Frontiers of Radiosurgery

OCTOBER 24 & 25, 2019
MILANO, ITALY

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Factors Affetcting Outcome in Image-guided Radiosurgery for Trigeminal Neuralgia

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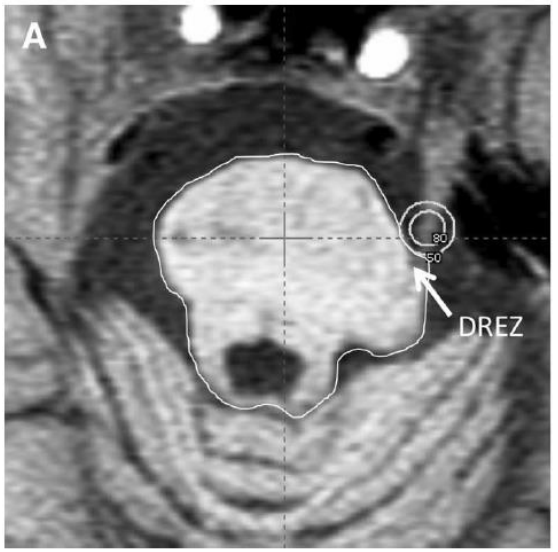
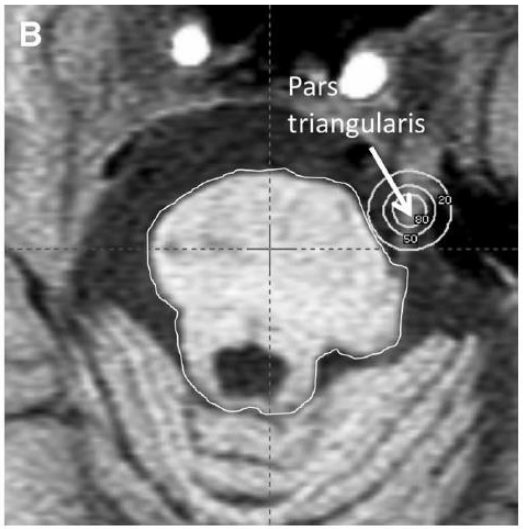
Radiosurgery: state-of-the art

- Ideal dose
  - Current practice: isocentric technique, 70 to 90 Gy max dose (4-mm isocenter)
- Isocenter location
  - Root entry zone (REZ)
  - Pars triangularis
  - Where 20 Gy isodose line is tangential to brainstem
- Due to isocentric geometry, a 4-mm span can be treated.
- Attempts to treat with two isocenters create a hot spot in the middle and result in no pain improvement but higher hypestesia





