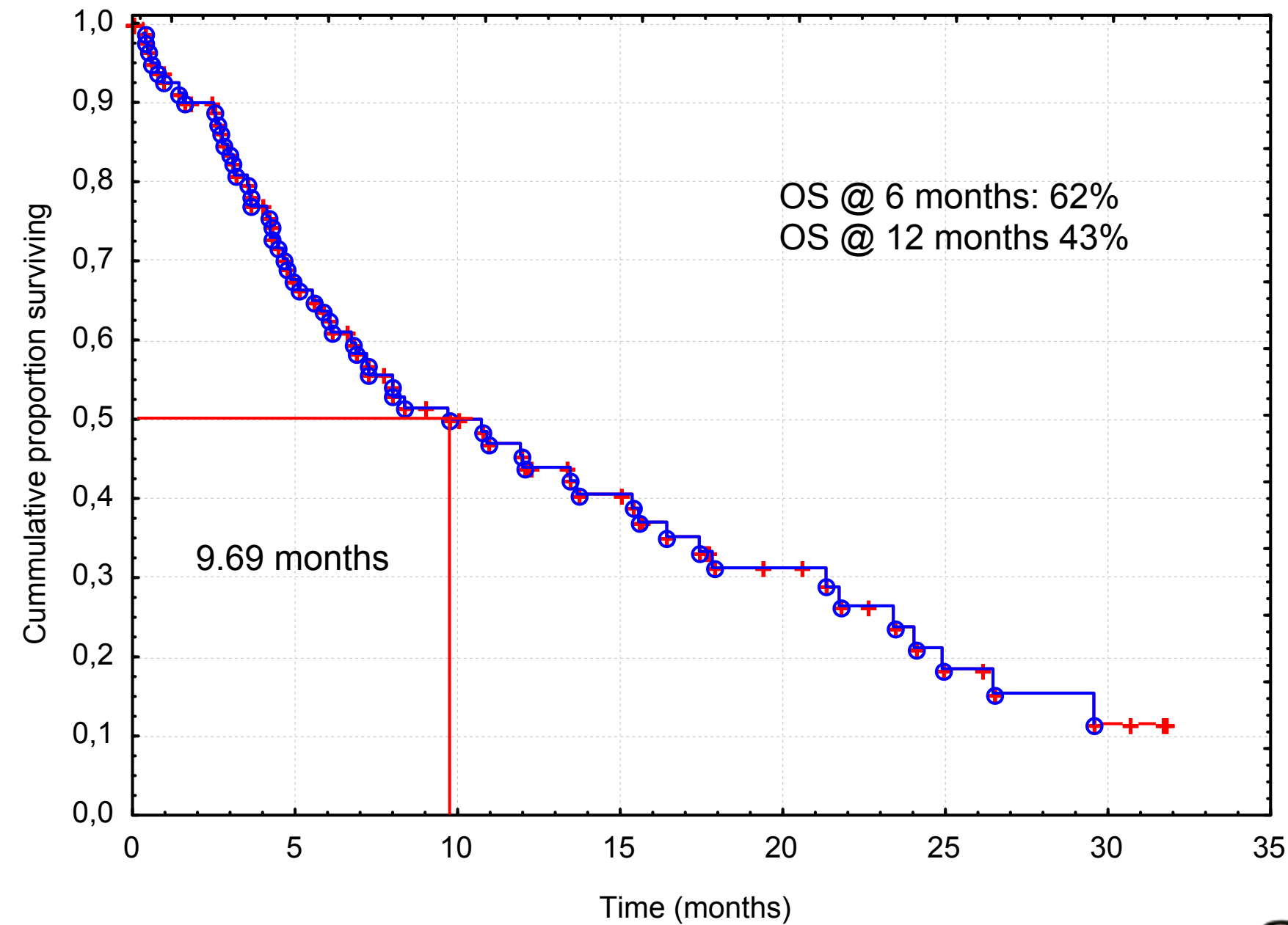
Single fraction: 8-24 Gy

Two fractions: 6-12 Gy

Three fractions: 5-8 Gy

# Overall survival

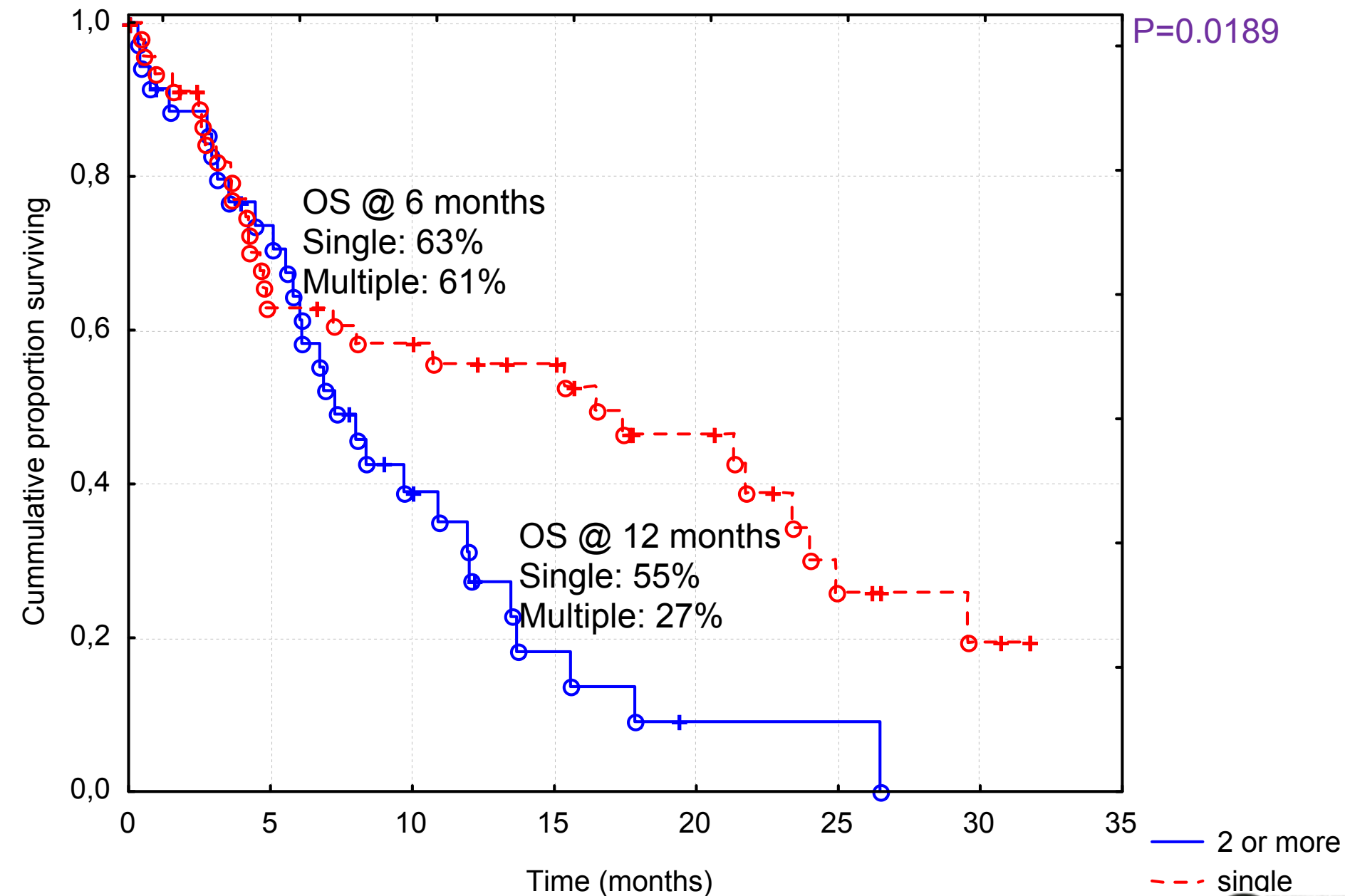
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# Overall survival - single vs. multiple metastases

○ Complete + Censored

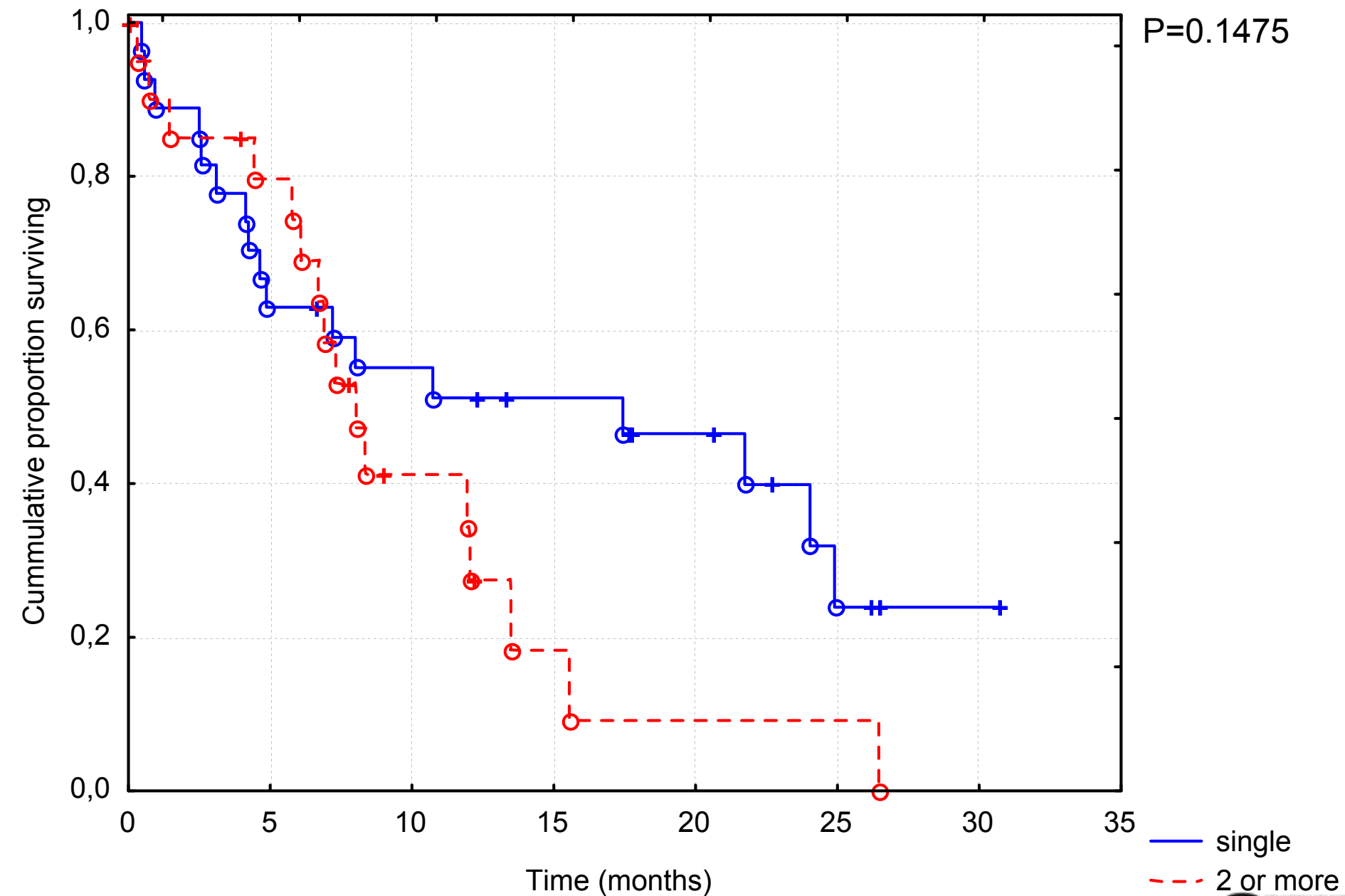
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# OS, fractionated treatment, single vs. multiple metastases

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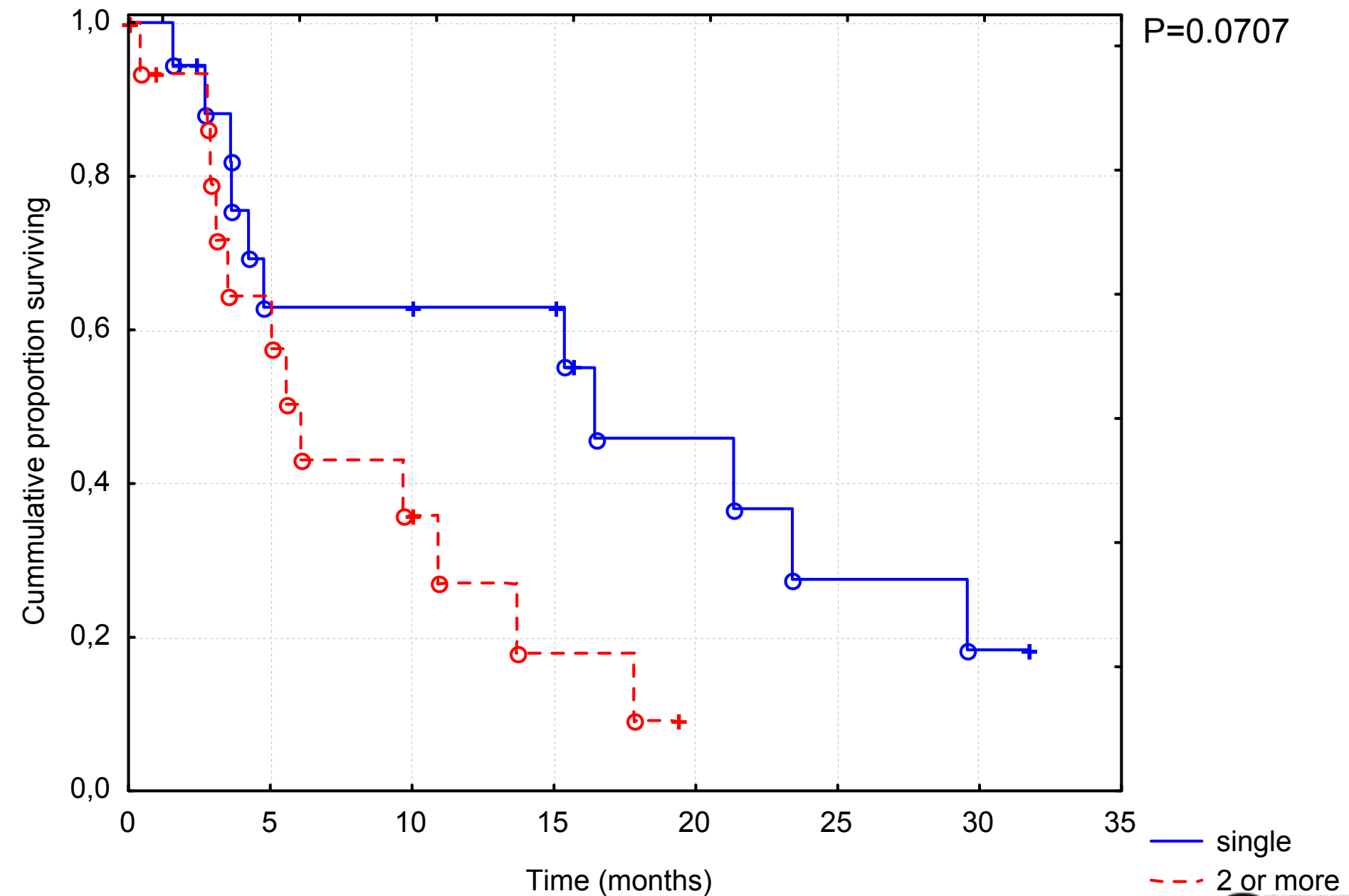
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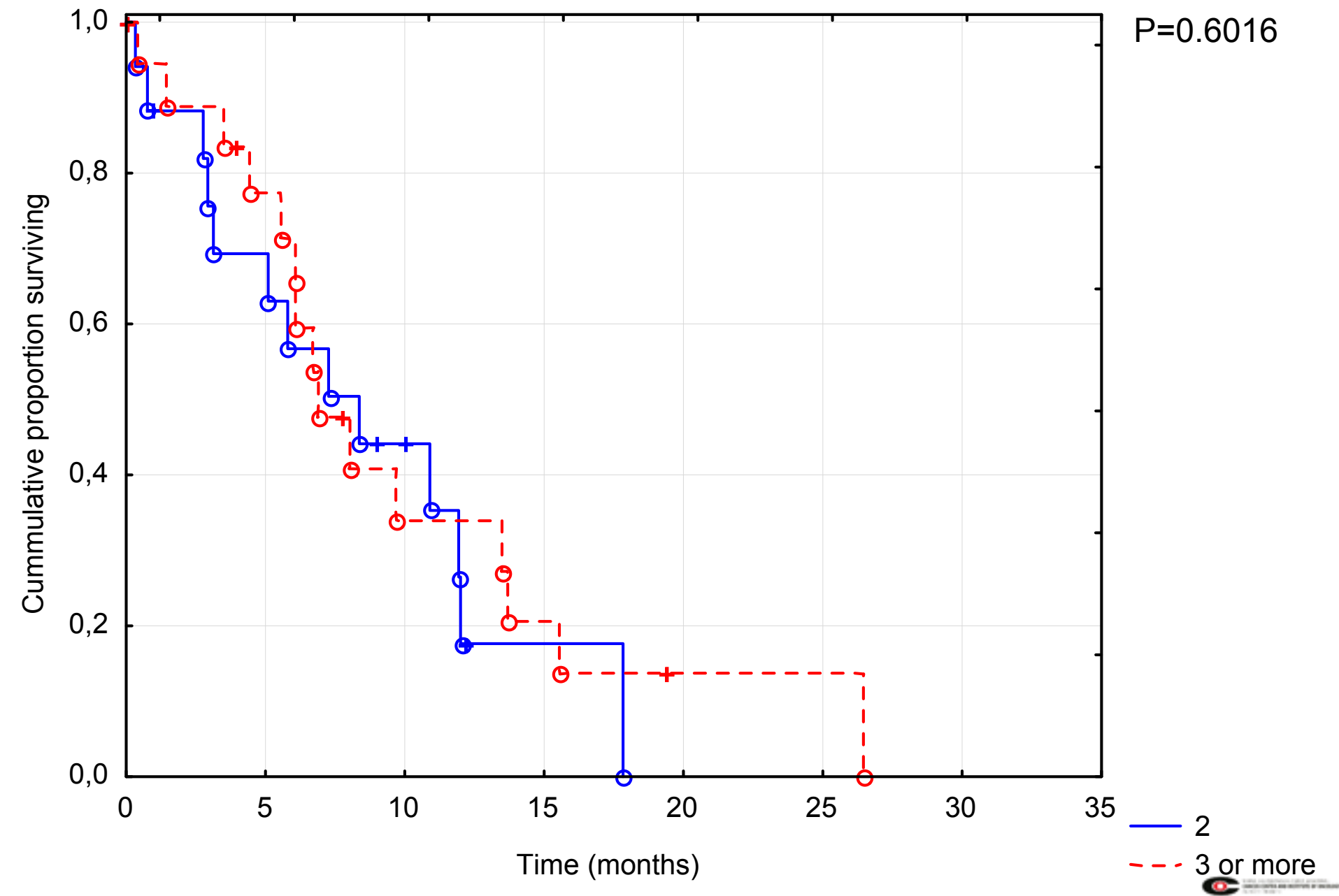
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# Overall survival, 2 vs. 3 or more metastases

