Cvek *et al. Radiation Oncology* (2025) 20:33
https://doi.org/10.1186/s13014-025-02608-9

Radiation Oncology

RESEARCH Open Access

# Stereotactic radiosurgery as neuromodulation of refractory angina: an initial case series

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## Abstract

**Background** This intervention pilot case series assessed 40-Gy stereotactic radiosurgery (SRS) neuromodulation applied to the bilateral stellate ganglion (SG) as a bailout procedure for patients with refractory angina pectoris (RAP).

**Materials and methods** The local institutional review board approved this feasibility study. In three patients with RAP, after repeated good response, symptoms were temporarily relieved after anaesthetic blockade of the left SG under ultrasound guidance. Radiosurgical neuromodulation with a dose of 40 Gy in one fraction was used for more permanent pain control. When RAP recurred after the initial SRS, right-sided procedures were considered after a confirmed positive response to right SG anesthetic block.

**Results** No acute or late radiation-related toxicities were observed. Two patients (67%) responded to bilateral SRS (follow-up: 60 and 48 months, respectively). From baseline to 24 months, their average prescribed nitrate package count decreased from 5.5 to 0 and remained low. Daily emergency nitrates declined from 20 to 30 to 1–2 applications, and walking distance improved from 10 to 20 m to 200–400 m and remained stable. Quality of life as measured with the EQ-5D and all domains of the Seattle Angina Questionnaire improved. The third patient received only unilateral SRS, had a temporary improvement for 6 months before a return to baseline, and died after 42 months of follow-up.

**Conclusions** Bilateral radiosurgical neuromodulation at 40 Gy appears to be feasible, safe, and effective as a bailout procedure for RAP.

**Keywords** Radiosurgery, Refractory angina

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## Background

Refractory angina pectoris (RAP) is defined as Canadian Cardiovascular Society (CSS) class III or IV angina [1], characterized by marked limitation or inability to perform ordinary physical activity without discomfort for ≥ 3 months, with objective evidence of myocardial ischemia despite optimal medical therapy, lifestyle modifications, and revascularization procedures [2, 3]. RAP predominantly affects males, with an estimated incidence of 0.3–1.7% in patients with coronary artery disease (CAD) [2, 4].

Neuromodulation represents an emerging nonpharmacological approach for improving quality of life in RAP [5] by interrupting the sympathetic signals responsible for vasoconstriction and pain [6]. Although invasive neuromodulatory procedures carry significant risks, with postimplant complication rates reaching 30–40% [7], various approaches targeting the stellate ganglion (SG) show promise such as transcutaneous/subcutaneous electrical nerve stimulation and spinal cord stimulation (SCS) [8, 9]. Ultrasound-guided C6 SG block, introduced by Kapral in 1995 [10], demonstrates feasibility and safety [11, 12] but provides only temporary relief [13]. Alternative approaches include radiofrequency-based percutaneous sympathectomy [14] and right SG block, which suppresses cardiac sympathetic function without significant blood pressure effects [15]. Surgical bilateral sympathectomy achieves permanent denervation, with reported improvements in symptoms, quality of life, and exercise capacity, although evidence remains limited because of small cohort sizes [16].

Radiosurgery is commonly considered to be effective through an ablative mechanism acting on neural tissue. Growing evidence also suggests that focal neuronal activity in the brain may be modulated via SRS in the absence of a visible lesion on magnetic resonance imaging or computed tomography [17]. Furthermore, extracranial radiosurgery may hyperpolarize neurons, inhibit sodium channels, shorten action potentials, and reduce pre-synaptic and post-synaptic responses. These effects may induce changes in neural tissue function through differential influences on various neuronal populations and through microenvironment remodeling that leads to neural modulation of function while preserving basic processing [18, 19]. In the past two decades, stereotactic body radiation therapy has emerged as a viable technique for delivering precise and high/ablative doses of radiation in a single shot or a limited number of fractions, including for head and neck cancer, thyroid cancer, and spinal tumors [20]. Optimal parameters for stereotactic radiosurgery–based neuromodulation remain uncertain, but depending on anatomical and volumetric specifics, doses in the 40–60 Gy range are most likely to achieve modulation without causing ablation [21].

