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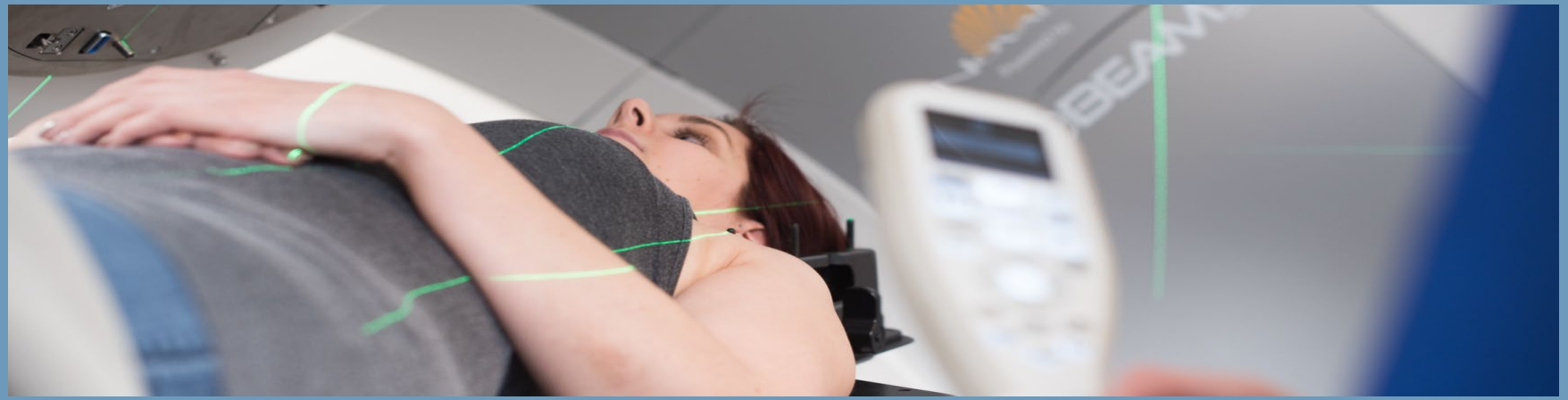
PREOP-2 A randomised trial of preoperative radiosurgery vs postoperative stereotactic radiotherapy for resectable brain metastases

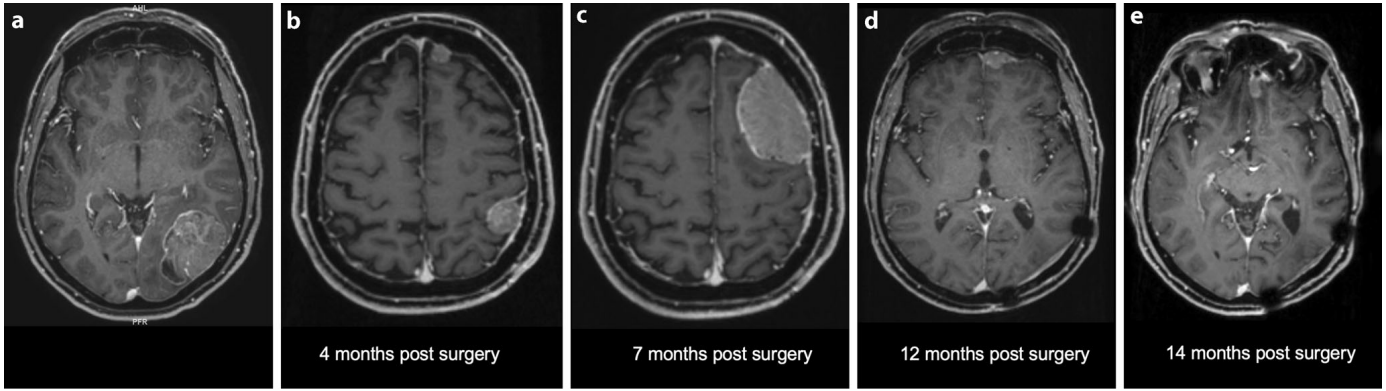
Susanne Rogers, MD PhD, Stv Chefärztin, Kantonsspital Aarau, Radio-Onkologie-Zentrum KSA-KSB