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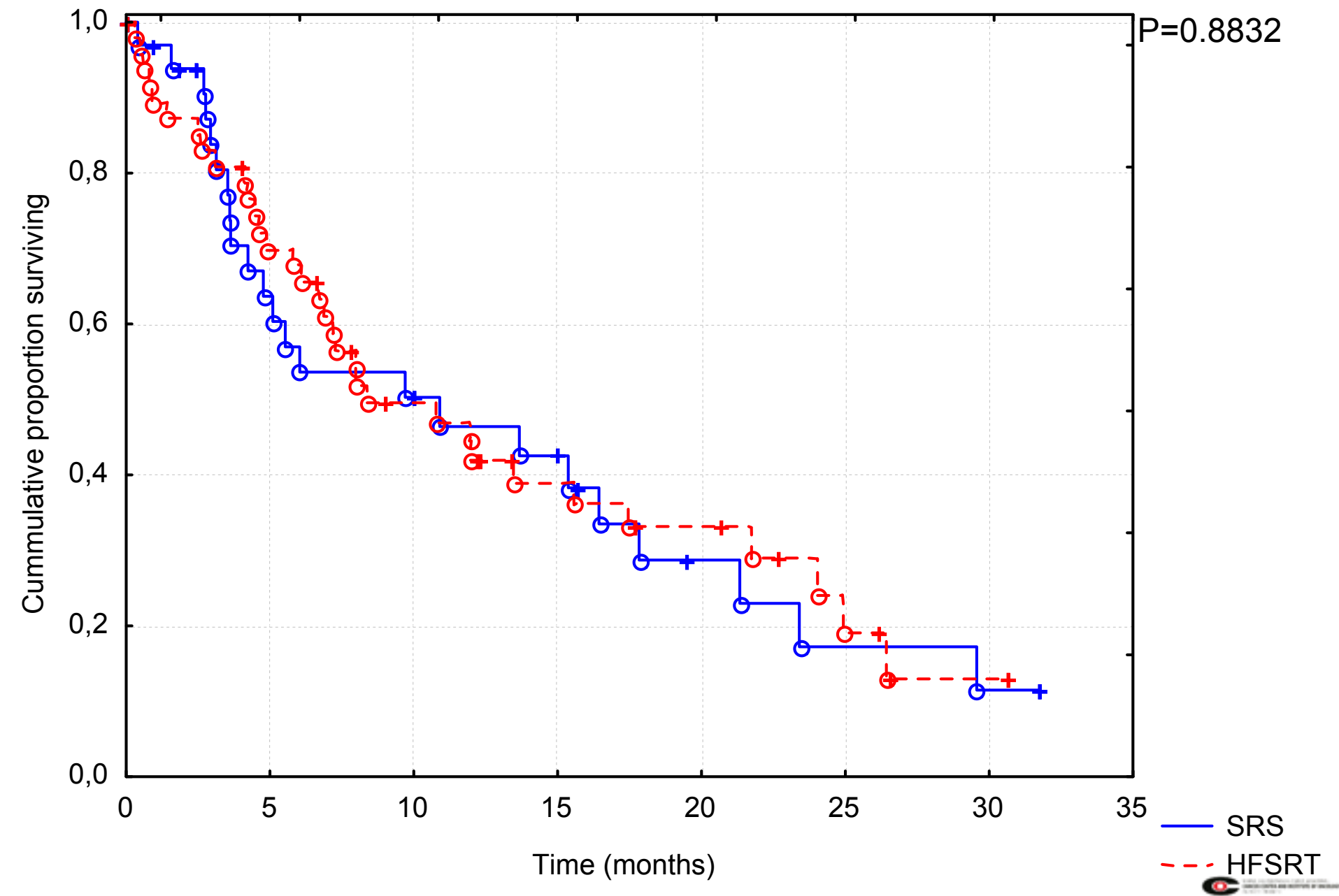
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# Overall survival - single vs. fractionated treatment

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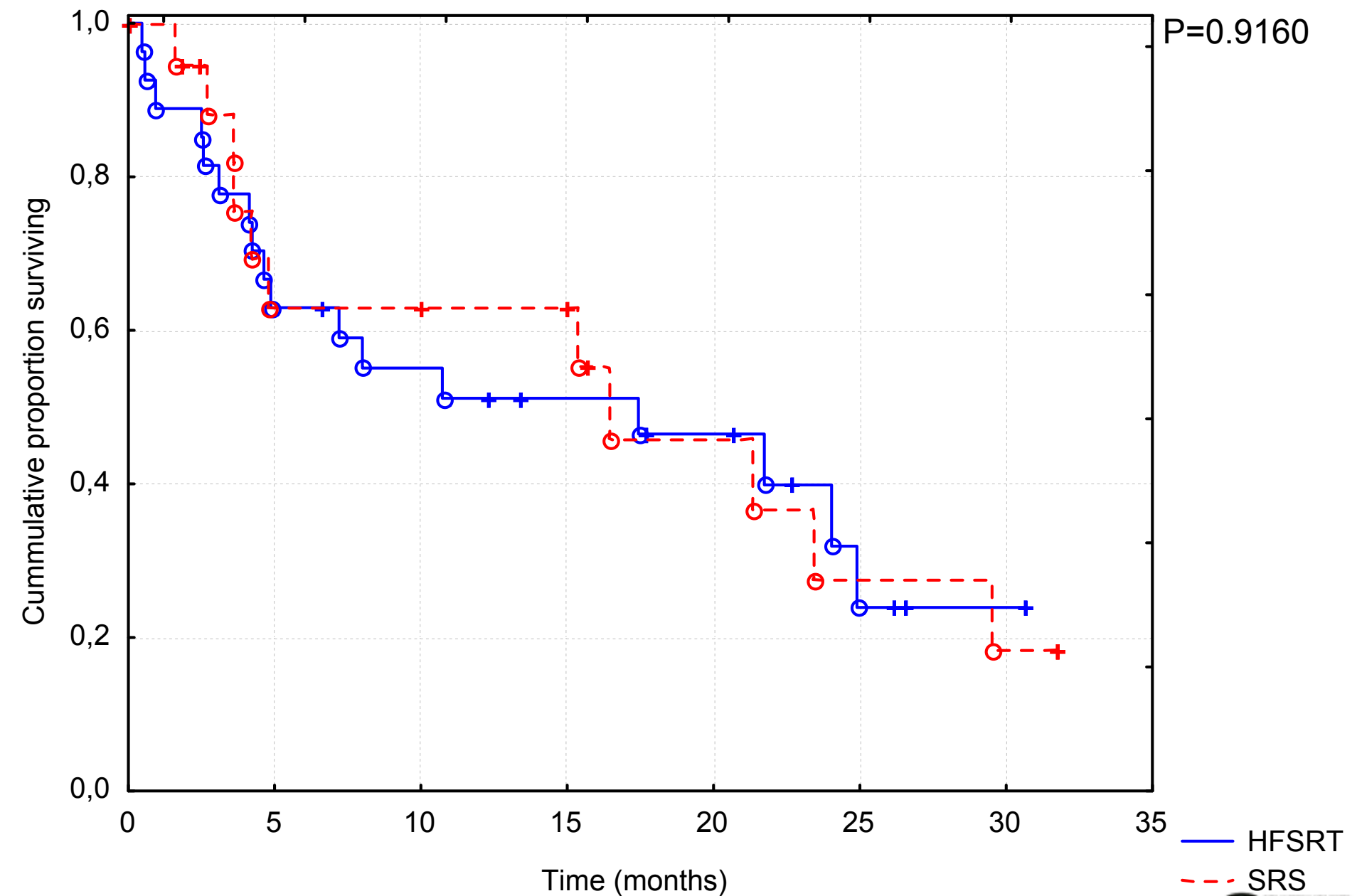
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# OS, single metastasis, SRS vs. fractionated treatment

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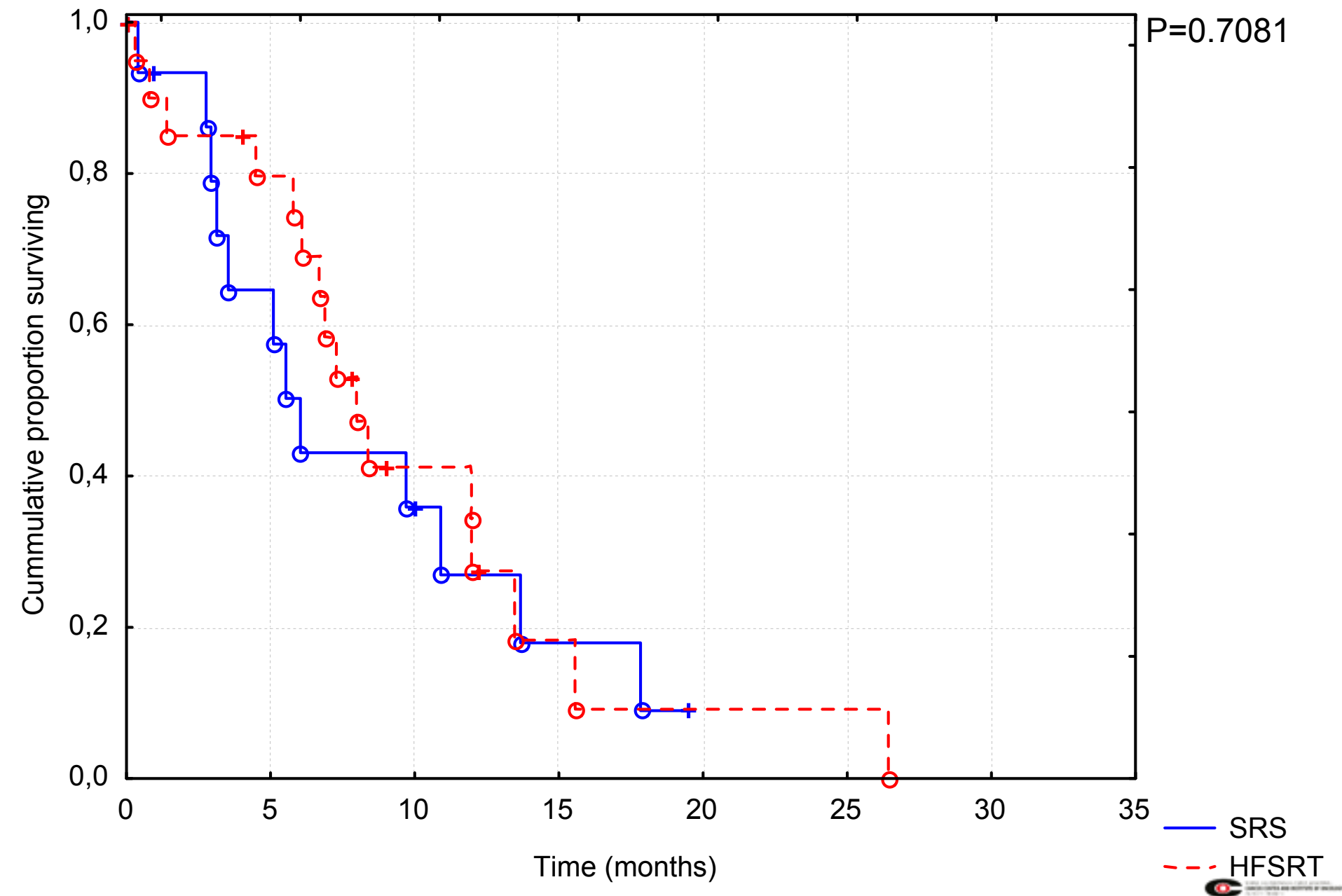
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# OS, 2 or more metastases, SRS vs. fractionated treatment

○ Complete + Censored

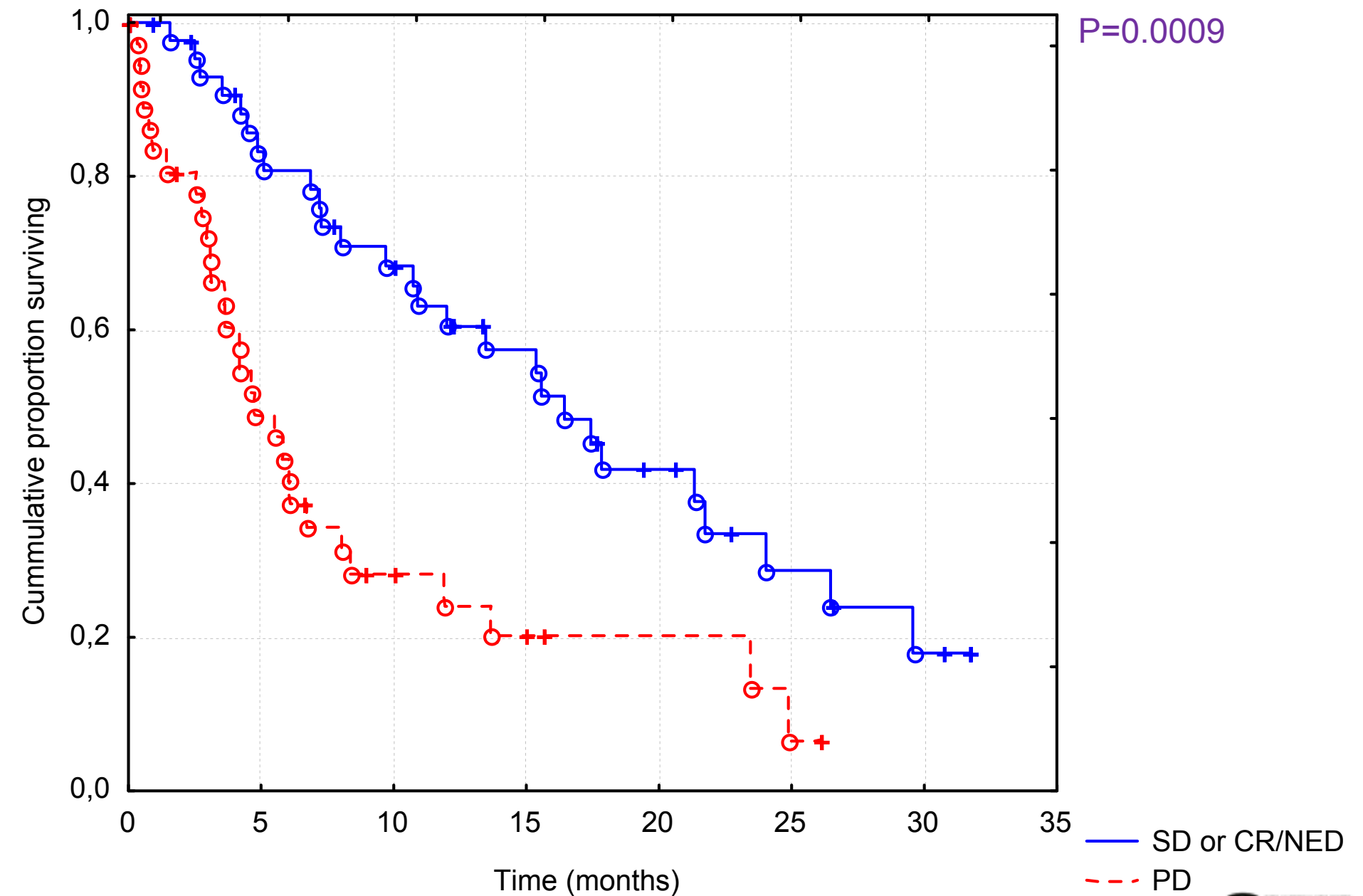
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# Overall survival - PD vs. SD or CR