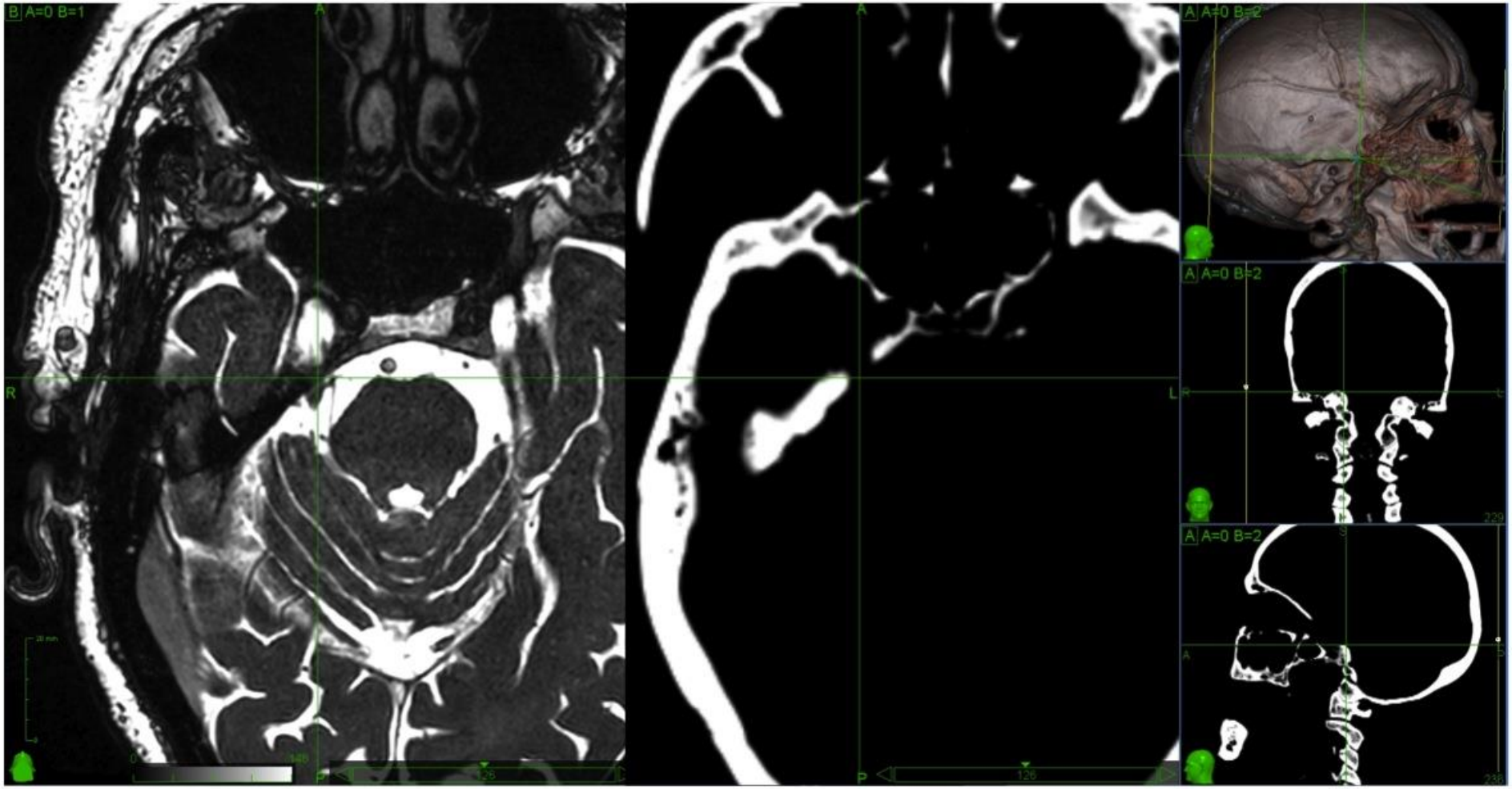
Radiosurgery for TN: Outcomes

High rates of early pain relief are followed by recurrence in about 50%

- Outcomes
  - **At least 50% reduction in pain in 77 to 95% of patients (11 refs.)**
- 4 studies report long-term results
  - Dhople et al. (**J Neurosurg 111:**351–358, 2009)
    - 102 pts, 5.6-year f/u (75 Gy)
    - 3-, 5-, 7-year freedom from pain: 41%, 34%, and 22%
    - Bothersome hypesthesia 6% (overall rate not reported)
  - Kondziolka et al. (**J Neurosurg 112:**758–765, 2010)
    - 107 pts, more than 5-year f/u (80 Gy)
    - 3-, 5-, and 10-year freedom from pain 71%, 46%, and 30%
    - Sensory dysfunction: 10.5%
  - Young et al. (**J Neurosurg 119:**1166–1175, 2013)
    - 250 pts 5.75-year f/u (90 Gy)
    - 170 patients (71.4%) were pain free and 213 (89.5%) had at least 50% pain relief
    - hypesthesia in 32.9% (very bothersome in 4.5%). Dry-eye syndrome in 22.4%, jaw weakness in 11.2%.
  - Regis et al. (**J Neurosurg 124**:1079–1087, 2016)
    - 497 pts. 3.63 years f/u (85 Gy)
    - 3-, 5-, 7-, and 10-year freedom from pain 71.8%, 64.9%, 59.7%, and 45.3%
    - The hypesthesia actuarial rate at 5 years was 20.4% and at 7 years reached 21.1%, but remained stable until 14 years

What‘s Different with CyberKnife?