Inhalt

- Rationale
- Vorbereitung
- Aktuellen Stand
- Nächste Schritte

Background: nodular leptomeningeal disease



Lee *et al*, Strahlentherapie und Onkologie 2021

Rationale for preoperative radiosurgery

- ✓ sterilise tumour cells disseminated at neurosurgery
- ✓ more accurate target volume delineation of intact metastases
- ✓ smaller planning margin
- ✓ irradiated tissue is subsequently resected
- ✓ no additional delay to postoperative systemic therapy
- ✓ patient convenience

Current evidence

Preoperative Radiosurgery for Resected Brain Metastases: The PROPS-BM Multicenter Cohort Study

Roshan S. Prabhu, MD, MS,*,† Reshika Dhakal, MD,* Zachary K. Vaslow, MD,‡ Tu Dan, MD,§ Mark V. Mishra, MD,‖ Erin S. Murphy, MD,¶ Toral R. Patel, MD,# Anthony L. Asher, MD,*,** Kailin Yang, MD, PhD,¶ Matthew A. Manning, MD,‡ Joseph D. Stern, MD,‡,** Ankur R. Patel, MD,†† Zabi Wardak, MD,§ Graeme F. Woodworth, MD,‡‡ Samuel T. Chao, MD,¶ Alireza Mohammadi, MD,§§ and Stuart H. Burri, MD*,†

- 242 patients
- 62.4% had a single BM
- 93.7% underwent GTR
- 98.8% were treated with a single fraction, med. dose of 15 Gy, med. GTV 9.9 cm^3
- Cavity local recurrence (LR) rates at 1 and 2 years were 15% and 17.9%
- 1 and 2-year rates of (all) LMD were 6.1% and 7.6%
- 1 and 2-year rates of any grade ARE were 4.7% and 6.8%
- Med. overall survival was 16.9 months and the 2-year OS rate was 38.4%
- 10/242 (4.1%) experienced grade ≥3 postoperative surgical complications
- Subtotal resection was a strong independent predictor of LR (hazard 9.1; $P < .001$)

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-021-03840-5

CLINICAL STUDY

Check for updates

Five fraction stereotactic radiotherapy after brain metastasectomy: a single-institution experience and literature review

S. Rogers[1] · A. Stauffer[2] · N. Lomax[1] · S. Alonso[1] · B. Eberle[1] · S. Gomez Ordoñez[1] · T. Lazeroms[1] · E. Kessler[1] · M. Brendel[3] · L. Schwyzer[2] · O. Riesterer[1,4]

	Literature	KSA series
Med. local control rate 1yr	81.6%	82.5%
Med. incidence LMD 1yr	16.2%	17.0%
Med. incidence radionecrosis 1yr	8.8%	0.0%

Strahlenther Onkol
https://doi.org/10.1007/s00066-022-01991-6

SHORT COMMUNICATION

Stereotactic radiosurgery and radiotherapy for resected brain metastases: current pattern of care in the Radiosurgery and Stereotactic Radiotherapy Working Group of the German Association for Radiation Oncology (DEGRO)

S. Rogers[1] · B. Baumert[2] · O. Blanck[3] · D. Böhmer[4] · J. Boström[5] · R. Engenhart-Cabillic[6] · E. Ermis[7] · S. Exner[8] · M. Guckenberger[9] · D. Habermehl[10] · H. Hemmatazad[7] · G. Henke[11] · F. Lohaus[12] · S. Lux[13] · S. Mai[14] · D. Minasch[15] · A. Rezazadeh[16] · C. Steffal[17] · S. Temming[18] · A. Wittig[19] · C. Zweifel[2] · O. Riesterer[1] · S. Combs[20]

Table 2 Details of current approaches to postoperative hypofractionated stereotactic radiotherapy as provided by 16 centres