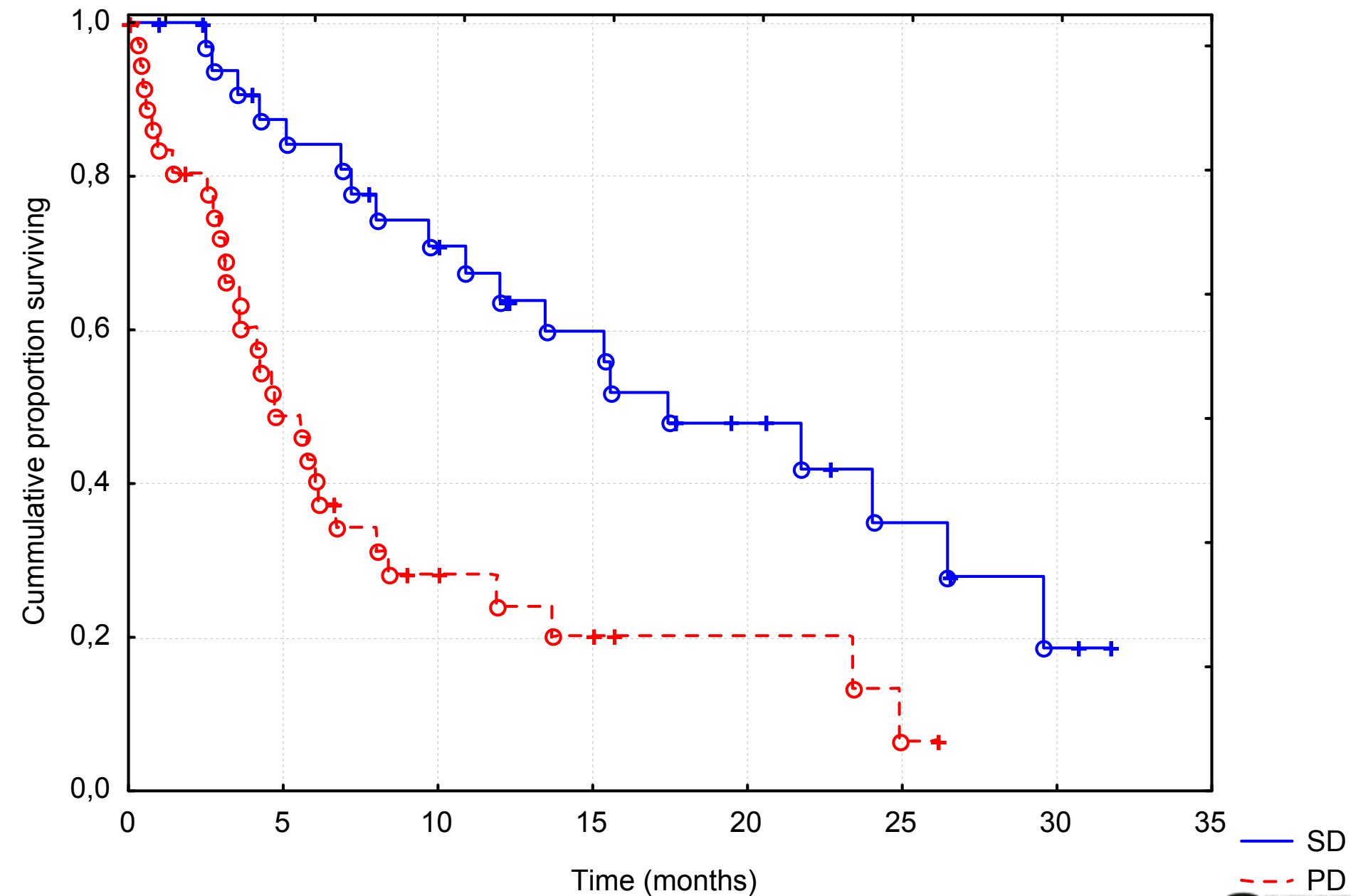
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P=0.0009



# Overall survival - systemic disease progressive vs. stable

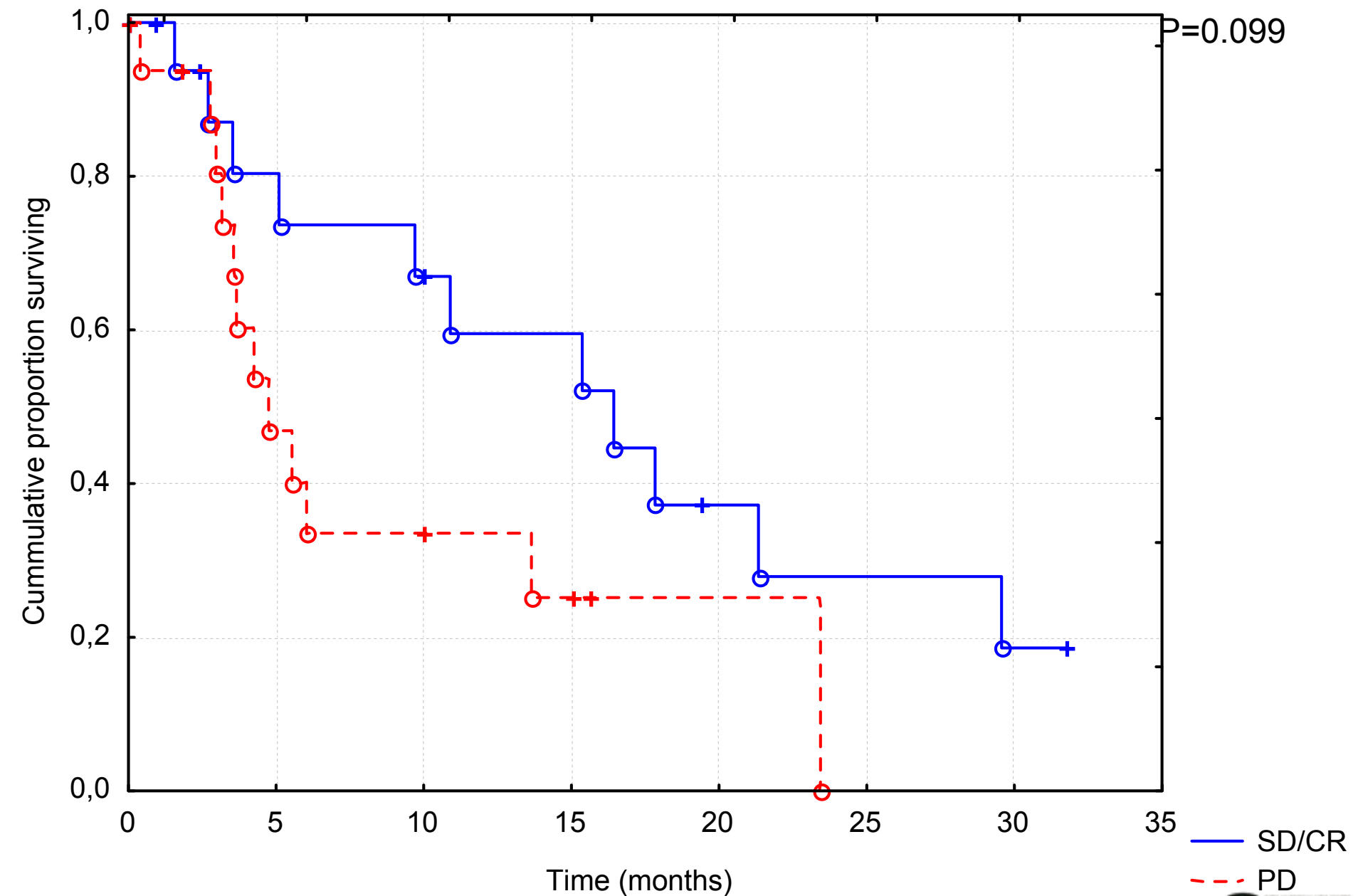
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# OS, single fraction treatment, PD vs SD or CR

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P=0.099

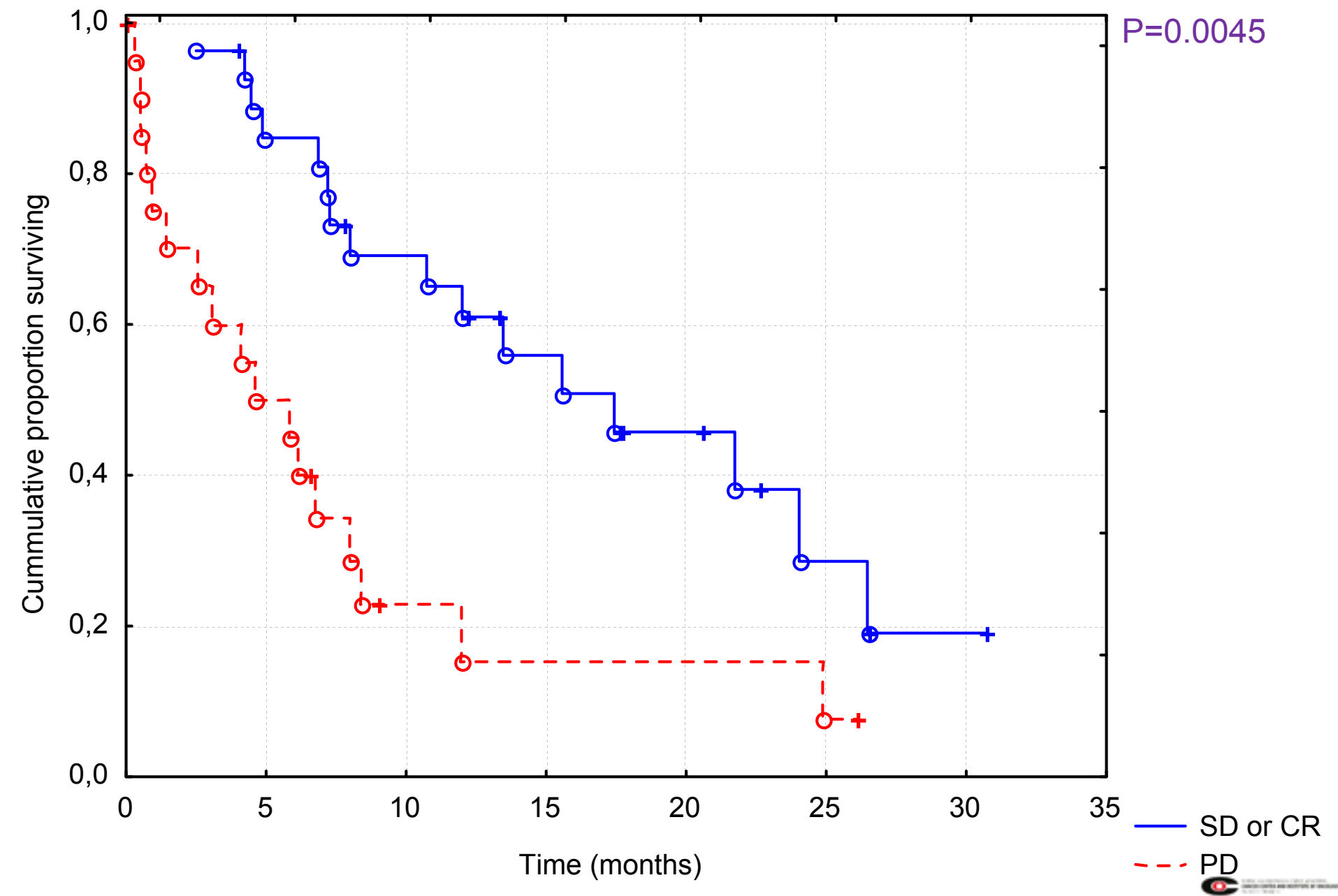




# OS, fractionated treatment, PD vs SD or CR

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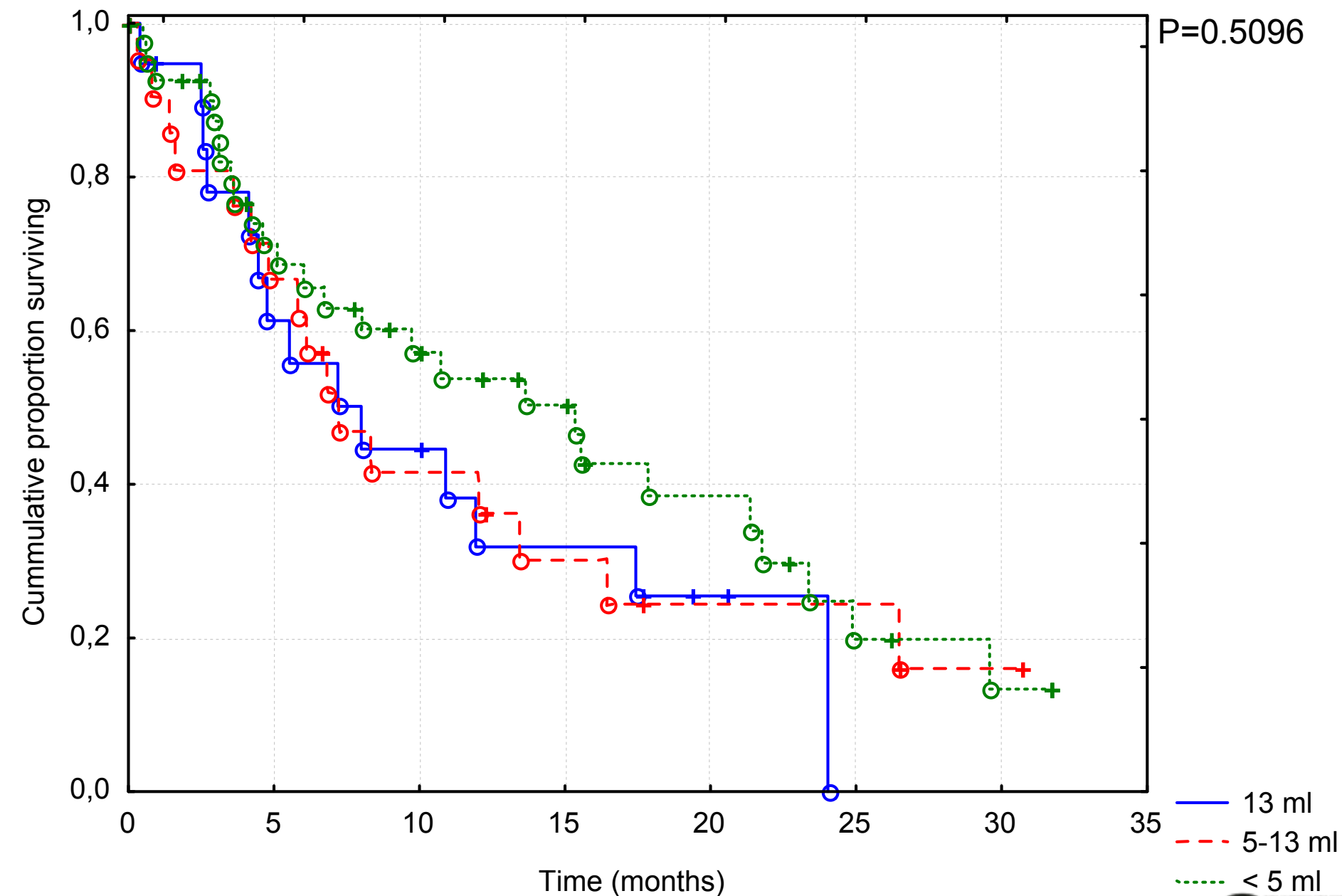
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# Overall survival according to volume of the largest lesion

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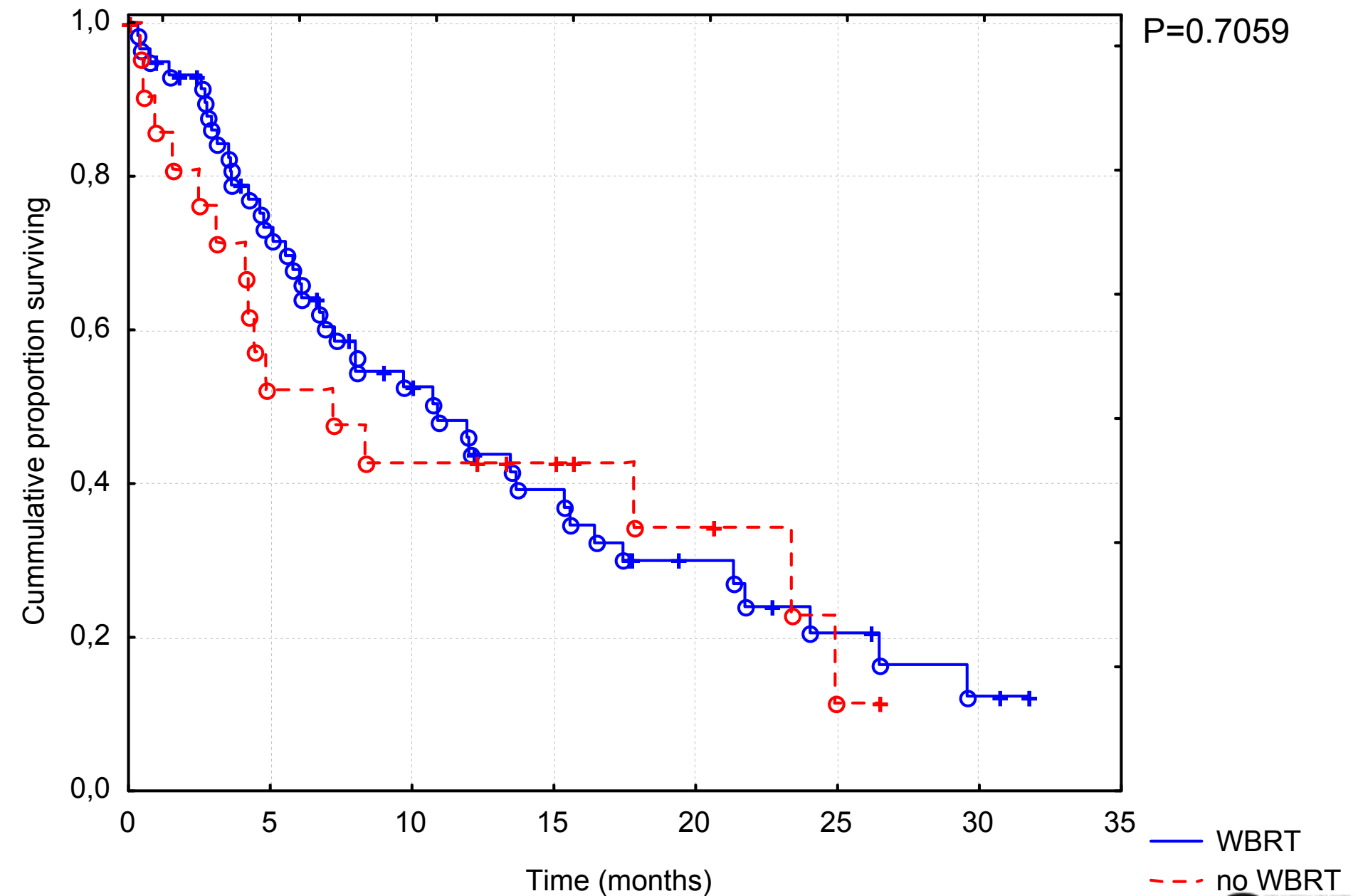
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# Overall survival, whole group, WBRT vs. no WBRT