We hypothesized that stereotactic radiosurgery–based neuromodulation delivering 40 Gy to the bilateral SG would be feasible, safe, and effective in reducing pain in RAP. This report describes a first case series of radiosurgical neuromodulation of the SG with long-term follow-up, providing evidence to support evaluation of this novel approach as a bailout strategy for patients with RAP whose conventional treatment options have been exhausted.

## Materials and methods

This feasibility intervention pilot case series was approved by the local institutional review board (IRB FNO 354/2021) as a bailout procedure for patients with RAP with repeated good response in terms of symptom relief after anesthetic blockade of the left SG. Patients were eligible for inclusion if they were age ≥ 18 years, had a life expectancy of ≥ 24 months, had a history of CAD, and had RAP treated with maximum doses of tolerated medication. Two certified, independent interventional cardiologists and two cardiac surgeons had to conclude that further revascularization (including coronary artery bypass grafting; CABG) was not possible, not effective, and/or too high risk. Dobutamine echocardiography or gated single-photon emission computed tomography of the myocardium confirmed the myocardial ischemia, and patients had to provide verbal and written informed consent. Exclusion criteria were as follows: myocardial infarction in the last 4 weeks, New York Heart Association class IV heart failure, pregnancy, and history of radiotherapy in the head and neck region. During study period the screening failure log file was provided.

### Interventions

Before the first radiosurgery, patients underwent two separate left SG blocks to confirm a treatment effect. Each block was performed under ultrasound guidance using a linear probe and via a 21-G needle applying 6–8 mL 0.5% bupivacaine. When angina symptoms recurred (typically between 6 and 9 months after left-sided radiosurgery), a right SG block was performed using the same technique. Only patients demonstrating a positive response to the right-sided block were considered for subsequent right-sided radiosurgery.

Patient immobilization was achieved using a three-point thermoplastic face mask. Supine native computed tomography scans (1-mm slices) were obtained, and the clinical target volume covering SG was delineated after identification of the longus coli muscle. No additional margins were applied, and sequential dose optimization of 40 Gy was performed to achieve at least 95% coverage of the planned target volume. Treatment has been delivered with CyberKnife system (Accuray, Sunnyvale, CA, USA) and Xsight Spine Tracking provided continuous

image guidance based on spine structures with pairs of orthogonal Xray images taken at a set frequency (at least 1pair per minute).

### Follow-up

Clinical outcomes were evaluated at baseline (-3 months) and then at 3-month intervals for the first 24 months, followed by annual evaluations for up to 60 months. Outcomes were measured based on prescribed nitrate packages, daily emergency nitrate consumption, walking distance, and patient-reported outcome measures, including the EuroQol Five-Dimensional Questionnaire (EQ-5D) and Seattle Angina Questionnaire (SAQ) with five subscales (Physical Limitation, Angina Stability, Angina Frequency, Treatment Satisfaction, and Quality of Life). Radiation-related toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Paired T-test was used for evaluation of statistical trends.

### Patients

All three patients were men, ages 64 (Patient 1), 71 (Patient 2), and 64 (Patient 3) years, with RAP and a long-standing history of CAD (diagnosed in 1984, 2008, and 1986, respectively). All had triple vessel disease and had undergone CABG in 1987, 2010, and 1986, respectively and had exhausted the possibility of any further revascularizations (Fig. 1). Patient 2 also had undergone multiple percutaneous coronary interventions (2002, 2011, 2012). Left ventricular ejection fraction was reduced in all patients (35%, 50%, and 25%, respectively). All patients had CCS class IV angina despite optimal medical therapy including beta-blockers (metoprolol succinate 100 mg, bisoprolol 10 mg, carvedilol 25 mg), trimetazidine (70 mg), and high-dose isosorbide mononitrate (100–120 mg). Two patients had diabetes mellitus, all had hypertension, and one had chronic obstructive pulmonary disease. The left-sided radiosurgery procedures were performed during December 2018 to February 2021. Two