Maximum number of BMs?	Maximum cavity size?	CTV definition	PTV margin (mm)	Number of fractions	Dose per fraction (Gy)	Prescription	Constraints to organs at risk according to	Technique
No	No	Visible cavity using pre- and postop MRI	CTV + 0–1	3 5	7–8 5.5–6	65–70%	Grimm et al. 2011 [6]	CyberKnife
NR	NR	Cavity + 2 mm	CTV + 1	7	5	95% covering isodose	NR	–
No	No	Cavity + residual tumour	CTV + 2	3 or 7	9 5	98–100% PTV to be covered with 90–95% isodose	Hanna et al. 2018 [7]	Dynamic conformal arcs or VMAT (linac)
NR	"larger"	NR	NR	6–7	5	NR	V12 < 10 cc	Gamma Knife
5–10	< 3 cm	Cavity on CT and MRI	Cavity + 1–2	11	3.8	95% covering isodose	Dmax = 90%	Non-coplanar arcs (linac)
1–3 BM	4 cm	Including surgical tract	CTV + 3	7	5	95% covering isodose	Brainstem and optic nerves < 54 Gy, normal brain ALARA	RapidArc (Varian, Palo Alto, CA, USA) (linac)
5	None; if considered too large we rather decide individually for ICRU prescription (mean; 95–107% ID), or 6 × 5 Gy or even whole brain in some cases	Cavity + residual tumour + 1–2 mm	CTV + 2	5 or 6	6 or 5	75–80% covering isodose	Brainstem Dmax 25 Gy Chiasma: max. 25 Gy V20Gy < 0.2 cm^3 Optic nerve: V25Gy < 0.03 cm^3	VMAT, 2 coplanar arcs (linac)
Max. 2 cavities and max 5 intact BMs	Max 7 cm	Cavity + residual disease	CTV + 2	5	6–7	80% PTV Dmean = 100%	Benedict et al. 2010 [8]	Linac
NR	NR	Cavity + 5 mm	CTV + 1	5	6	100%	NR	3D/VMAT/IMRT (linac)
NR	If PTV > 10 cm^3	Cavity + residual tumour	CTV + 2	3 or 5	8 6	70–80% isodose	NR	CyberKnife
NR	> 5 cm^3	NR	CTV + 2–3	5–7	5	95–100%	D2% brainstem 35 Gy Chiasma D2% 30 Gy Cochlea mean 24 Gy	Linac
None	No	Cavity	CTV + 2 mm	6	5	80%	Chiasma/optic nerves	VMAT (linac)

PREOP-1: a feasibility trial of preoperative radiosurgery for resectable brain metastases

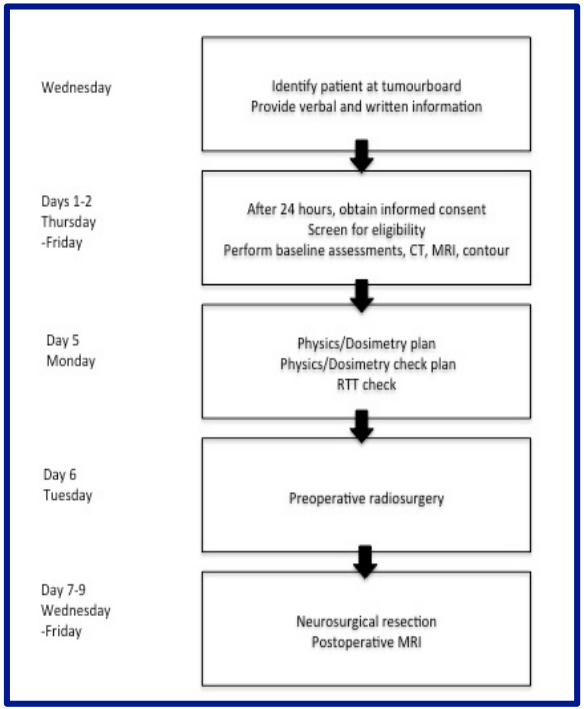
[1]S Rogers, [2]L Schwyzer, [1]N Lomax, [1]S Alonso, [1]T Lazeroms, [1]S Schwenne,[1]S Gomez, [2]S Berkmann, [2]A Tortora, [1]S Marbacher, [2]GA Schubert, [1]O Riesterer

[1]Center for Radiation Oncology KSA-KSB, Kantonsspital Aarau

[2]Department of Neurosurgery, Kantonsspital Aarau

Manuscript in preparation

Methods (DRKS00023579)