- Minimally invasive
- The non-isocentric approach introduces a series of new and unexplored issues for treatment
- With a non-isocentric technique, the dose is not the only parameter to consider
- Actually, volume of the treated nerve and the dose received by the surrounding structures must be taken into consideration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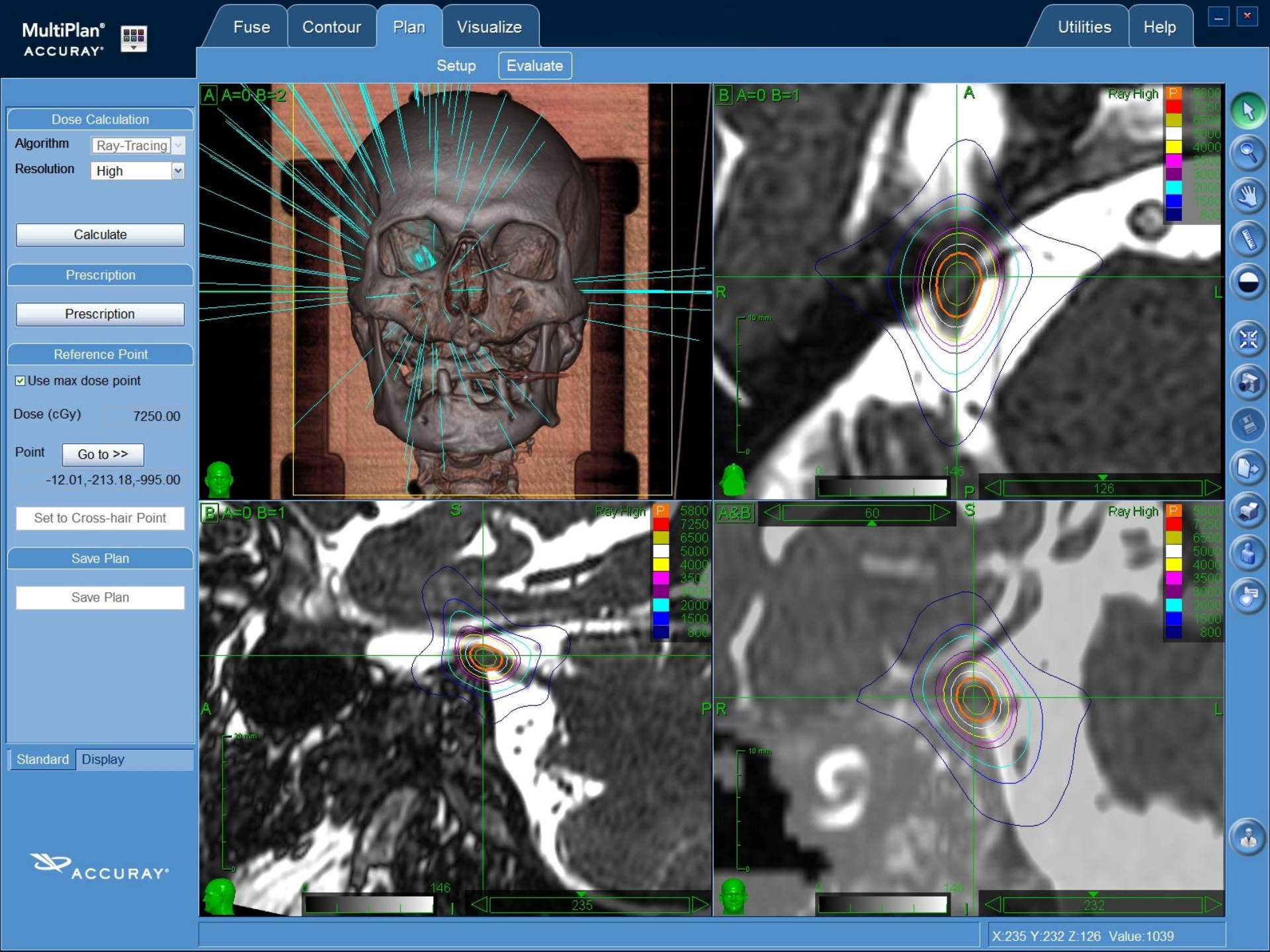
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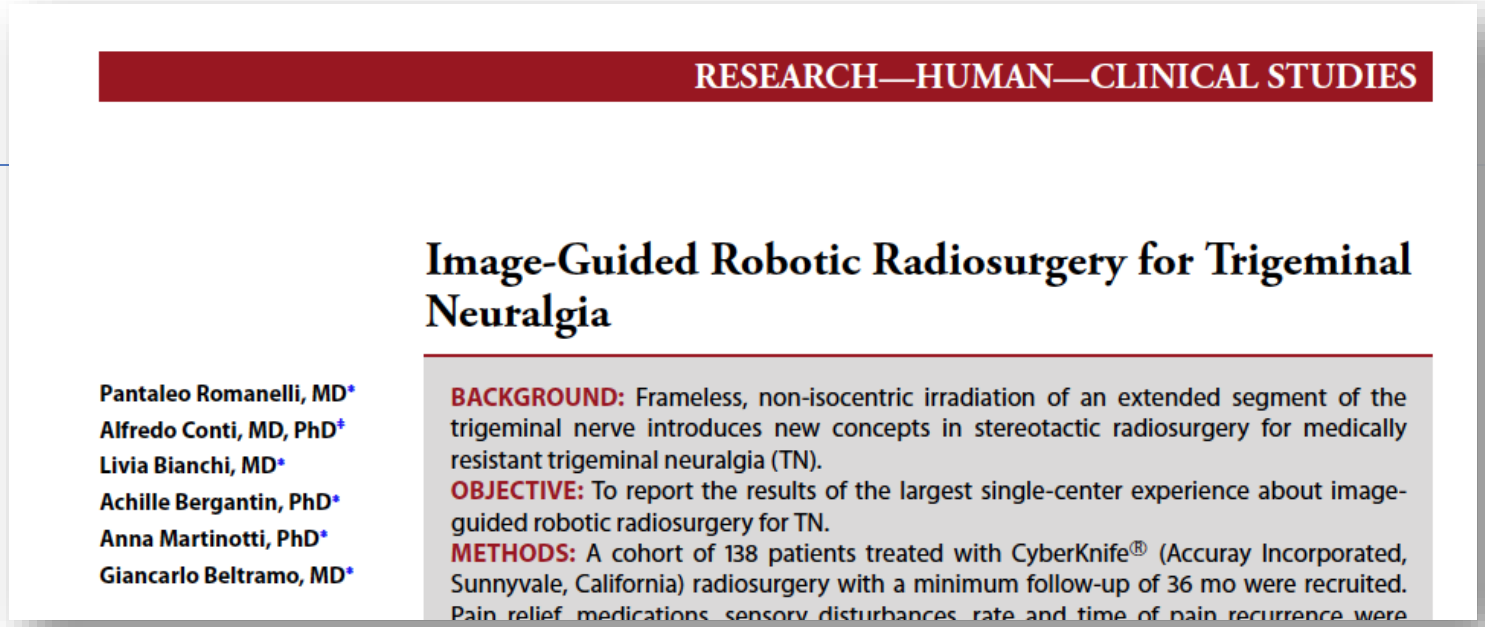