○ Complete + Censored

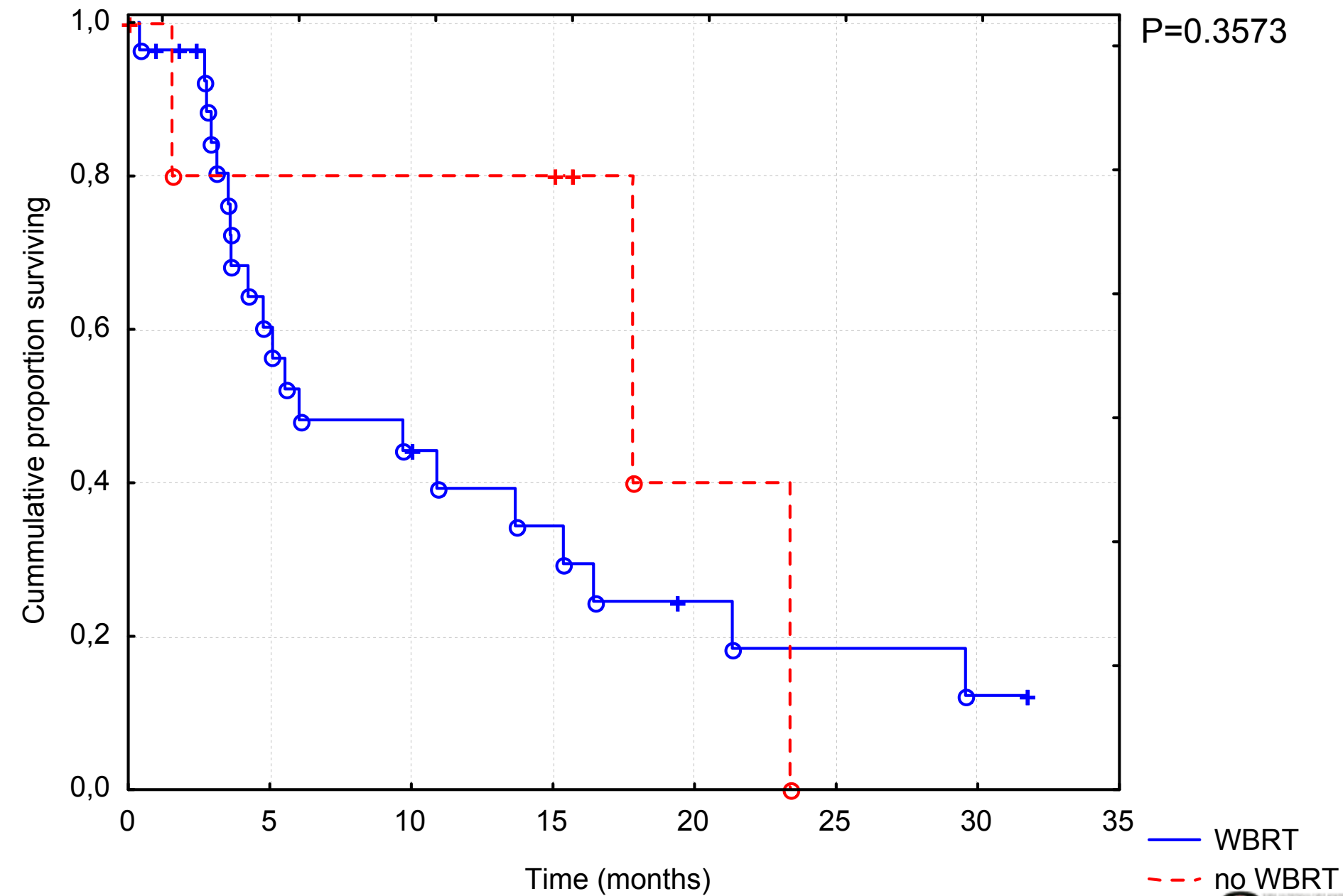
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# OS, WBRT vs. no WBRT for single fraction

○ Complete + Censored

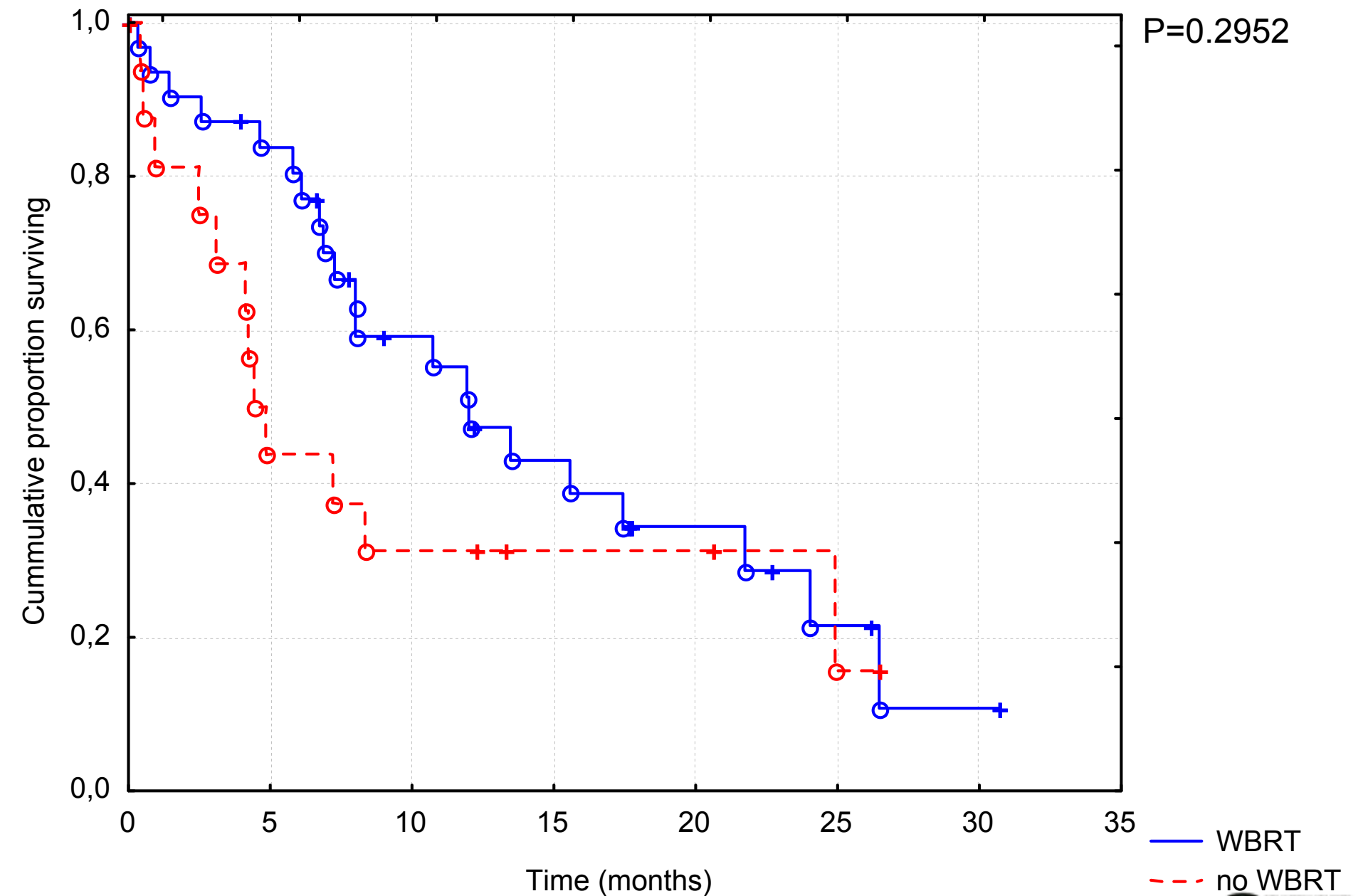
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# OS, WBRT vs. no WBRT for fractionated treatment

○ Complete + Censored

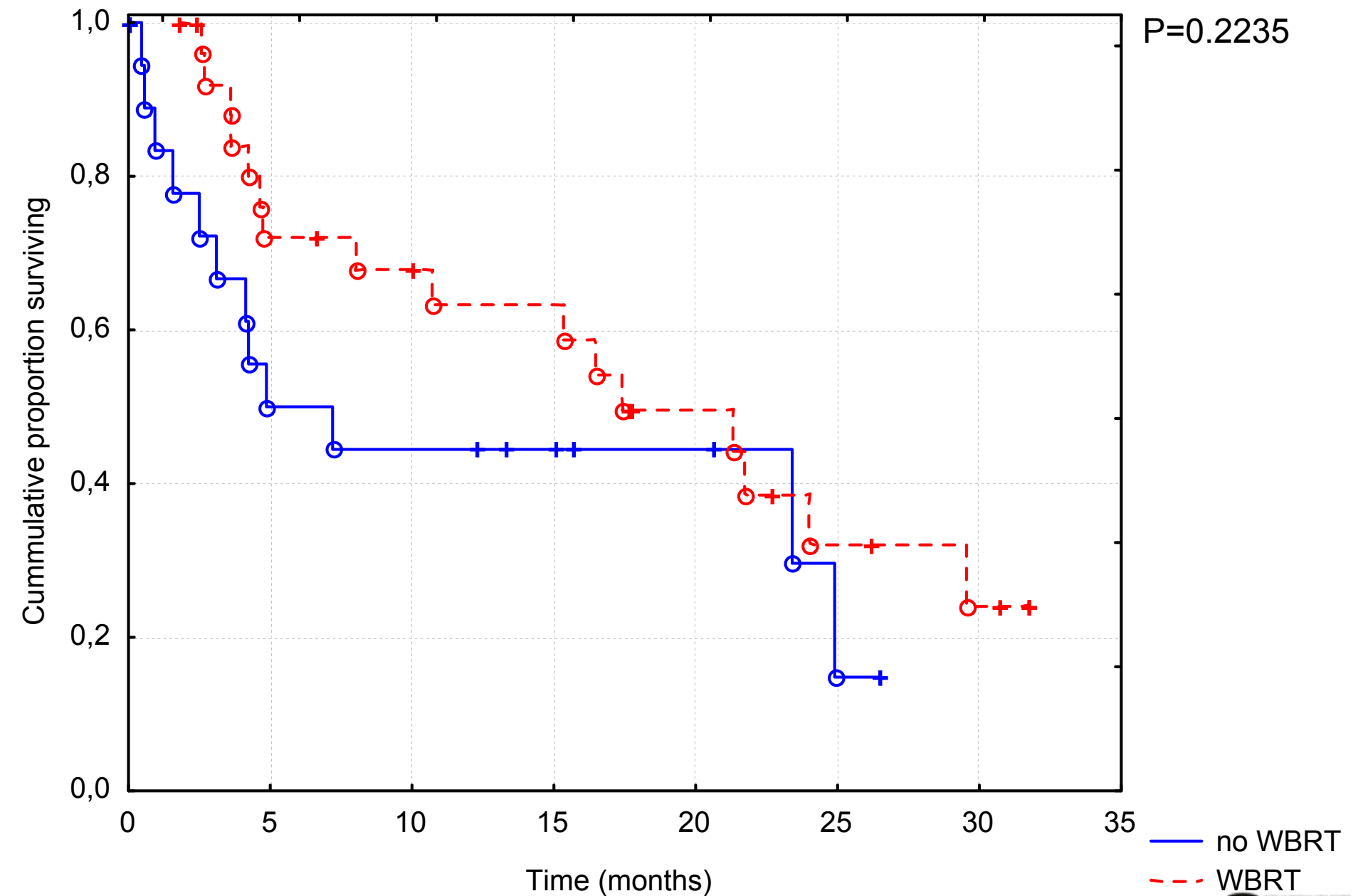
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# OS, WBRT vs. no WBRT for single metastasis

○ Complete + Censored

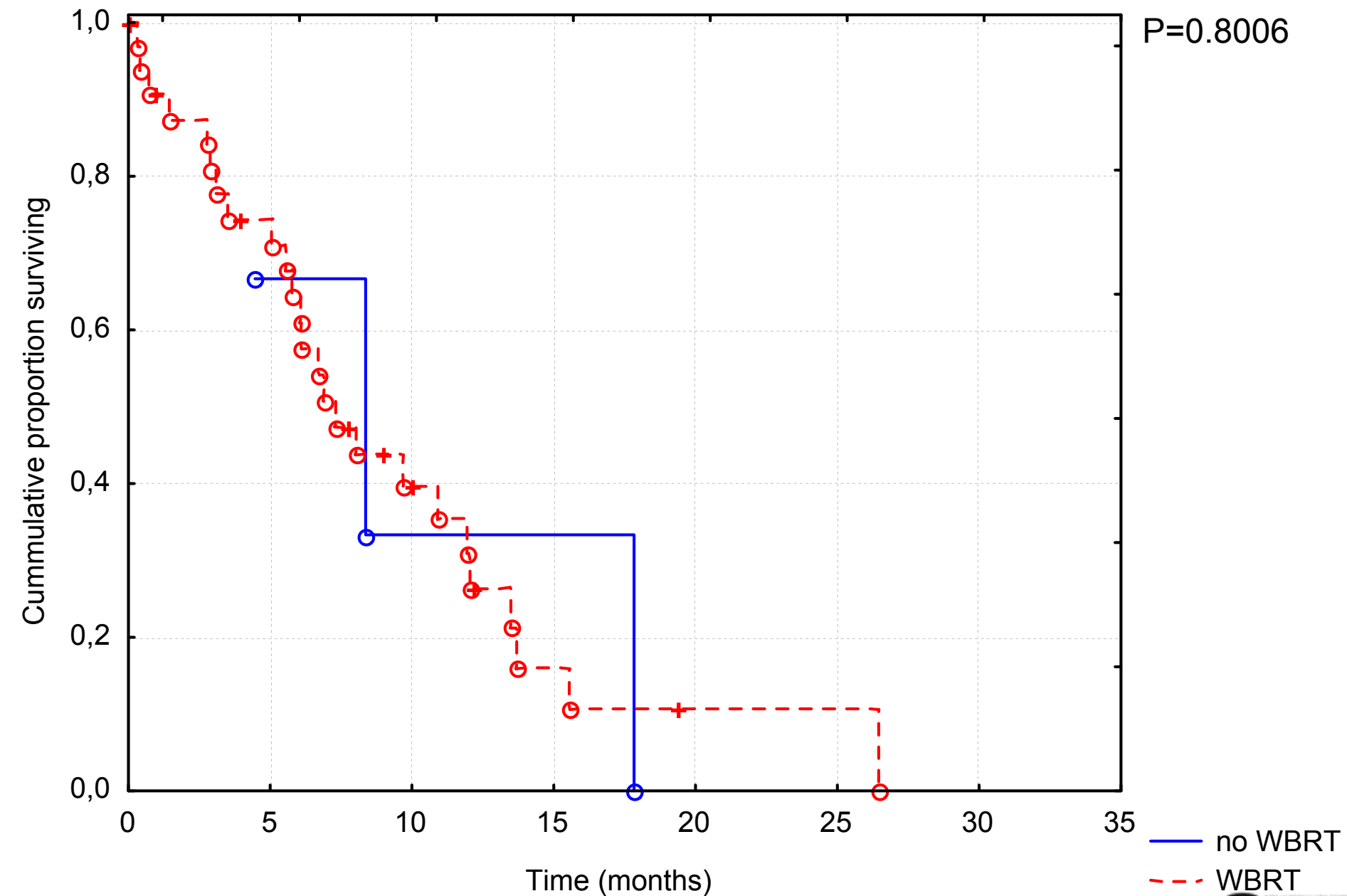
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# OS, WBRT for 2 or more metastases

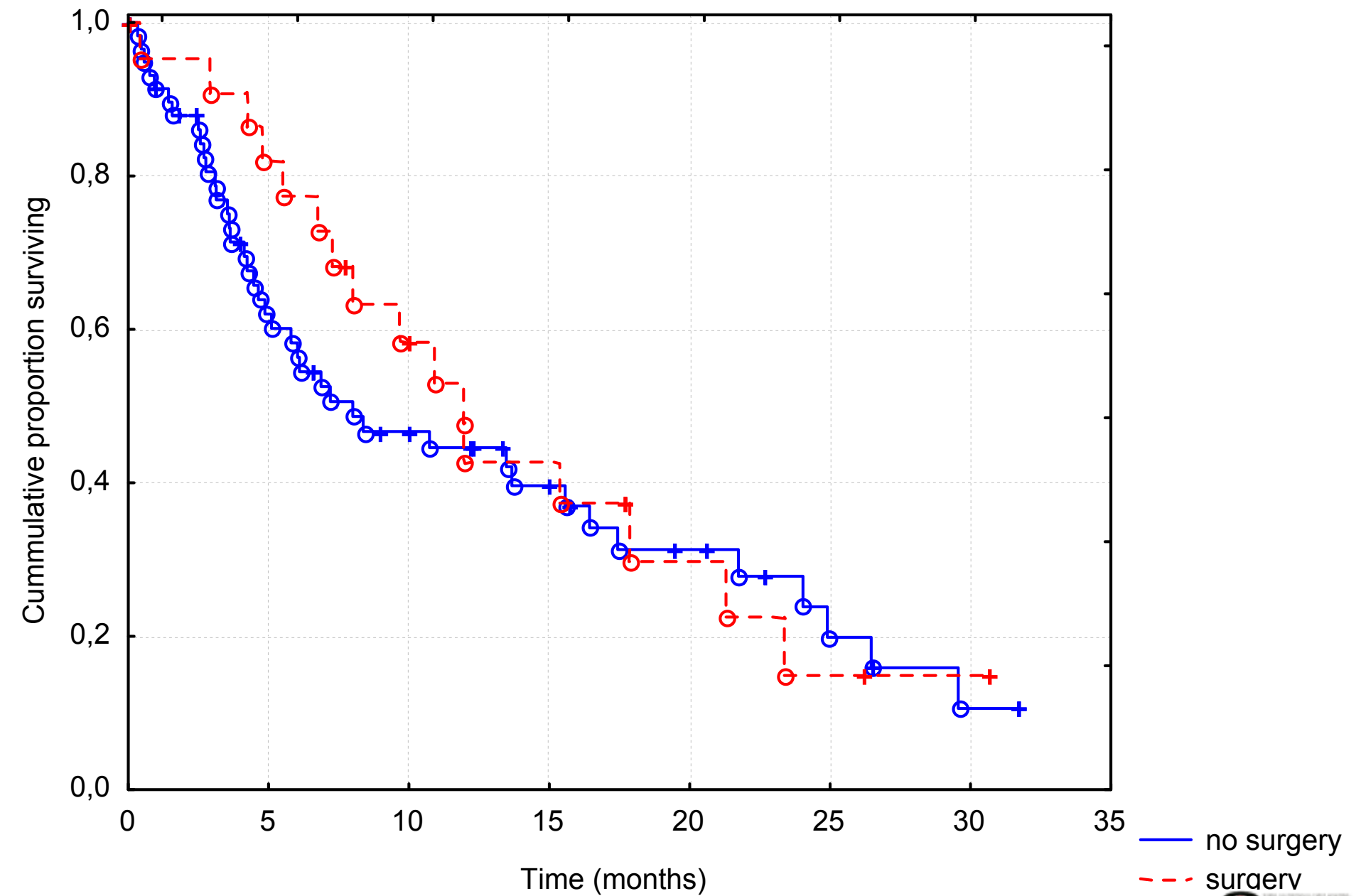
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P=0.8006