- histological diagnosis of a solid tumour
- brain metastases on T1Gd MRI
- 1 BM <4cm indicated for resection, up to 3 other BMs <2.5 cm for SRS or fSRT
- indication for elective neurosurgical resection given at a neurooncology tumorboard
- no LMD unless adjacent and can be resected
- gross total resection anticipated
- estimated prognosis 12 months
- no prior brain tumour, irradiation or surgery
- no contraindication for MRI or steroids

Results

Patient characteristics	N=12
Gender M:F	3: 9
Age (yrs) median (range)	65 (41-77)
Karnofsky performance status (%) median (range)	70 (70-100)
Histology -Non-small cell lung cancer -Melanoma -Oesophageal cancer -Colorectal cancer -Breast cancer	 4 2 2 3 1
Median number of BMs per patient (range)	1 (1-3)
Synchronous: metachronous BM	3: 9 (25%)
Location of BM for resection -frontal lobe: cerebellum	 9: 3
Symptomatic BM for resection Y: N -neurocognitive symptoms -cerebellar symptoms -Broca's aphasia	8:4 (66.6%) 5/8 2/8 1/8
Extracranial metastases Y:N	10:2 (83.3%)
Synchronous systemic treatment Y:N	3:9 (25%)

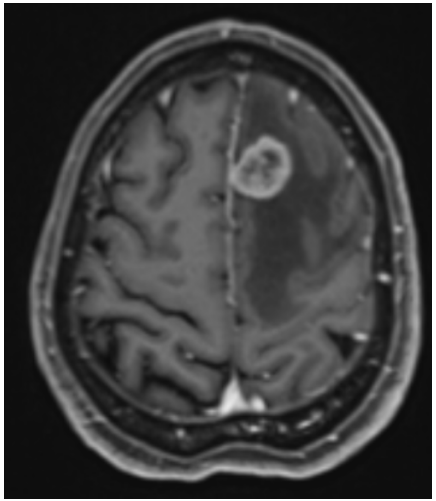
Dosimetric features median (range)	
Gross tumour volume (GTV) (cm^3)	9.6 (4.1 to 16.3)
Diameter of planning tumour volume (cm)	3.7 (2.8-4.7)
Planning tumour volume (PTV) (cm^3)	12.7 (9-26)
Radiosurgery dose (Gy)	16 (14-19)
Prescription isodose (%)	70.4 (69.1-77.7)
Maximum dose (Gy)	23.7 (19.7-25.3)
Dose to 99% of PTV (Gy)	16.1 (11.7-18.4)
Mean dose to PTV (Gy)	20.3 (17.2-22.2)
Dose to 2% of PTV (Gy)	22.9 (19.2-25)
Conformity index	1.16 (1.1-1.3)
Gradient index	2.5 (2.2-2.7
Volume of structure 'brain –GTV' receiving 10 Gy (cm^3)	12.7 (7.5-21.5)

Results

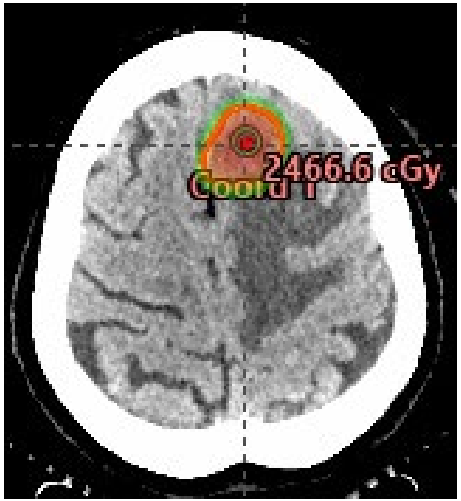
13 patients recruited, 1 patient did not receive preop SRS due to theatre availability

Clinical outcomes	(n=7 evaluable for MR-based endpoints)	
No. of working days from referral to preop SRS	median (range)	5.5 (1-10)
No. of working days from preop SRS to resection	median (range)	1.0 (0-5)
No. of working days from referral to resection	median (range)	6.5 (1-15)
Leptomeningeal recurrence		0/7
Local control		6/7
Distant brain failure		1/7
Salvage SRS/WBRT		1/7
Toxicity grade 2 alopecia		1/12
Alive at last follow-up		6/12