RESEARCH—HUMAN—CLINICAL STUDIES

Image-Guided Robotic Radiosurgery for Trigeminal Neuralgia

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BACKGROUND: Frameless, non-isocentric irradiation of an extended segment of the trigeminal nerve introduces new concepts in stereotactic radiosurgery for medically resistant trigeminal neuralgia (TN).
OBJECTIVE: To report the results of the largest single-center experience about image-guided robotic radiosurgery for TN.
METHODS: A cohort of 138 patients treated with CyberKnife® (Accuray Incorporated, Sunnyvale, California) radiosurgery with a minimum follow-up of 36 mo were recruited. Pain relief, medications, sensory disturbances, rate and time of pain recurrence were

Format:
Abstract

Full text links

ELSEVIER FULL-TEXT ARTICLE

World Neurosurg. 2017 Jul;103:702-712. doi: 10.1016/j.wneu.2017.04.102. Epub 2017 Apr 26.

Frameless Stereotactic Radiosurgery for Treatment of Multiple Sclerosis-Related Trigeminal Neuralgia.

Conti A[1], Pontoriero A[2], Iatì G[2], Esposito F[3], Siniscalchi EN[4], Crimi S[4], Vinci S[5], Brogna A[6], De Ponte F[4], Germanò A[3], Pergolizzi S[2], Tomasello F[3].

Author information

RESPONSE RATE

Systematic Review of Literature

	Year	Response Rate	Percentage
Romanelli et al.	2003	7/10	70%
Lim et al.	2005	38/41	89.6%
Lim et al.	2006	26/29	89.6%
Patil et al.	2007	4/7	57%
Villavicencio et al.	2008	64/95	67%
Adler et al.	2009	33/46	72%
Borchers et al.	2009	45/46	97.8%
Fariselli et al.	2009	22/33	67%
Tang et al.	2011	11/14	78.6%
Lazzara et al.	2013	15/17	88%
Karam et al.	2014	18/25	72%
Singh et al.	2016	142/163	87.1%
Conti et al.	2017	23/27	85.2%
Romanelli et al.	2018	129/138	93.5%
Zhang et al.	2018	55/66	83.3%
Pooled		**632/757**	**83.5%**