OS, surgery: yes vs. no

○ Complete + Censored

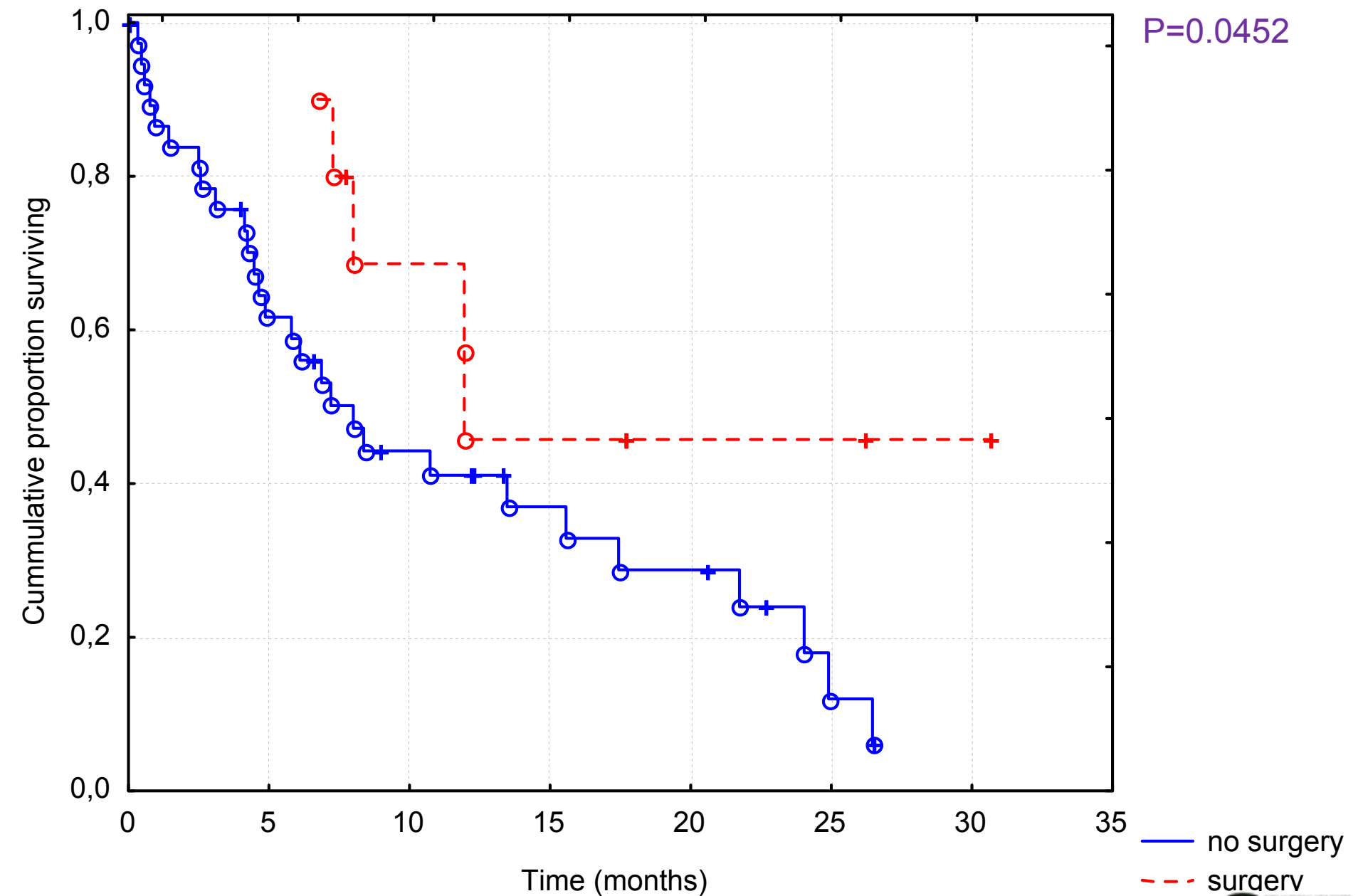




# OS, surgery vs. no surgery for fractionated treatment

○ Complete + Censored

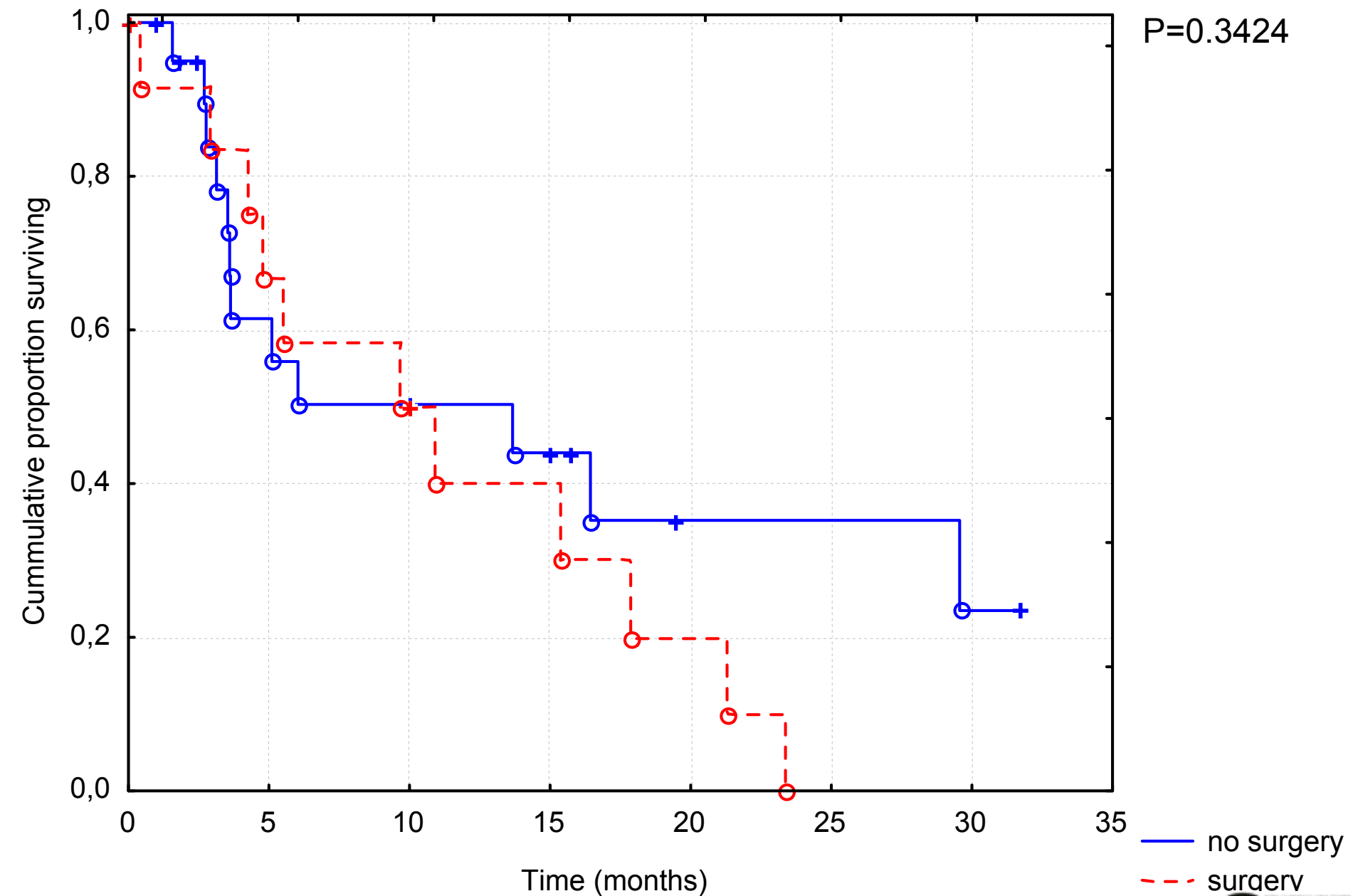
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# OS, surgery vs no surgery - single fraction treatment

○ Complete + Censored

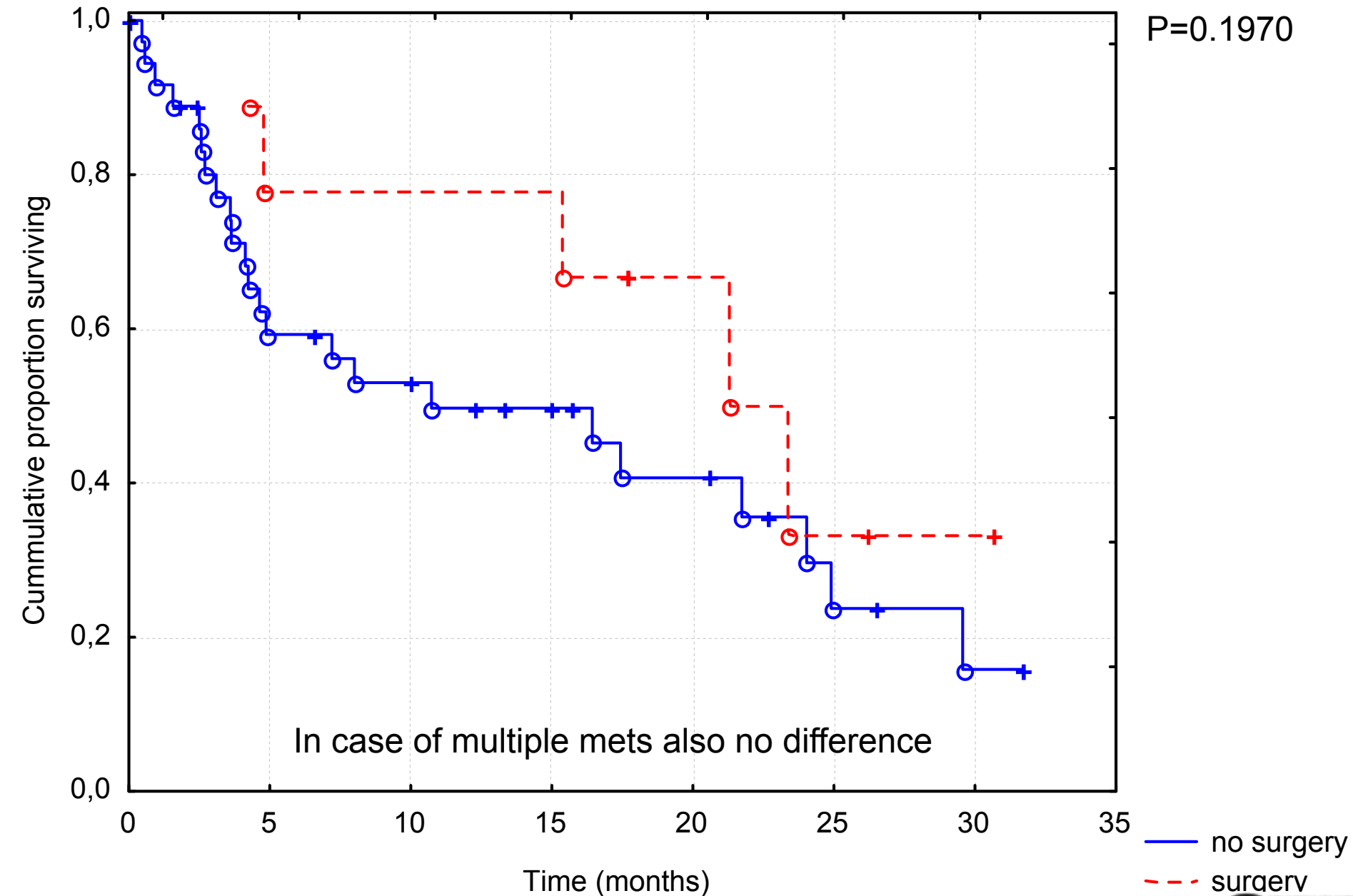
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# OS, surgery: yes vs. no, single metastasis

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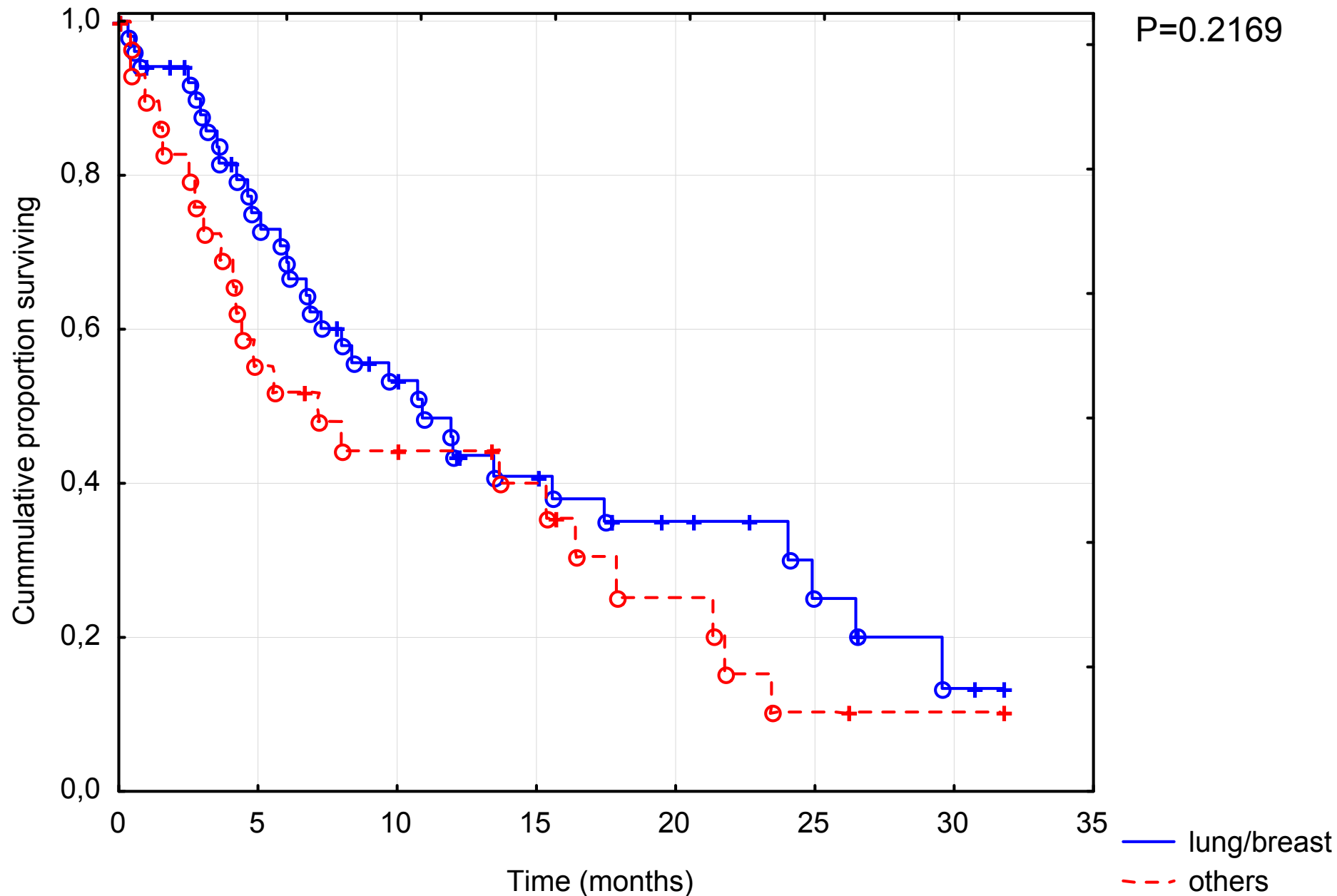
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# Overall survival, lung and breast cancer patients vs. others