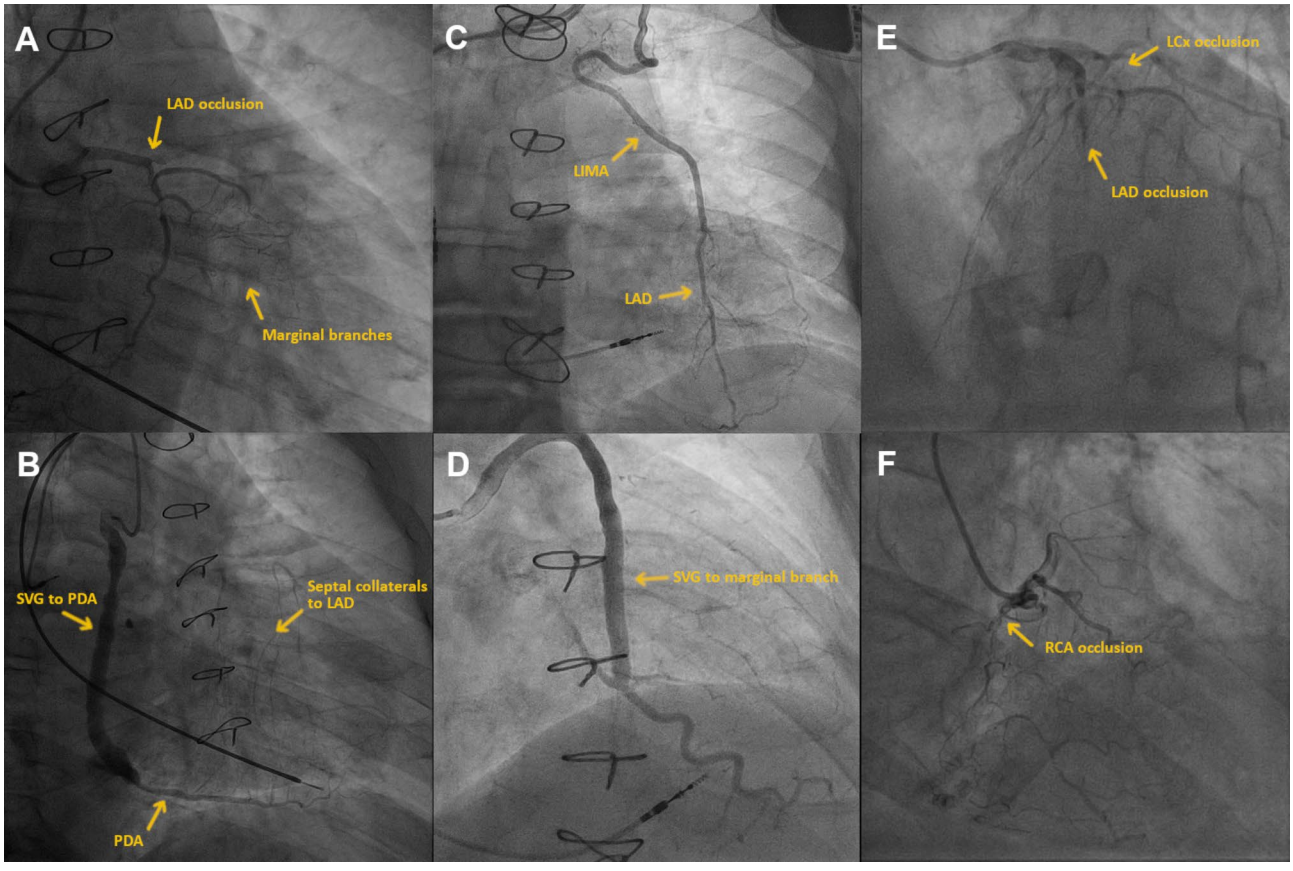


**Fig. 1** Coronary angiography and bypass graft assessment in three patients with refractory angina pectoris. **Panel A**: Case 1– Left Coronary Artery (LCA): Demonstrates diffusely diseased left circumflex artery (LCx) and chronic total occlusion (CTO) of the left anterior descending artery (LAD). **Panel B**: Case 1– Saphenous Vein Graft (SVG): Patent bypass graft to posterior descending artery (PDA) with heterocollateral flow to LAD. Right coronary artery (RCA) demonstrates chronic total occlusion (not visualized). **Panel C**: Case 2– Left Internal Mammary Artery (LIMA): Patent bypass graft to left anterior descending artery (LAD). **Panel D**: Case 2– Saphenous Vein Graft (SVG): Patent bypass graft to obtuse marginal branch (OM). Additional finding: Chronic total occlusion of left main coronary artery (LMCA) and diffusely diseased right coronary artery (RCA) (not visualized). **Panel E**: Case 3– Left Coronary Artery (LCA): Demonstrates diffusely diseased and proximally occluded left anterior descending (LAD) and left circumflex (LCx) arteries. **Panel F**: Case 3– Right Coronary Artery (RCA): Demonstrates proximal chronic total occlusion (CTO) with homocollateral circulation

**Table 1** Patient baseline characteristics and treatment history

| Characteristic | Patient 1 | Patient 2 | Patient 3 |
|---|---|---|---|
| Age | 64 | 71 | 64 |
| Sex | Male | Male | Male |
| Body mass index | 34.1 | 30.8 | 25.8 |
| CAD diagnosis year | 1984 | 2008 | 1986 |
| Number of affected coronary vessels | 3VD | 3VD | 3VD |
| CABG | 1987 | 2010 | 1986 |
| PCI | No | 2002, 2011, 2012 | No |
| LVEF | 35% | 50% | 25% |
| Diabetes mellitus | Yes | Yes | No |
| Hypertension | Yes | Yes | Yes |
| COPD | No | No | Yes |
| Angina CCS Class | IV | IV | IV |
| Beta-blocker use | Metoprolol succinate 100 mg | Bisoprolol 10 mg | Carvedilol 25 mg |
| Trimetazidine use | Yes (70 mg) | Yes (70 mg) | Yes (70 mg) |
| CA blocker use | No | Amlodipine 2.5 mg | No |
| Prolonged nitrate use | Isosorbide mononitrate 120 mg | Isosorbide mononitrate 100 mg | Isosorbide mononitrate 100 mg |