Toxicity

Systematic Review of Literature

Complications	Number of patients (%)
Facial numbness (not bothersome)	101 (12.3%)
Facial numbness (bothersome)	70 (9%)
Decreased corneal reflex	11 (1.4%)
Increase in trigeminal distribution anesthesia	7 (0.9%)
Anesthesia dolorosa	6 (0.8%)
Generalized pain	5 (0.6%)
Masticator weakness	5 (0.6%)
Nausea	4 (0.5%)
Trismus	3 (0.4%)
Diplopia	2 (0.3%)
Urticaria	2 (0.4%)
Hearing loss	3 (0.1%)
Paresis	1 (0.1%)
Other not specified	9 (4.1%)

Setting and Study Design

A Cooperative Study

- The patients data were retrospectively analyzed. Data were pooled from the CyberknifeCenter at Charité Universitätsmedizin Berlin (BerCK), the CyberKnife Center at University of Messina, Italy (MesCK) and the CyberKnife Center at the Centro Diagnostico Italiano, Milan (MilCK).
- 296 procedures were performed in 262 patients between 2009-2018.
- Clinical follow up was carried out 3-6 months after CK-SRS and then once a year. We included the latest available follow up in this analysis.
- The end-points analyzed were: i) effects on pain scores, ii) effects on medication, iii) occurrence of sensory disturbance, iv) rate of pain recurrence.

Methods

Pain level was scored using the Barrow Neurological Institute (BNI) pain scale

- I: no trigeminal pain, no medication;
- II: occasional pain, not requiring medication;
- IIIa: no pain, continued medication;
- IIIb: controlled with medication;
- IV: some pain, not adequately controlled with medication;
- V: severe pain, no pain relief

For hypoesthesia evaluation, we used the BNI facial hypoesthesia scale

- I: no facial numbness;
- II: mild facial numbness, not bothersome;
- III: facial numbness, somewhat bothersome;
- IV: facial numbness, very bothersome

- We dicothomized the pain response as sufficient or inadequate after SRS as BNI grades I-IIIb and IV-V, respectively. Similarly, we defined a clinically not significant or bothersome numbness as BNI grades I-II and III-IV, respectively

- We also recorded any possible trigeminal motor deficits.