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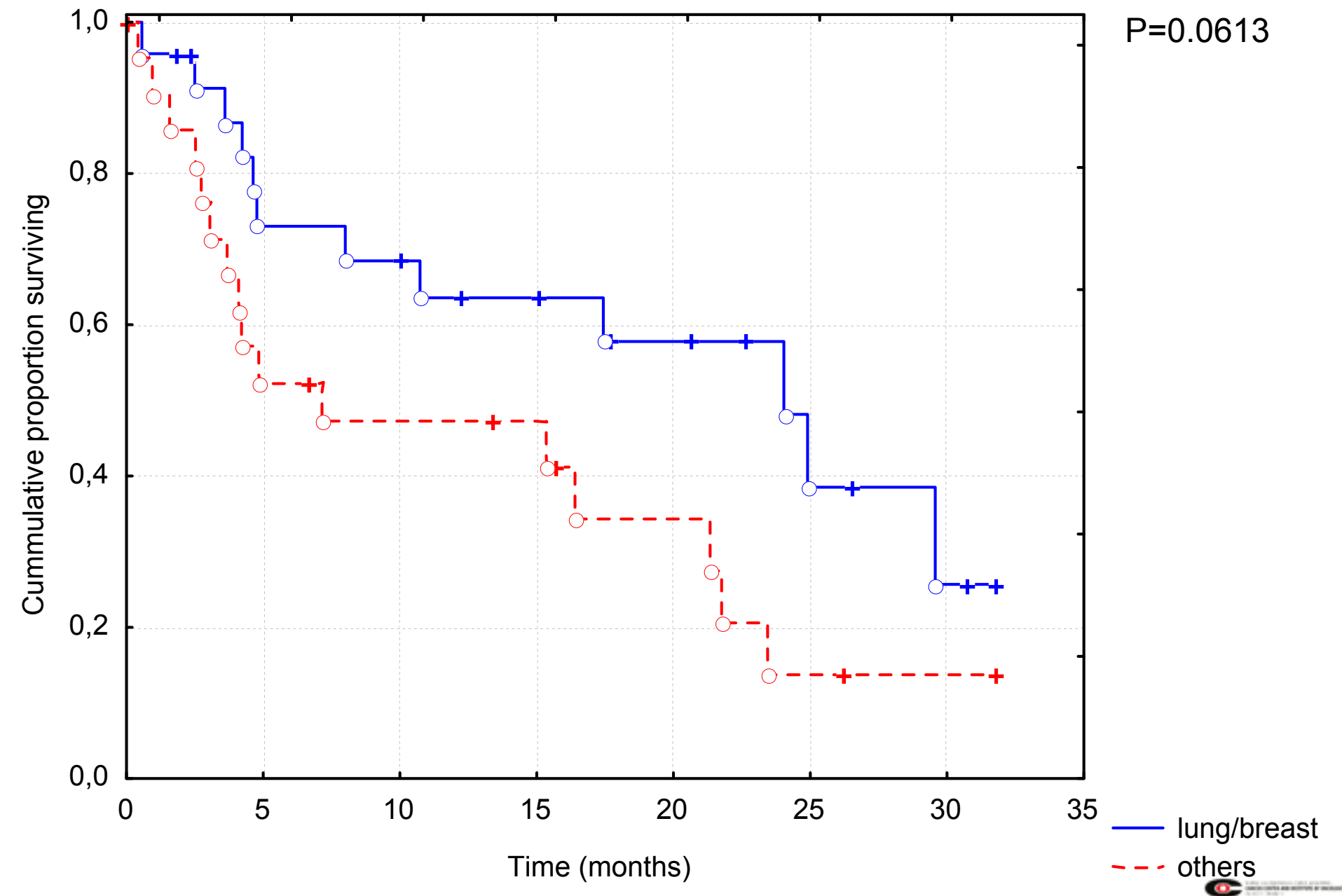
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# OS, breast/lung cancer patients vs. others, single metastasis

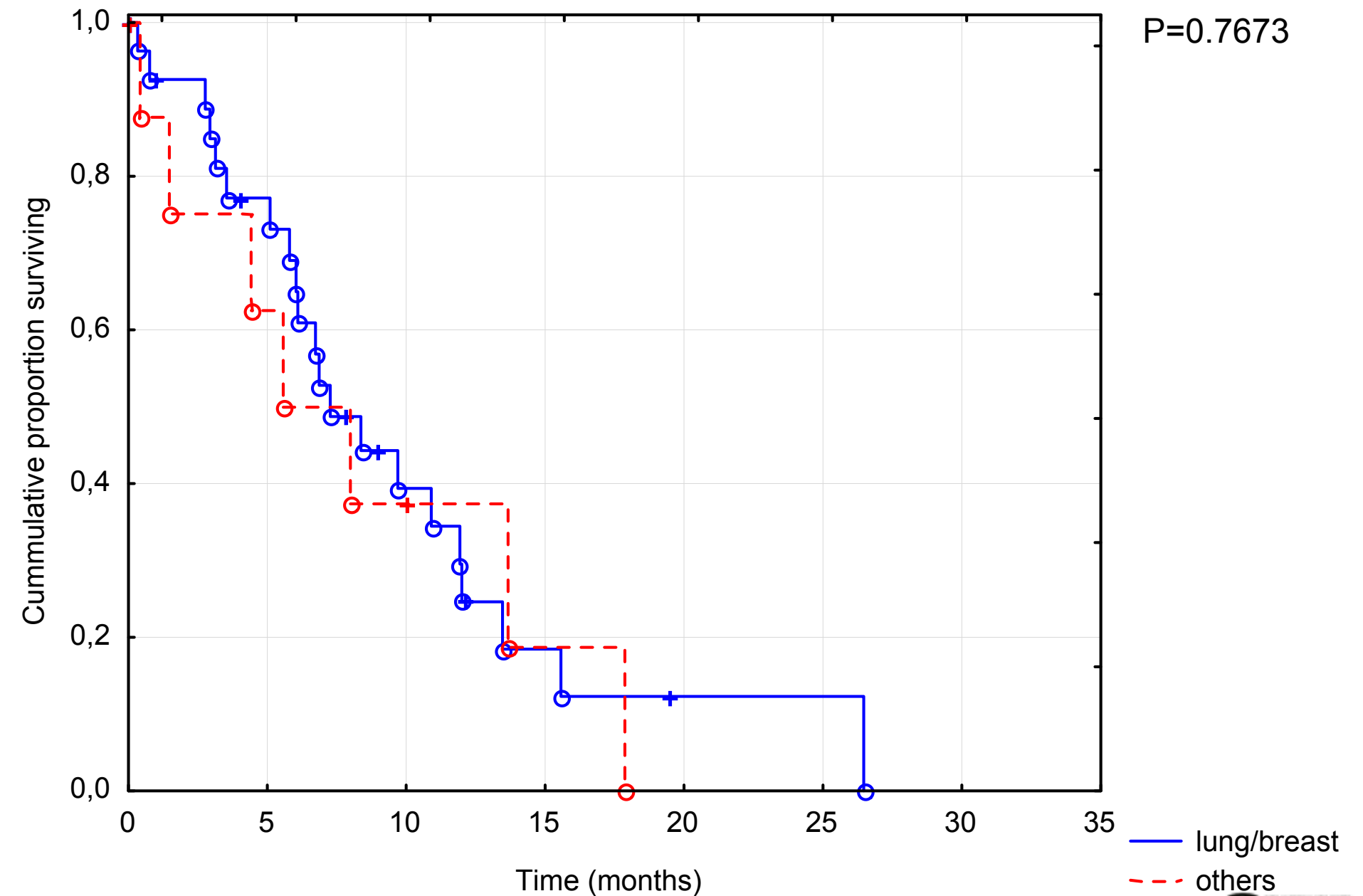
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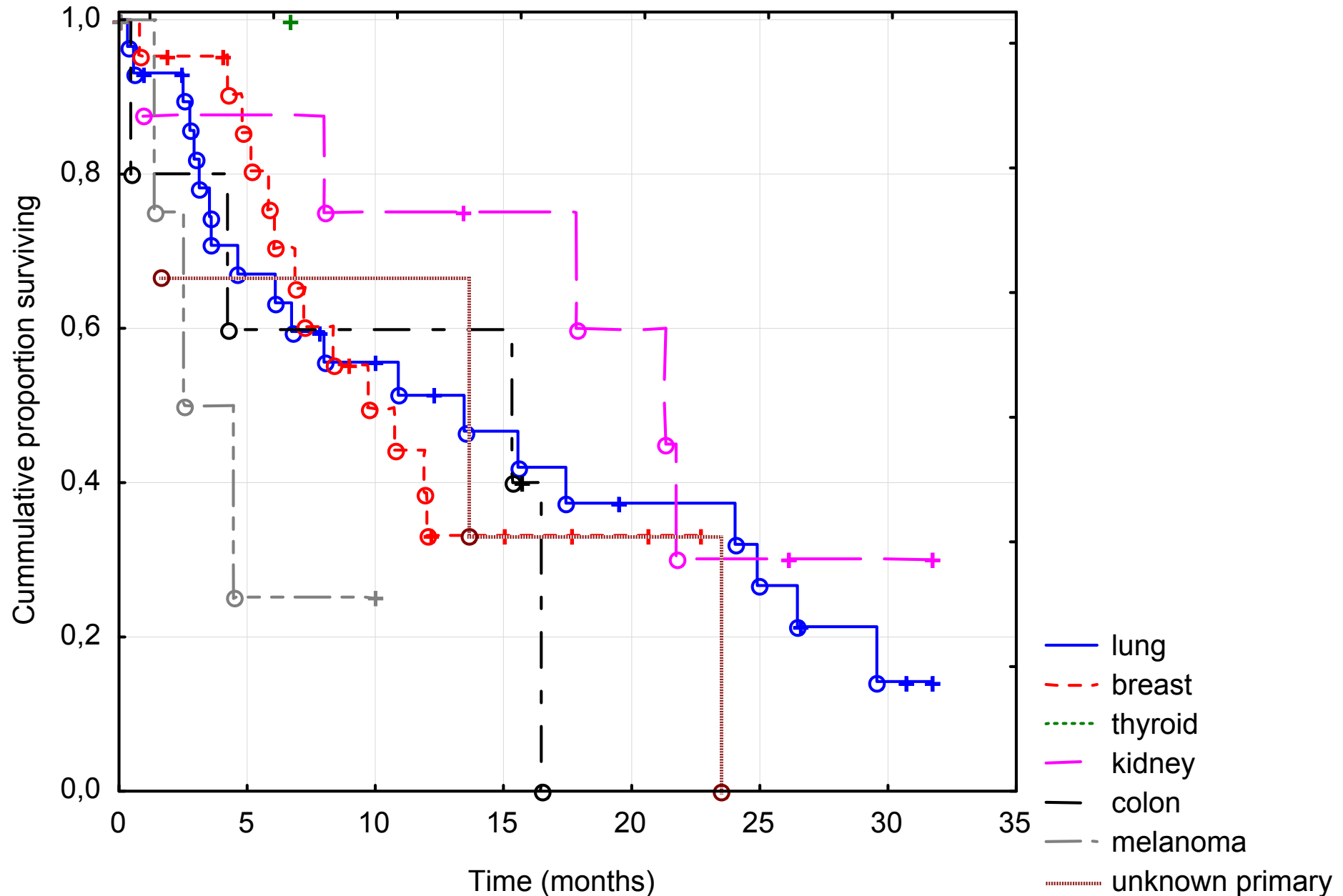
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P=0.7673



# Overall survival - primary diagnosis

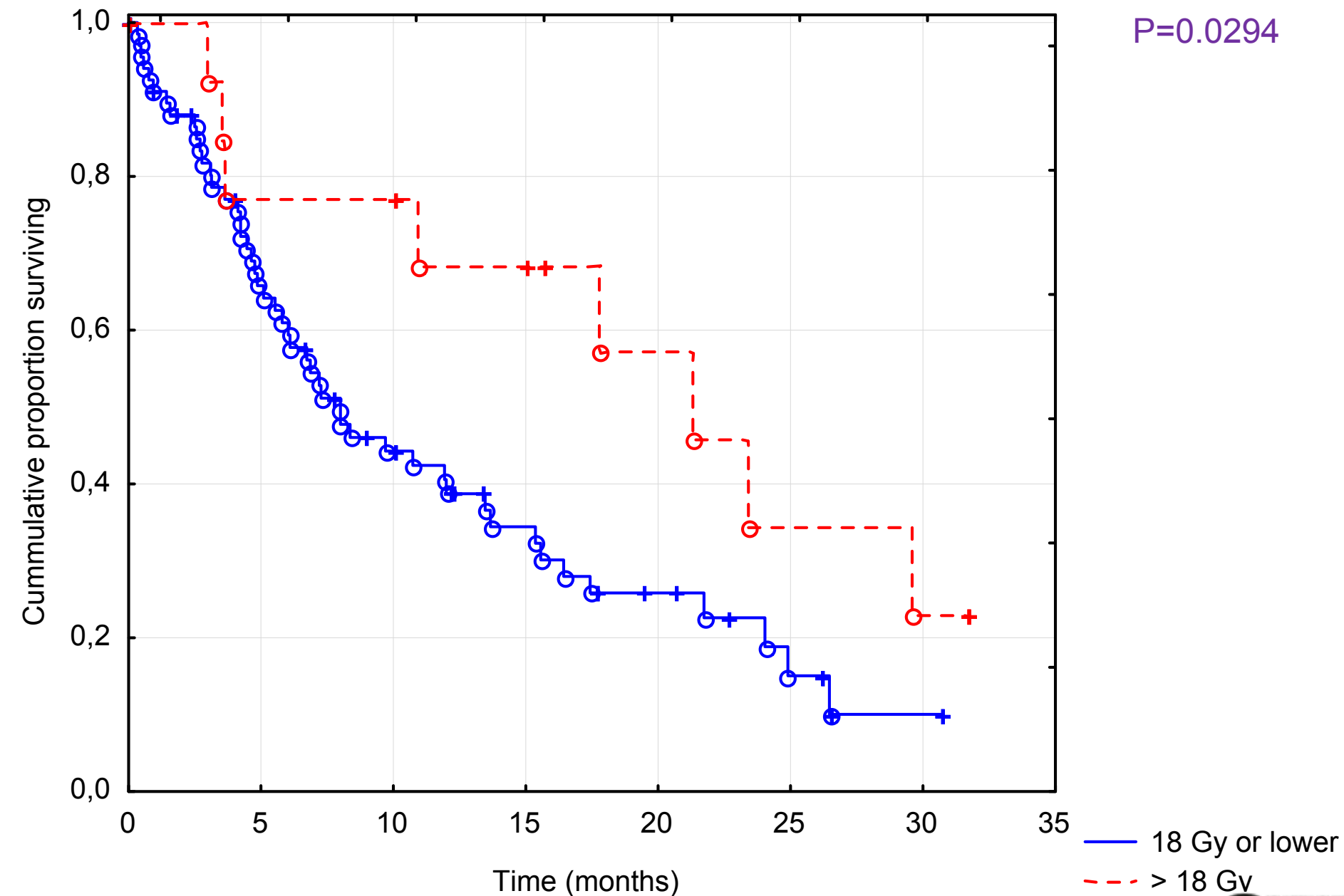
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# OS, whole group, the influence of the fraction dose