| SRS 1 date | 13.12.2018 | 18.11.2020 | 14.02.2021 |
| SRS 2 date | 18.11.2019 | 22.10.2021 | NA |
| Status at last follow-up | Alive (60 months) | Alive (48 months) | Died (42 months, 05.08.2024) |

3VD: triple vessel disease; CA: calcium channel; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CCS: Canadian Cardiovascular Society; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; N/A: not applicable; PCI: percutaneous coronary intervention; SRS: stereotactic radiosurgery

patients received bilateral treatment (a second procedure after 11–12 months), and one patient received only unilateral treatment and died in August 2024. Basic patient information is shown in Table 1. The screening failure log file included 7 patients (Three patients declined the experimental method and four patients were ultimately deemed ineligible due to various contraindications).

## Results

No acute or periprocedural complications were seen in any of the five sessions among the three patients. For all three patients, the radiation-related parameters with 40 Gy in one fraction are given in Table 2 and treatment plans in Fig. 2. Two of the three patients (patients 1 and 2) had a response to the SRS, and the third patient was deemed not to have experienced a response because of technical complications or incomplete treatment (Table 3). No late radiation-related toxicity was seen in any of the three cases.

**Table 2** Dosimetric parameters

| Patient | SRS | Target | | | | Organs At Risk | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PTV | | | | Spinal Cord | | Esophagus | | ACI | AV | |
| | | Volume (cc) | CI | HI | Coverage | D 0,035 cc | D 0,035 cc | D 1,2 cc | D 0,035 cc | D 5 cc | D 0,035 cc | D 0,035 cc |
| 1 | 1 | 0,41 | 1,43 | 1,28 | 95,60% | 1,3 | 1,1 | 0,9 | 8,9 | 1,8 | 9,6 | 18,2 |
| | 2 | 0,41 | 1,48 | 1,3 | 94,90% | 4,1 | 3,2 | 1,9 | 13,3 | 3,4 | 11,7 | 25,1 |
| 2 | 1 | 0,41 | 1,22 | 1,3 | 96,10% | 1,5 | 0,9 | 0,5 | 6,6 | 1 | 8,5 | 18,8 |
| | 2 | 0,32 | 1,15 | 1,19 | 97,62% | 1,8 | 1,4 | 1,1 | 17 | 2,4 | 15,3 | 30,6 |
| 3 | 1 | 0,59 | 1,14 | 1,27 | 99,73% | 1,2 | 1 | 0,7 | 12,5 | 1,2 | 11,1 | 9,2 |