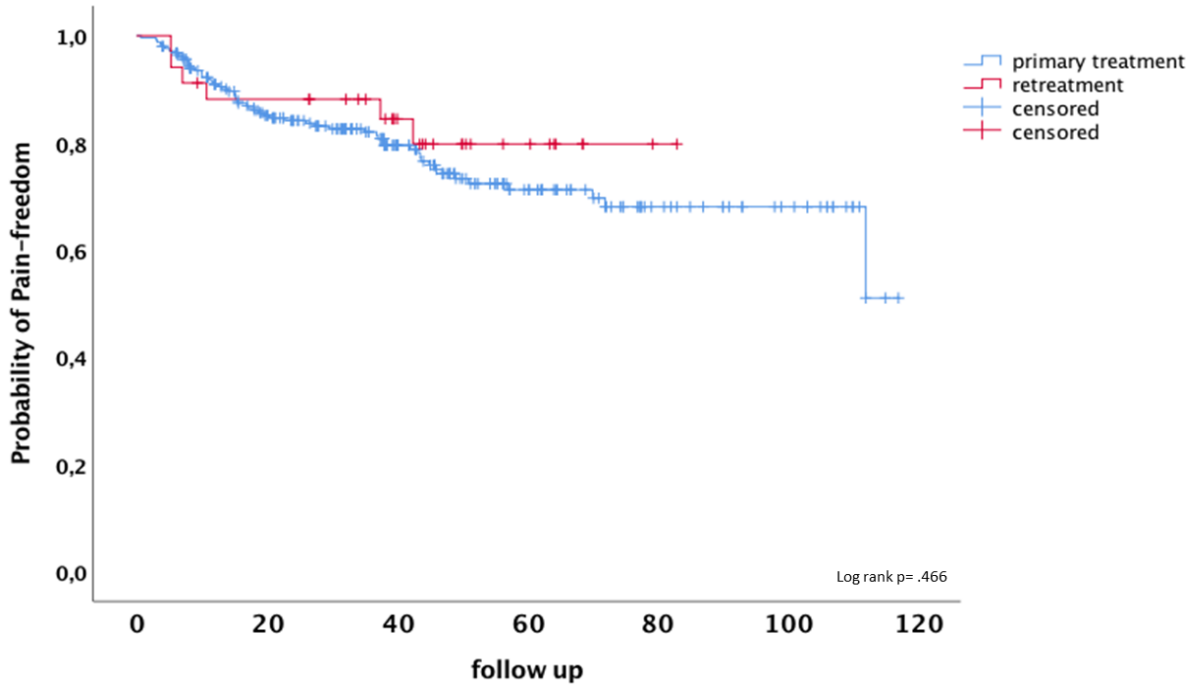
Patients demographic characteristics

Patients	262
Gender M/F	1:1.4
Age at the treatment time (years)	
Median (range)	64 (22-91)
Follow-up (months)	
Mean (sd)	40.7 (±29)
Median (range)	38 (0.7-117)
Retreatments	34
Multiple Sclerosis (n)	17(6.5%)

Summary of treatment parameters in three centers (Messina: MesCK, Milan: MilCK, Berlin: BerCK; PD: prescribed dose, max.: maximal)

		N	Mean ± SD	Median	Min	Max
Volume mm3	**MesCK**	176	29±14.3	25	5.0	103.3
	MilCK	80	27.7±12.3	30	10.0	70.0
	BerCK	40	23.8±12.8	20	10.0	60.5
	overall	296	28±13.7	25	5.0	103.3
PD (Gy)	**MesCK**	176	57.7±6.7	60	35.0	90.0
	MilCK	80	57.4±2.6	58	38.0	60.0
	BerCK	40	60.2±4.1	60	49.0	70.0
	Overall	296	58±5.6	60	35.0	90.0
Isodose (%)	**MesCK**	176	83±3.2	83	73.0	90.0
	MilCK	80	80±0.4	80	78.0	80.0
	BerCK	40	80±3.2	80	70.0	85.0
	Overall	296	81.6±3.1	80	70.0	90.0
Max. Dose (Gy)	**MesCK**	176	70±8.1	71.3	42.7	112.5
	MilCK	80	72±3.3	72.5	47.5	75.0
	BerCK	40	75.7±4	75	70.0	87.5
	Overall	296	71.1±7	72.4	42.7	112.5
Mean Dose (Gy)	**MesCK**	176	63.7±7.3	65.3	38.8	101.3
	MilCK	80	64.7±2.9	65.3	42.8	67.5
	BerCK	40	68.1±3.8	67.5	59.8	80.1
	Overall	296	64.5±6.2	65.3	38.8	101.3
Integral Dose (mJ)	**MesCK**	176	2±0.9	1.6	0.3	6.7
	MilCK	80	1.8±0.8	1.9	0.6	4.4
	BerCK	40	1.6±0.8	1.4	0.7	4.0
	Overall	296	1.8±0.9	1.6	0.3	6.7