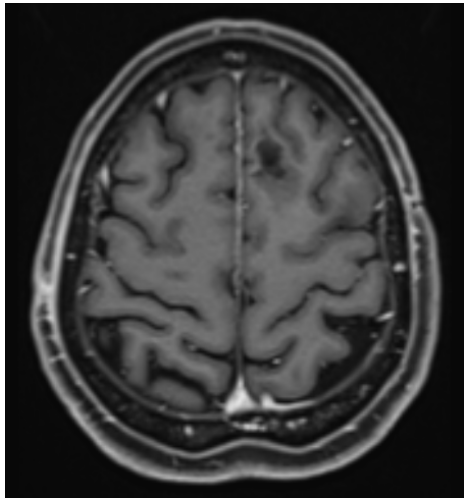
58 yr female, synchronous metastatic CRC



Nov. 2020



DM 3.2 cm, PTV 9.6 cm^3
1 x 17 Gy @70%



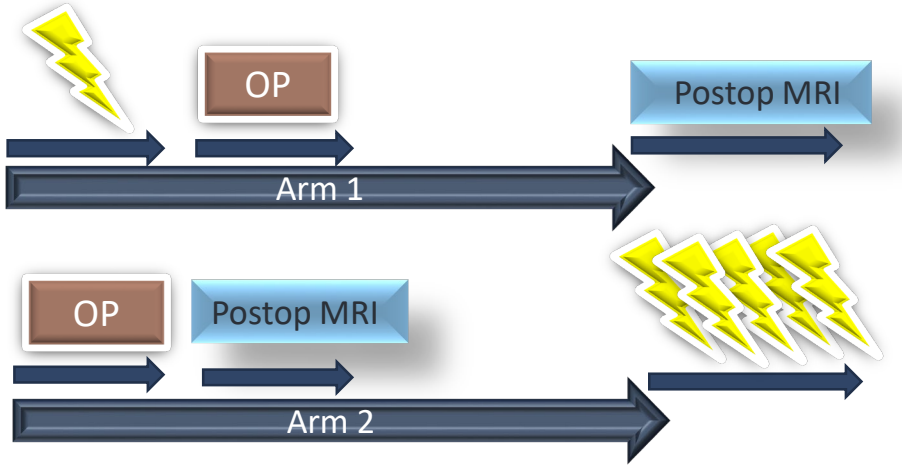
12 mth FU after GTR

Conclusions

- preoperative SRS was feasible in 12/13 patients and safe in 12/12
- one acute toxicity (alopecia grade 2) at 3 months, which recovered by 6 months
- this protocol consitutes the experimental arm of a randomised trial which compares the efficacy of preoperative SRS with postoperative fSRT (PREOP-2)

PREOP-2: a randomised international Phase III trial

- Hypothesis: Reduction in the incidence of leptomeningeal recurrence from 17% following postoperative fSRT to 4% following preoperative SRS
- Primary endpoint: incidence of LMD
- n=160 (CTU USB)



Key Inclusion criteria

1. MRI-diagnosis of a clearly demarcated contrast-enhancing brain metastasis up to 4.0 cm diameter indicated for neurosurgical resection. Up to 3 other brain metastases suitable for primary SRS/ SRT
2. Gross total resection of metastasis predicted by neurosurgeon
3. Survival estimated by primary clinician > 12 months
4. Karnofsky performance status ≥60
5. Histological diagnosis of a malignant primary or metastatic tumour
6. Ability to take steroids
7. No contraindication to MRI

Key Exclusion criteria

1. >10 mm midline shift, effacement of the 4th ventricle or other sign of raised intracranial pressure requiring urgent decompressive surgery
2. Leptomeningeal disease in the CSF or on MRI (unless localized and can be irradiated then resected with the metastasis)
3. Radiosensitive histology: germ cell tumour, small cell lung cancer, lymphoma, multiple myeloma
4. More than 4 brain metastases or the diameter of the metastasis for resection >4.0 cm.
5. More than 1 metastasis requiring resection
6. Prior radiation to the brain (SRS/SRT to lesion to be resected and /or WBRT)
7. Prior resection of a primary or secondary brain tumor
8. Prior radionuclide therapy within 30 days, prior anti-VEGF therapy within 6 weeks
9. Unable to tolerate radiosurgery immobilization and treatment
10. Inability to give informed consent