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P=0.0294

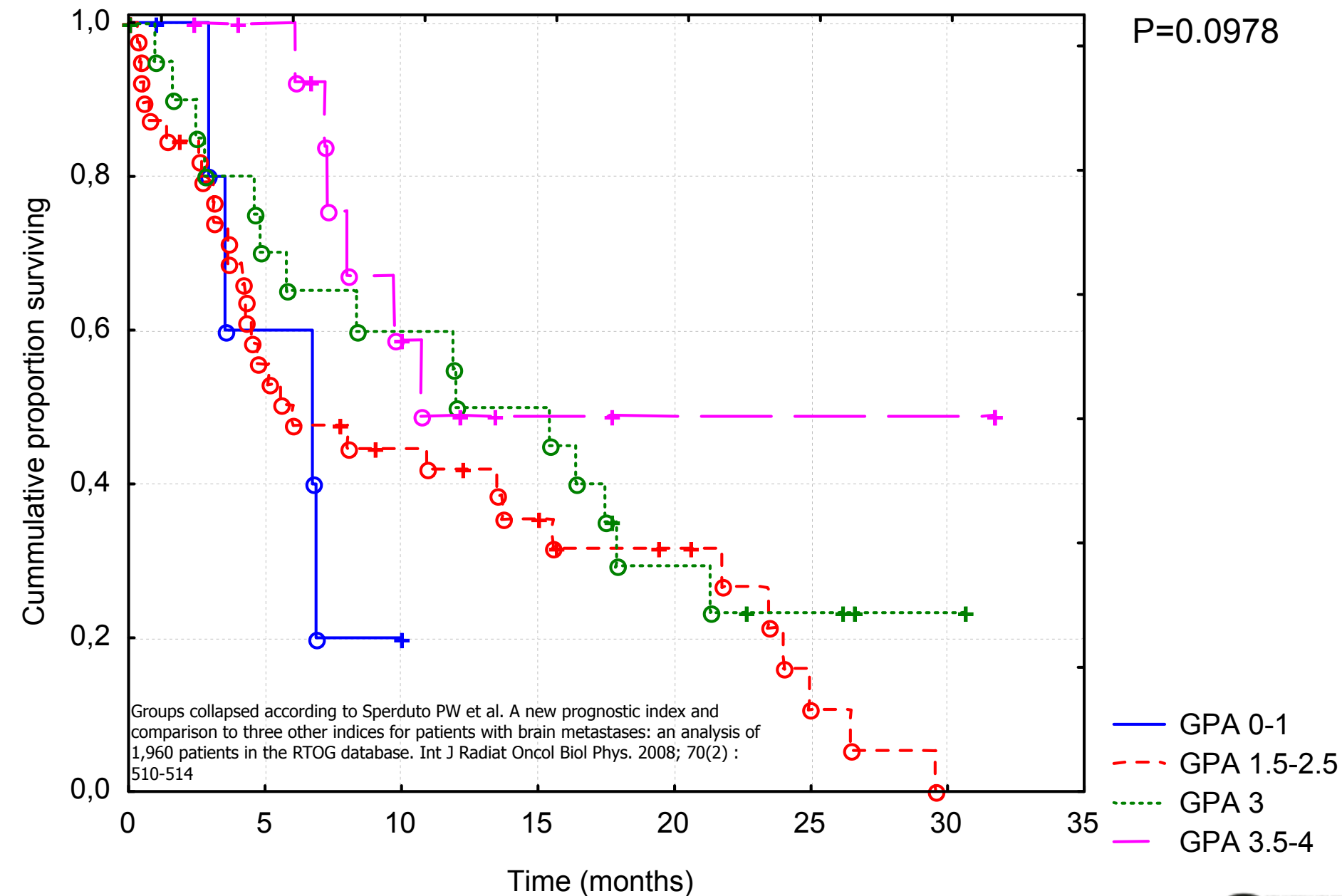




# Overall survival - Graded Prognostic Assessment

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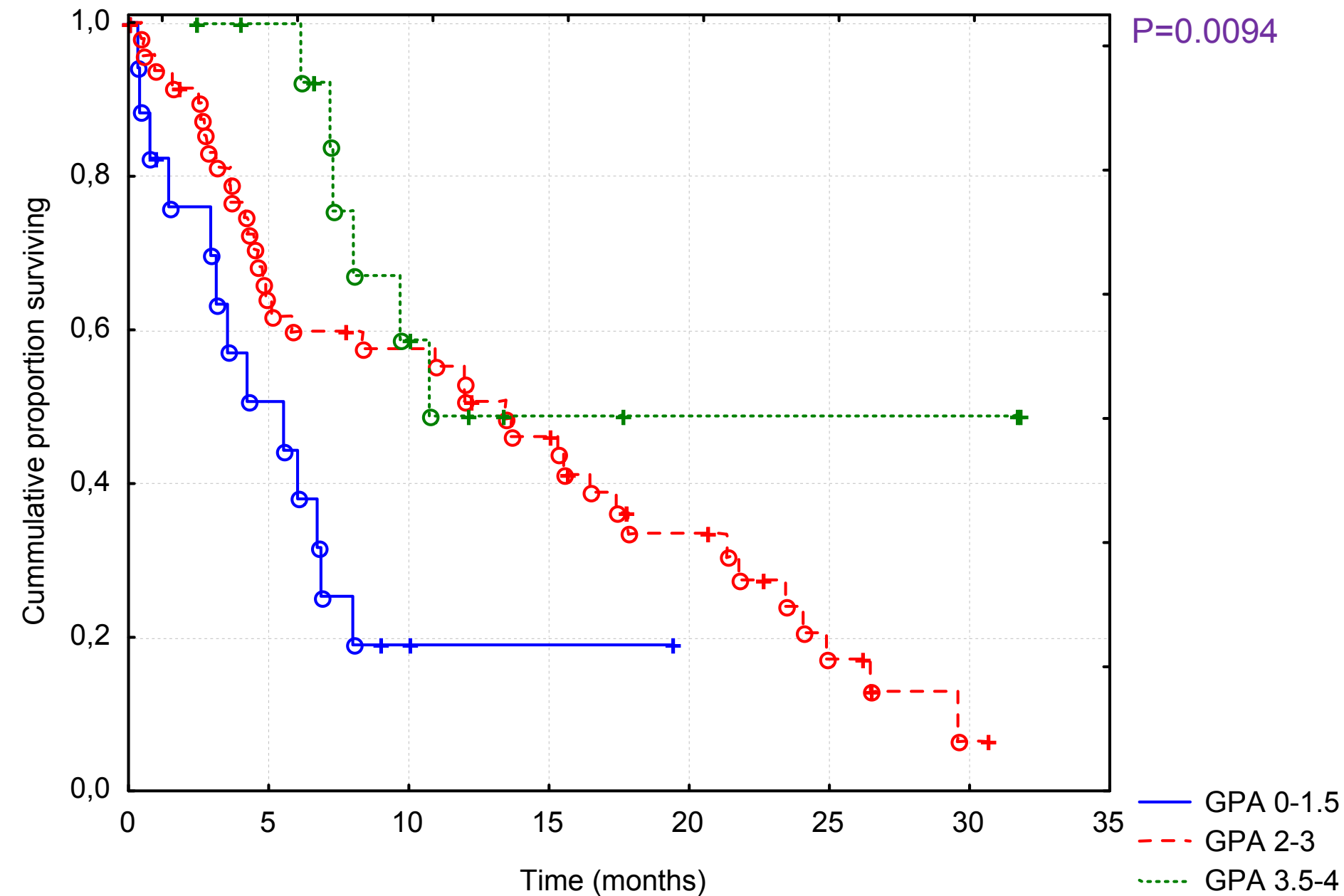
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# Overall survival, Graded Prognostic Assessment, 3 groups

○ Complete + Censored

P=0.0094

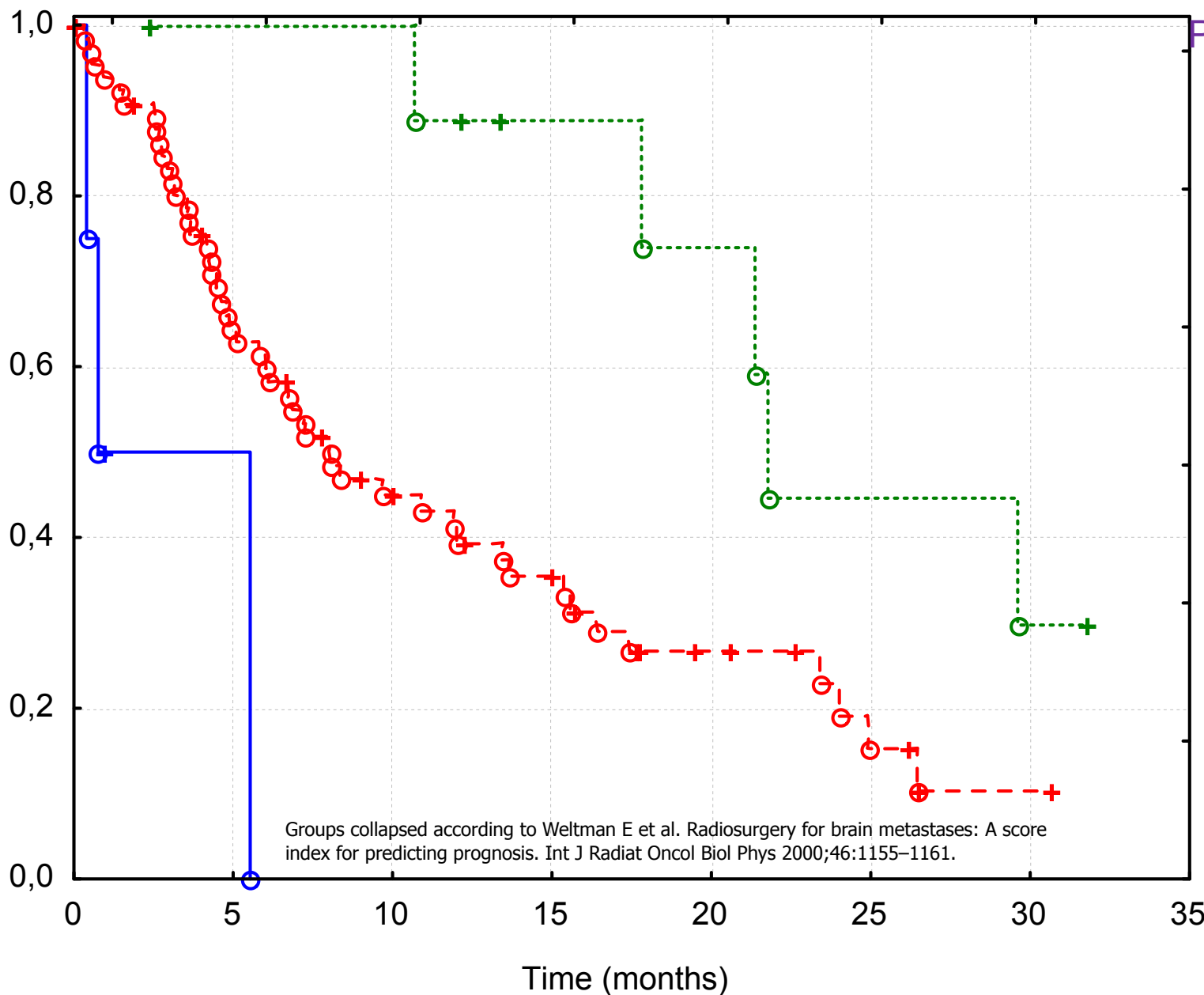


# Overall Survival - Score Index for Radiosurgery

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P=0.0023

Cummulative proportion surviving

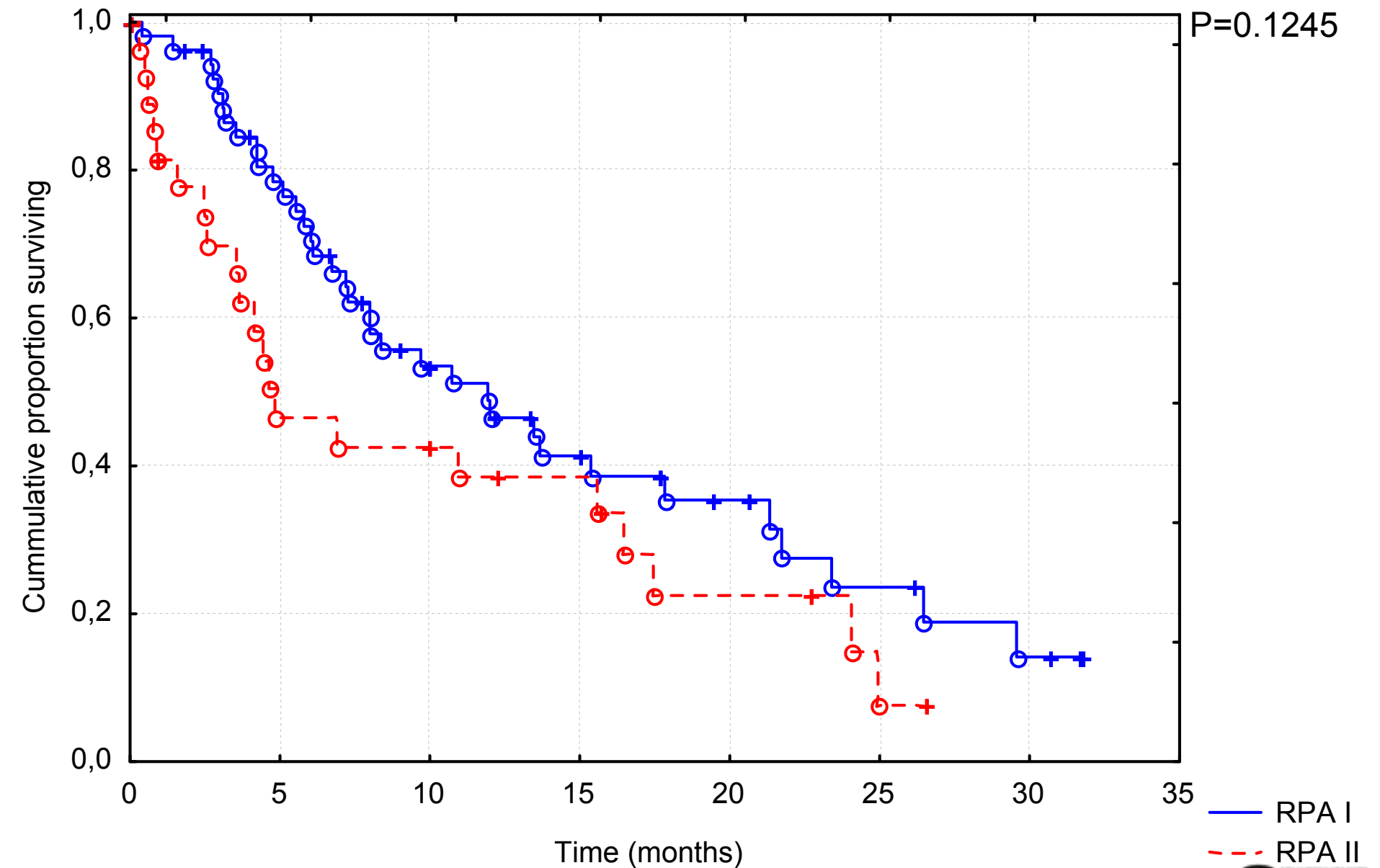


— SIR 1-3  
- - - SIR 4-7  
... SIR 8-10

# Overall survival - Recursive Partitioning Analysis no RPA III patients in the group

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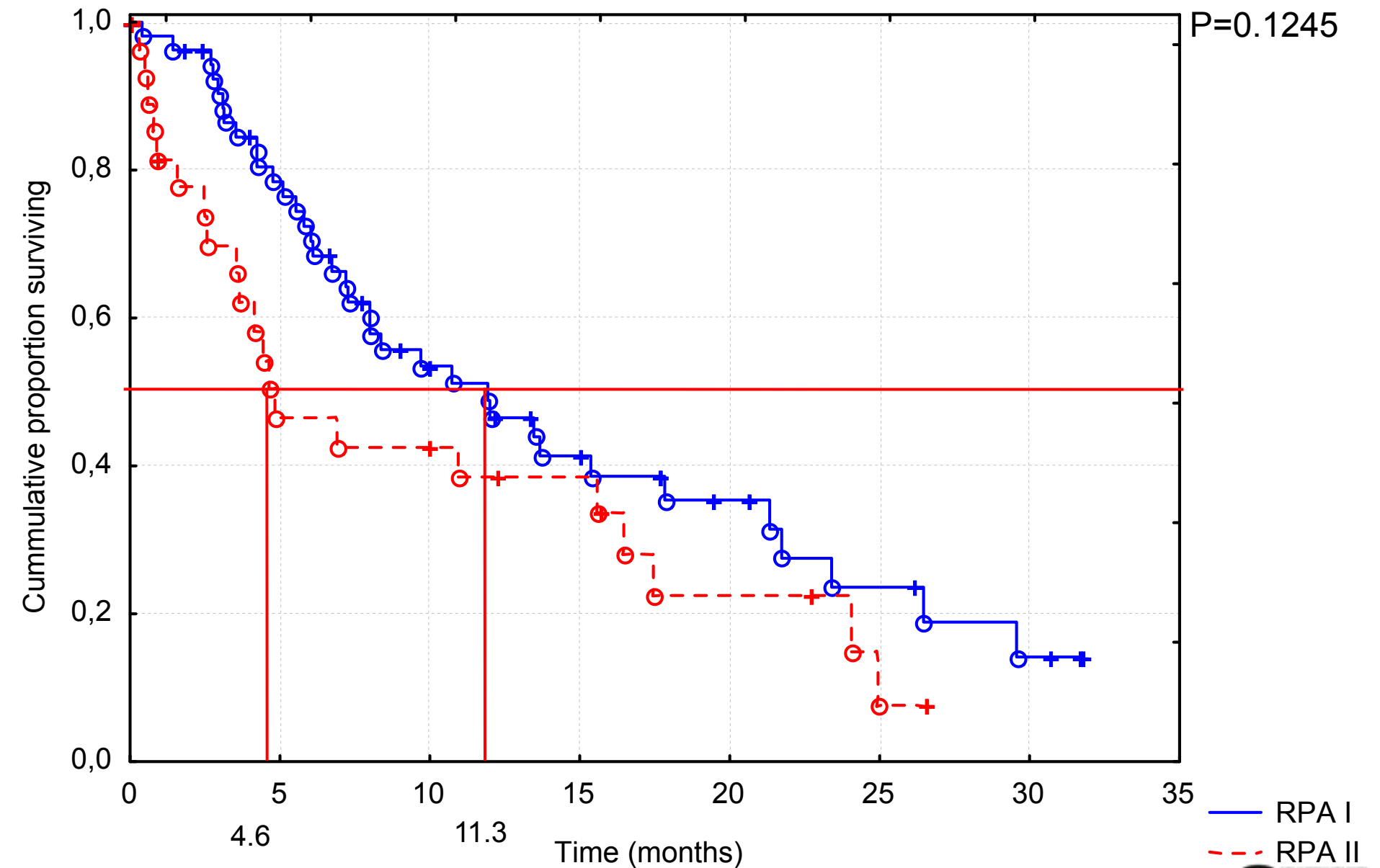
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# Overall survival - Recursive Partitioning Analysis no RPA III patients in the group