Kaplan Meier curve for pain relief divided in primary and retreatment

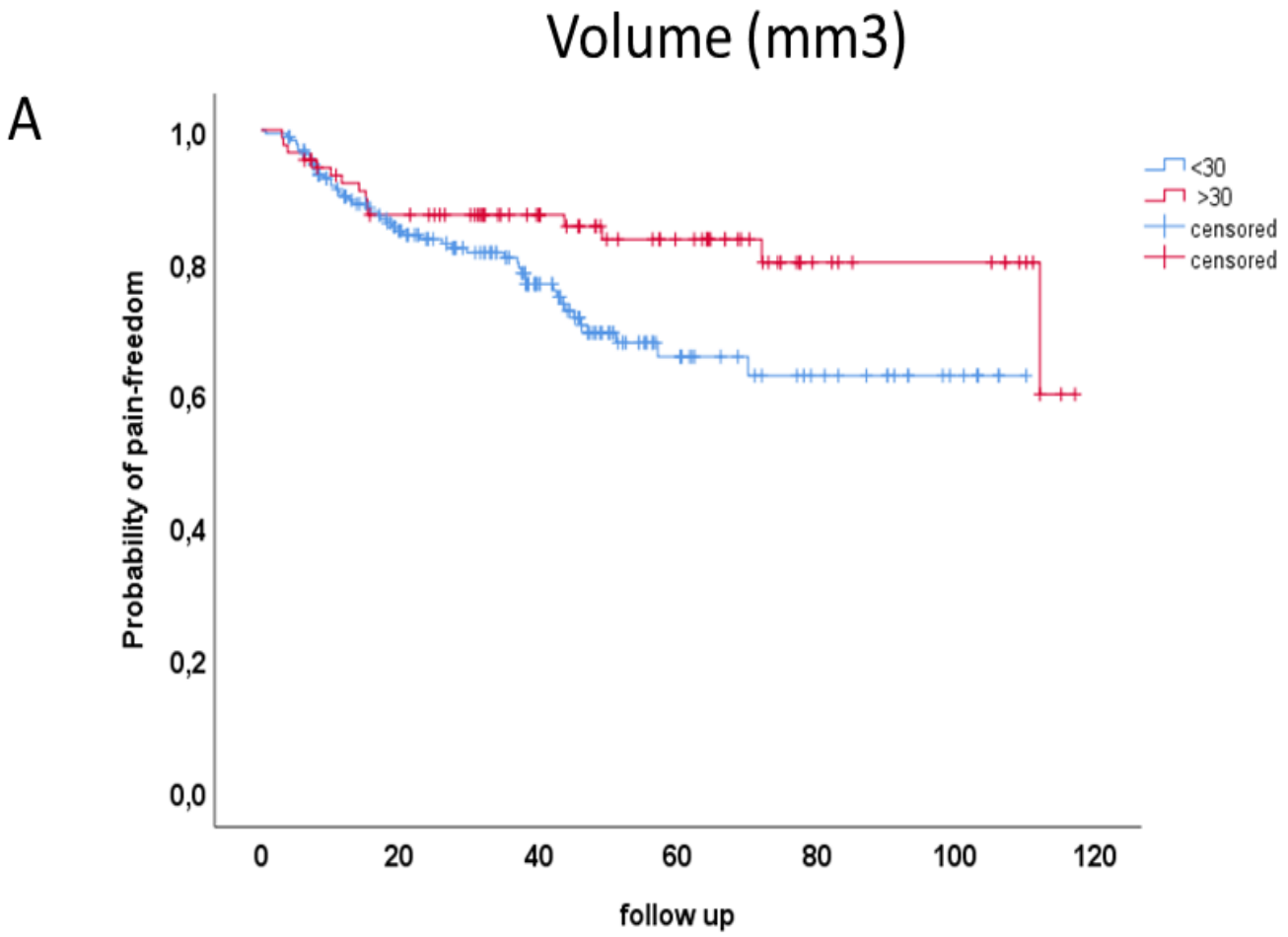


	6	12	24	36	48	60 mos.
Primary	96.8%	90.9%	84.2%	81.4%	74.2%	71.2%
Retreatment	91.2%	88.1%	88.1%	88.1%	79.8%	79.8%