CI: conformity index, HI: homogeneity index, ACI: internal carotid artery, AV: vertebral artery. D: dose in a given volume in Gy

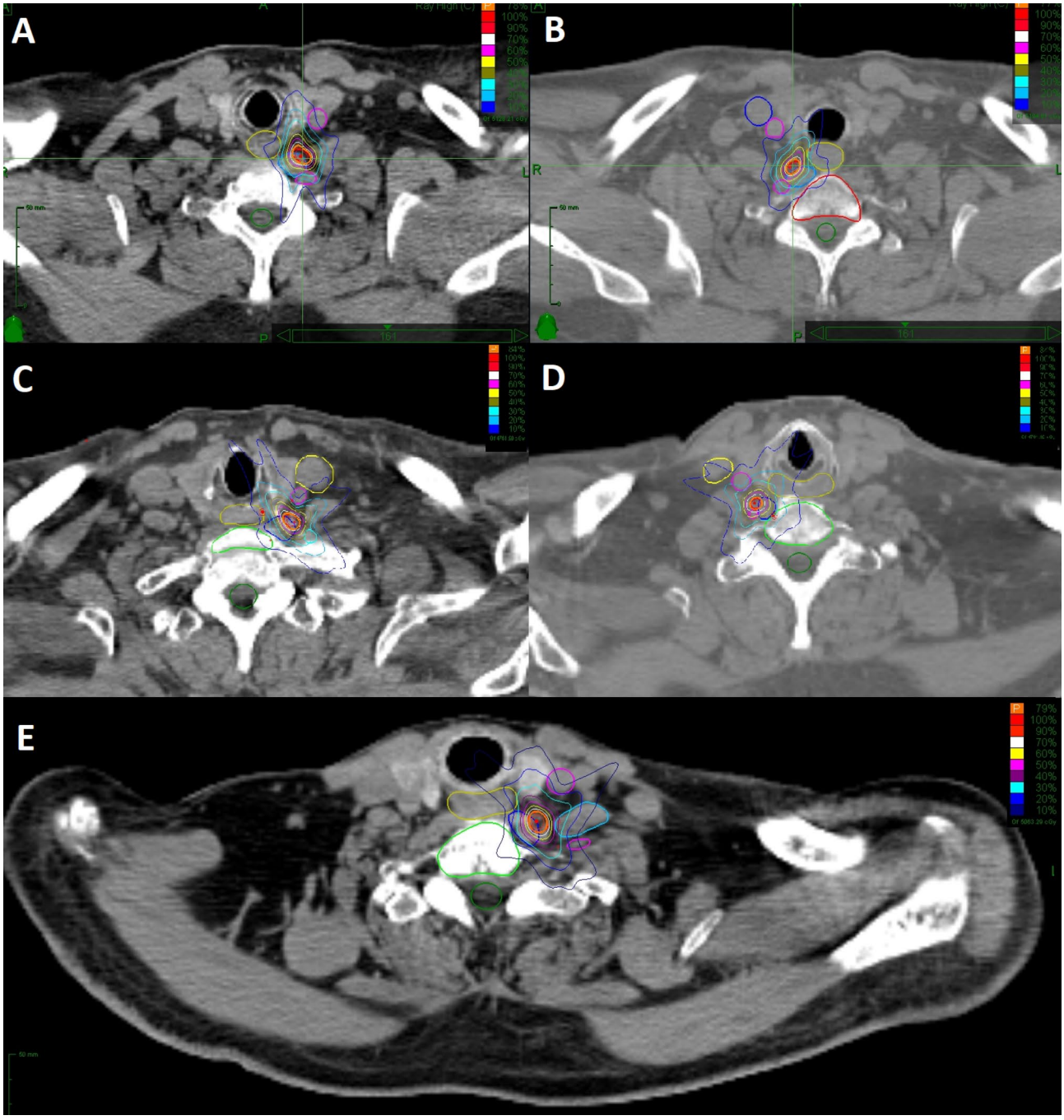


**Fig. 2** Radiosurgery treatment plans. Case 1 (**A**: 1st irradiation, 40 Gy/78% isodose line. **B**: 2nd irradiation, 40 Gy/77% isodose line), case 2 (**C**: 1st irradiation, 40 Gy/77% isodose line. **D**: 2nd irradiation, 40 Gy/84% isodose line) and case 3 (**E**: 1st irradion, 40 Gy/79% isodose line). The thick orange line represents the prescribed isodose line and and overlaps the PTV delineation (the thin red line)

### Responder cases

The first case has been already reported in detail as a case report, illustrating safety and efficacy [22]. Both responders underwent SRS of the left SG, followed by SRS of the right SG 12 months later. Following the first SRS procedure, both patients experienced a significant reduction in prescribed nitrates from 5 to 6 packages at baseline to 1–2 packages at 12 months, further decreasing to 0 after the second SRS, with this effect maintained through 48–60 months of follow-up. Daily emergency nitrate use showed a similar pattern, decreasing from 20 to 30 applications at baseline to 5 applications at 6–9 months, with some fluctuation before the second SRS, and stabilizing at 0–1 applications after bilateral treatment through the entire follow-up period. Walking distance improved markedly from 10 to 20 m at baseline to 200 m by 6–9