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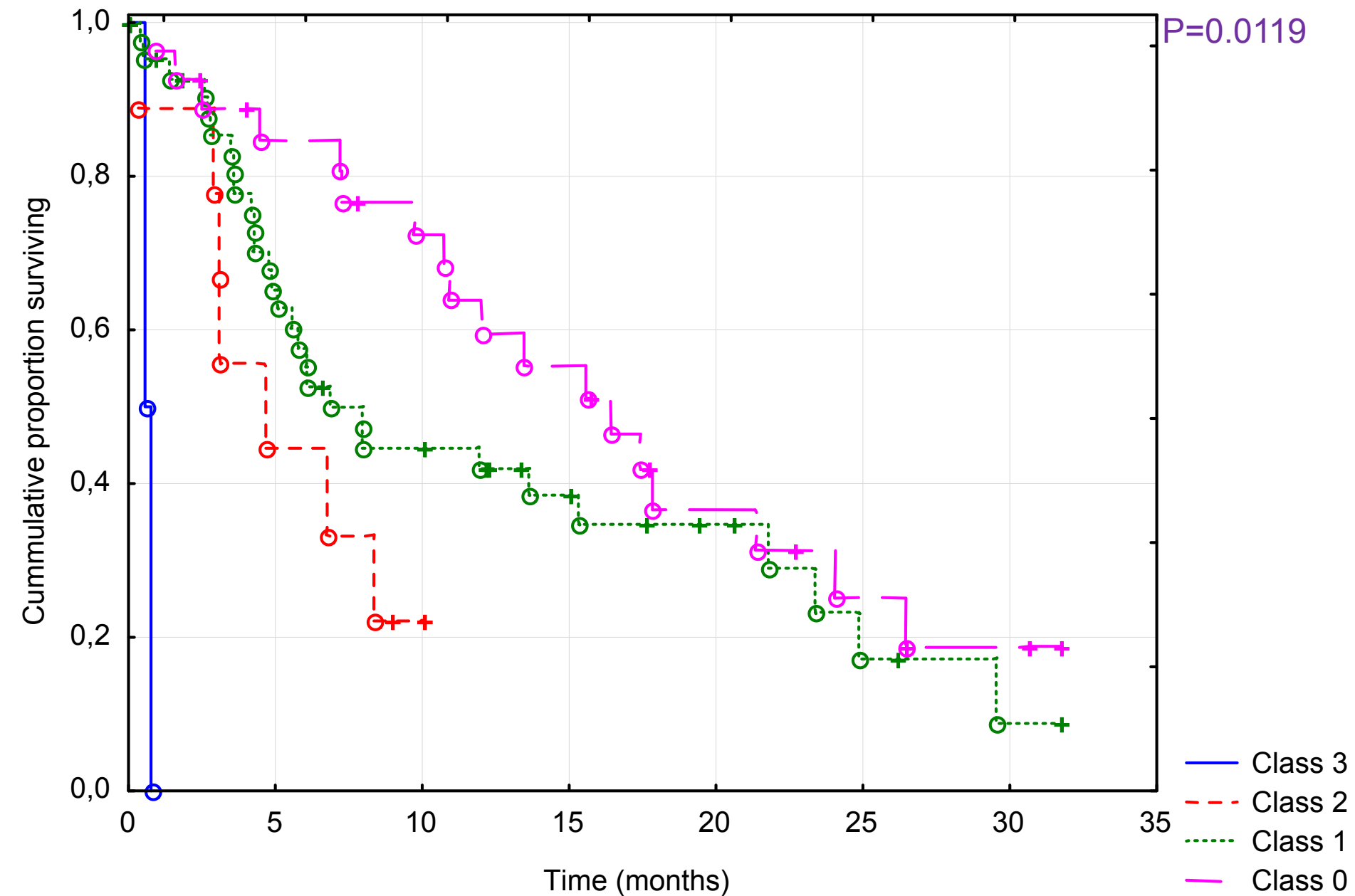
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# Overall survival - Basic Score for Brain Metastases

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P=0.0119



# Results – median survival

	Median survival (months)	
Class	Current study	RTOG database*
RPA I	11.3	7.7
RPA II	4.6	4.5
BSBM 3	15.7	7.0
BSBM 2	6.9	5.1
BSBM 1	3.9	3.4
BSBM 0	0.5	2.2
SIR 1-3	0.8	2.1
SIR 4-7	8	6
SIR 8-10	21.6	8.8
GPA 0-1	5.1	2.6
GPA 1.5-2.5	5.5	3.8
GPA 3	12	6.9
GPA 3.5-4	10.6	11

\* Sperduto PW et al. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008; 70(2) :510-514



# Cox proportional hazard model results

	Significant variables from included in the model		
	Model I Significant in univariate analysis	Model II* Proposed prognostic	Model III* Proposed prognostic
	p	p	p
Primary breast/lung	0.03	0.053	-
Primary site (all included)	-	-	0.005
Single lesion	0.11	0.044	0.03
BSBM	0.016	0.008	0.01
SIR (collapsed)	0.04	0.18	0.14

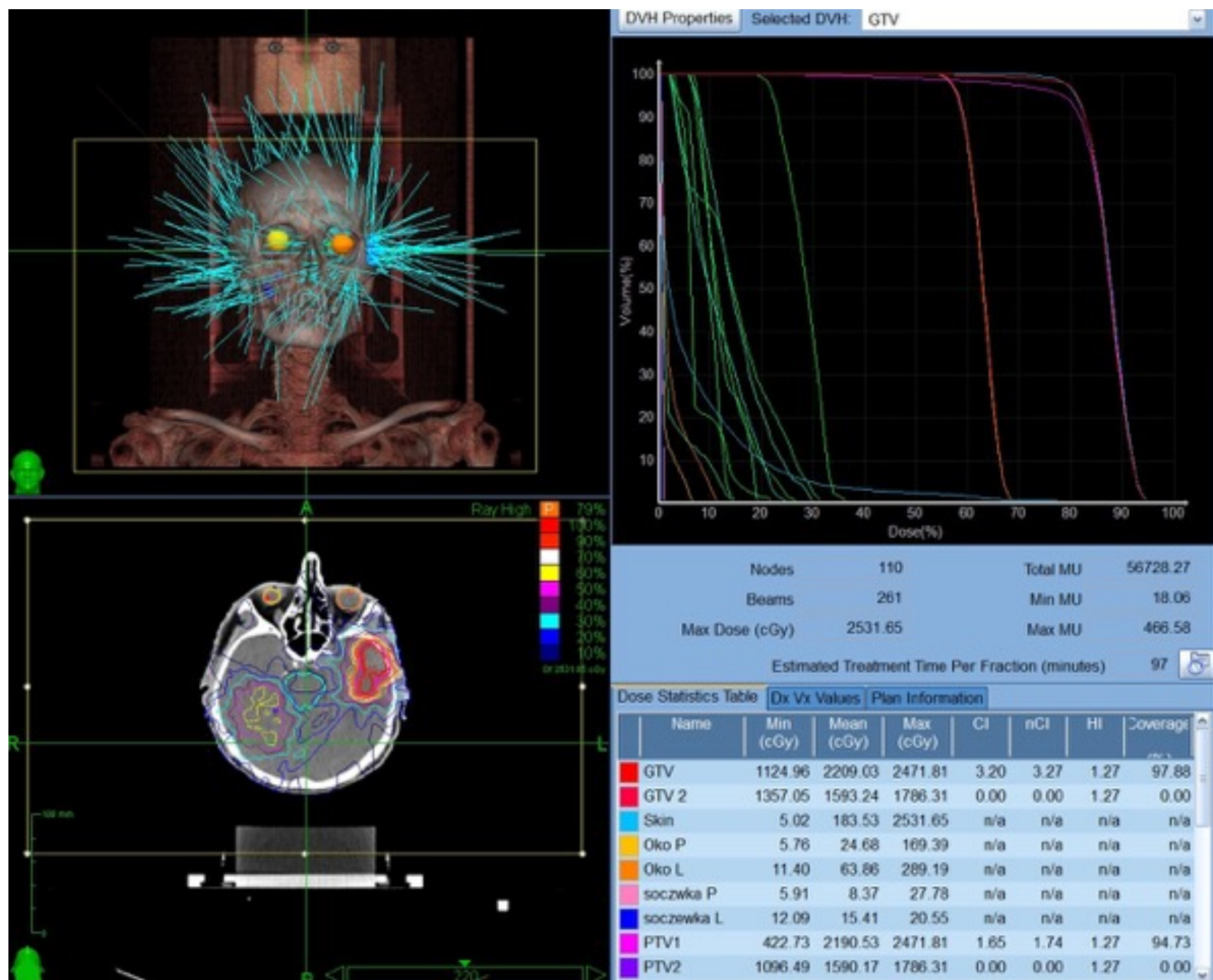
\*Primary site: lung or breast versus others, prognostic variables commonly proposed in the literature included

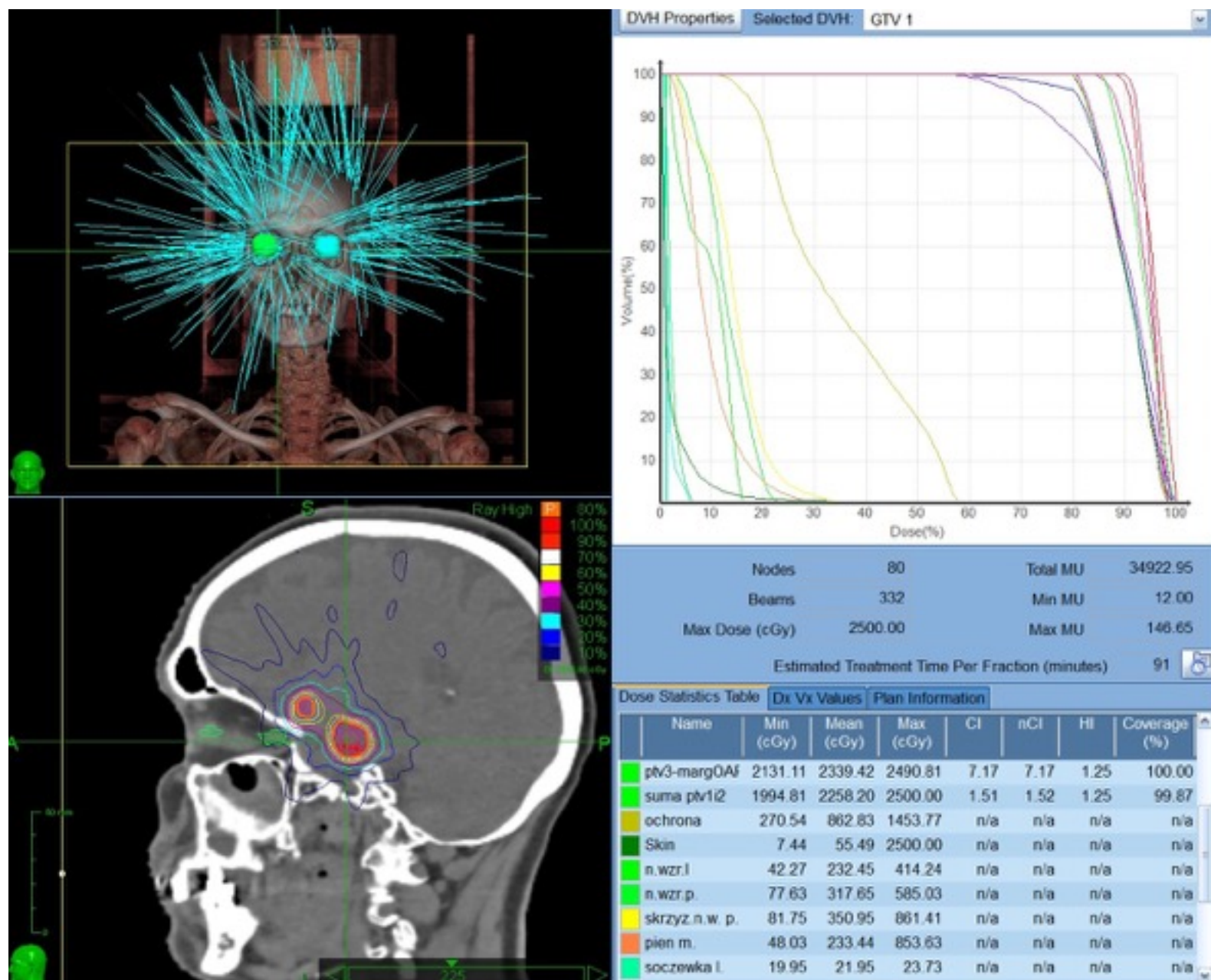
\*\* Primary site: all localizations included, as well as prognostic variables commonly proposed in the literature



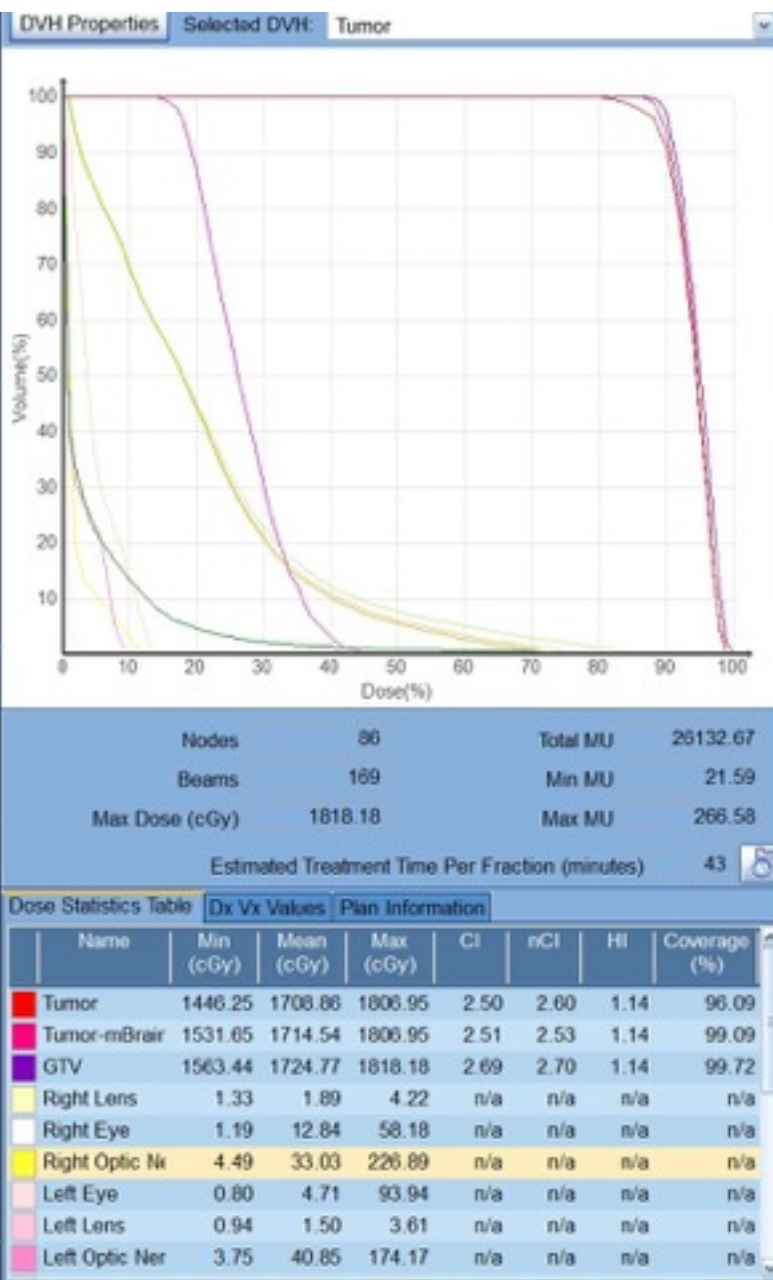
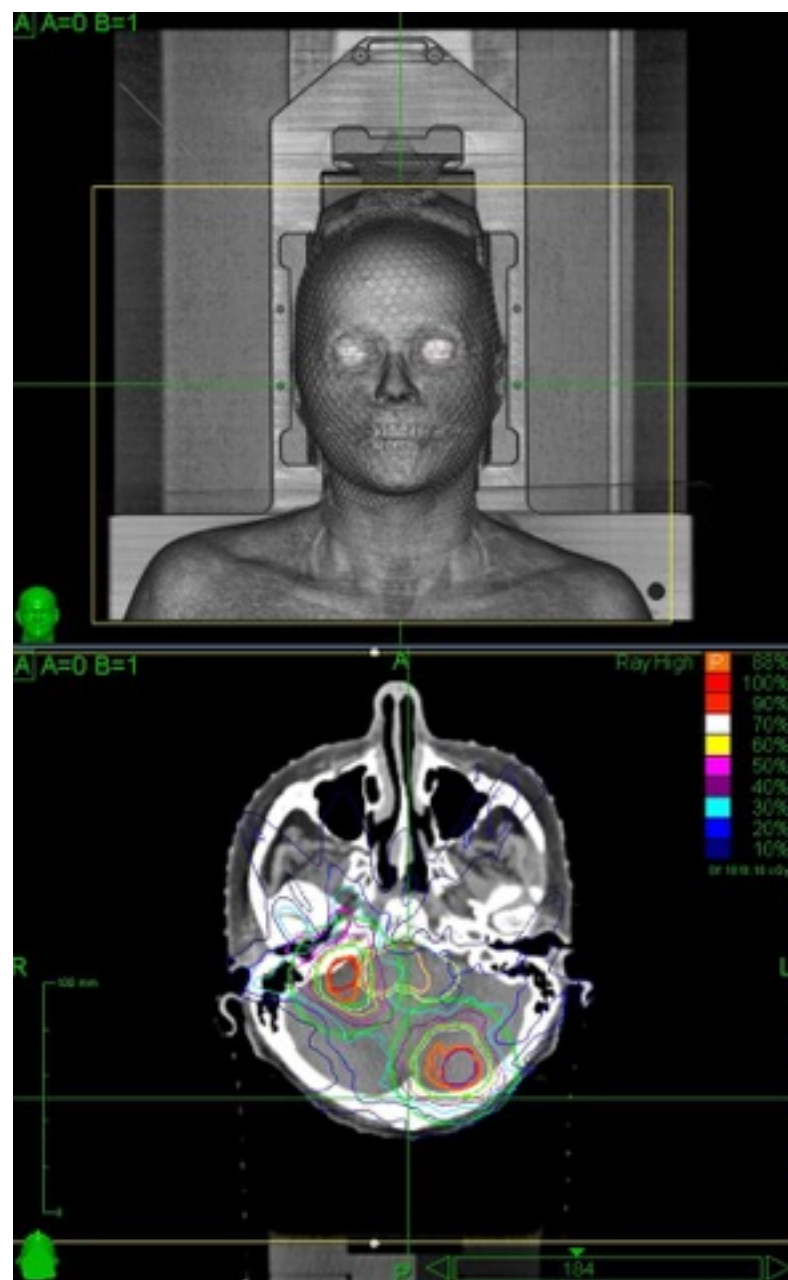
## Results – local control

- ✓ Evaluation of response in imaging data not available in 44 patients (52%)
- ✓ Median local control 20 months
- ✓ Local control better in patients with one lesion ( $p = 0.0064$ )
- ✓ No difference between single fraction and fractionated treatment
- ✓ No difference between smaller and larger volume lesions ( $> 13$  ml and  $< 2$  ml)
- ✓ Comparison of outcomes in patients with single and oligo- or multiple metastases with respect to subsequent variables deemed inaccurate due to small sample size









# Conclusions

- ✓ Stereotactic radiosurgery and fractionated stereotactic radiotherapy produce similar results in terms of overall survival
- ✓ Overall survival depends on the primary diagnosis, number of metastases (single versus more) and BSBM score
- ✓ Patients with 2 lesions and 3 or more metastases benefit from the stereotactic treatment in a similar way

# Acknowledgement

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