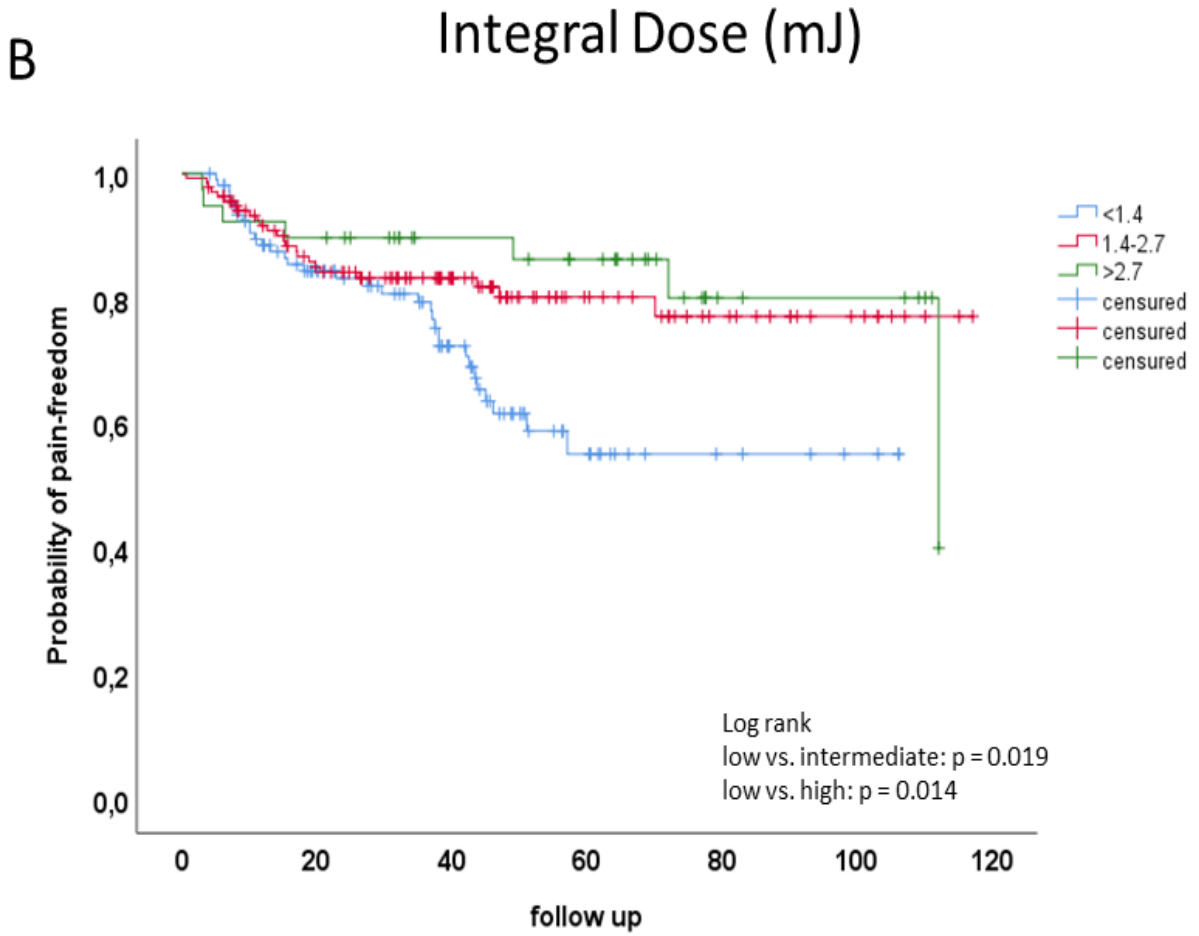
Radiometric Parameters and Pain Outcome

Variables	Patient (n)	χ^2 and p value
		Pain
Volume (<30 mm^3 vs. >30mm^3)	205 vs. 91	χ^2 = 4.675, p = **0.031**
Integral dose (<1.4, 1.4-2.7, >2.7)	114 vs. 144 vs. 39	low vs. intermediate: χ^2 = 5.5.02, **p = 0.019** low vs. high: χ^2 = 6.026, **p = 0.014** intermediate vs. high, χ^2 = 0.221, p = 0.638
Mean dose (<63 vs. >63 Gy),	75 vs. 221	χ^2 = 1.803, p = 0.179
Maximal dose (<72 vs. >72 Gy)	132 vs. 164	χ^2 = 2,756, p = 0.097
Prescribed dose (<58 vs. >58 Gy)	130 vs. 166	χ^2 = 0.44, p= 0.838

Kaplan Meier comparison of the curves of pain-freedom probability according to target volume (<30mm3 vs. >30 mm3)



Kaplan Meier comparison of the curves of pain-freedom probability according to integral dose (<1.4 mJ; 1,4-2,7->2,7 mJ)



Univariate and multivariate analysis for factors affecting occurrence of numbness

	Univariate Analysis			Multivariate Analysis		
	p value	**HR**	**95% CI**	**p value**	**HR**	**95% CI**
Age	.477	.993	.974-1.013			
Gender	.439	.807	.470-1.388			
Volume	**.031**	1.021	1.002-1.040	.972	.996	.784-1.264
Prescribed Dose	**.012**	.939	.894-.986	.853	.985	.841-1.154
Integral Dose	**.100**	1.272	.955-1.696	.838	1.472	0.37-59.357
Mean Dose	.449	1.018	.972-1.065			
Maximal Dose	**.011**	.950	.913-.988	.726	.978	.862-1.109
Retreatment	**.000**	.093	.042-.209	**.000**	.102	.044-.237
MS	.223	.520	.182-1.487			

Conclusions

This study represents the largest frameless CKS series that analyzes possible treatment parameters as predictors of outcome in addition to the description of efficacy and safety profile of the technique.

Our study confirmed that single treatment parameters are not enough to predict treatment efficacy of SRS in TN.

The integral dose including mean dose and nerve volume is apparently relevant, as it may differ significantly in treatments using apparently similar dose and volume constraints. Our study supports the concept of personalized radiosurgery for the best treatment outcome and warrants future prospective studies.