Primary and secondary endpoints

- The primary endpoint is the incidence of leptomeningeal disease defined as new subarachnoid, ventricular, parenchymal nodular, focal or diffuse pial enhancement, ependymal, subfalcine or cranial nerve enhancement on contrast-enhanced T1-weighted MRI imaging by a neuro-radiologist blinded to the allocated irradiation, defined from the day of randomisation to the date of diagnosis

- The secondary endpoints are local control of the surgical cavity, distant brain failure (new brain metastases), radionecrosis defined as contrast enhancement and oedema in the radiation field

- Overall survival, incidence of neurological death, quality of life (EORTC QLQ-C30 general score and the BN-20 brain module), acute and late toxicity

Study intervention

- The control arm is the standard of care of postoperative hypofractionated stereotactic radiotherapy to the surgical cavity in 5 fractions following resection of the brain metastasis.
- The interventional arm is single fraction preoperative radiosurgery to a brain metastasis identified for neurosurgical resection
- Other small brain metastases may be irradiated after 6 weeks according to the local investigator's judgement. The therapy of extracranial metastases is at the discretion of the local team.

Recruitment, screening and informed consent procedure

- Identification at a neuro-oncology tumour board (weekly or ad hoc)
- Patients will be asked for their decision after a minimum of 15 hours, given the nature of their medical condition
- Independent randomisation after informed consent, eligibility checklist using REDCap (USZ)

Requirements

1) Quality-assured single fraction radiosurgery processes and facilities (platform-independent)

2) Close co-operation with neurosurgeons

TIPS

- Motivated neurosurgeon (Rapport) for early referrals, ad hoc Tumorboards
- Motivated local PI (Neuro TB)
- Give patient ICF and obtain consent next morning
- Reserve planning CT/MRI slots for pre-op RC
- Motivated planning team for quick turnaround

Current state of affairs

- 7 KSA patients approached and randomised
- Multicentre Swiss study

- Submitted to Ethics committees in Kiel and Innsbruck in last 2 weeks Thank you!

DEGRO
ARBEITSGRUPPE RADIOCHIRURGIE/ STEREOTAXIE

- PREOP-2 protocol ready for publication: Co-investigators (signed letter of intent) as co-authors – deadline end of October

Next steps…

- Letter of intent : susanne.rogers@ksa.ch or radioonkologie-forschung@ksa.ch
- Submit protocol to local Ethics Committee with (positive) lead EC verdict to facilitate process
- Sign contract between institutions
- Access to REDCap for randomisation and data entry

Thank you

Forschungsrat KSA

KSA Kantonsspital Aarau

krebsliga aargau

Dose prescription preoperative single fraction SRS

Planning Target Volume (PTV cm^3= GTV + 1mm)	Prescribed dose (Gy)
<2.5	20
2.6-5	19
5.1-7.5	18
7.6-10	17
10.1-17.5	16
17.6-22.4	15
22.5-27.4	14
27.5-35	13
>35	12

There are no published dose constraints for the normal brain for preoperative SRS, however the RTOG 9805 prescription with a 20% dose reduction has been used for over 100 patients without severe toxicity [38]. The above schedule has been used in the PREOP-1 study.

Experimental Arm 1

- The GTVpreop is defined as the outer border of the contrast-enhanced metastasis to be resected, including any contact with the dura, sinus or local meningeal enhancement
- PTVpreop = GTVpreop + 1mm margin
- Up to 3 other non-resected metastases (max. 2.5 cm diameter) may be irradiated with definitive single session radiosurgery. Larger brain metastases can be irradiated with hypofractionated stereotactic radiotherapy after metastasectomy according to the local PI's preference
- Radiosurgery may be delivered as soon as the treatment plan is ready and up to and including the day of neurosurgery

Control Arm 2

- HfSRT should be delivered within 30 days postoperatively
- An MRI for planning (minimum contrast-enhanced T1 MPR sequence) should be acquired on the day of the CT if possible.
- The CTVpostop is defined as the outer border of the surgical cavity including any residual tumour with 5mm-10mm extension along the dura and sinus if there was pre-operative contact according to the consensus guidelines
- PTVpostop = CTVpostop +2mm