**Table 3** Summary of patient outcomes before and after stereotactic radiosurgery (SRS) of stellate ganglion for refractory angina

| Characteristic | | Months relative to the first STAR procedure | | | | | | | | | | | | Paired T-test ("-3" vs., "48") p-value |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | -3 | 3 | 6 | 9 | 12 (STAR 2) | 15 | 18 | 21 | 24 | 36 | 48 | 60 | |
| Nitrates Prescribed | P1 | 6 | 5 | 3 | 2 | 3 | 3 | 0 | 0 | 0 | 1 | 1 | 1 | 0,000 |
| | P2 | 5 | 5 | 4 | 1 | 2 | 2 | 1 | 0 | 0 | 0 | 0 | NA | |
| | P3 | 6 | 5 | 5 | 6 | 6 | 5 | 6 | 6 | 5 | 6 | NA | NA | |
| Daily Emergency Nitrates | P1 | 30 | 25 | 10 | 5 | 15 | 15 | 0 | 1 | 1 | 0 | 1 | 1 | 0,116 |
| | P2 | 20 | 20 | 5 | 5 | 20 | 10 | 5 | 1 | 2 | 0 | 0 | NA | |
| | P3 | 20 | 15 | 5 | 20 | 25 | 20 | 30 | 20 | 25 | 20 | NA | NA | |
| Walking Distance | P1 | 10 | 50 | 100 | 200 | 100 | 100 | 200 | 200 | 200 | 200 | 200 | 200 | 0,120 |
| | P2 | 20 | 50 | 200 | 200 | 100 | 100 | 300 | 300 | 400 | 300 | 300 | NA | |
| | P3 | 10 | 40 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | NA | NA | |
| EQ-5D index value | P1 | 0.5 | 0.6 | 0.7 | 0.8 | 0.7 | 0.7 | 0.8 | 0.8 | 0.9 | 0.9 | 0.9 | 0.9 | 0,042 |
| | P2 | 0.55 | 0.6 | 0.75 | 0.8 | 0.7 | 0.7 | 0.85 | 0.85 | 0.9 | 0.85 | 0.9 | NA | |
| | P3 | 0.5 | 0.6 | 0.6 | 0.55 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.4 | NA | NA | |
| SAQ Physical limitation | P1 | 30 | 40 | 50 | 60 | 40 | 50 | 70 | 80 | 70 | 80 | 80 | 80 | 0,033 |
| | P2 | 35 | 40 | 60 | 50 | 50 | 50 | 75 | 75 | 80 | 75 | 80 | NA | |
| | P3 | 30 | 35 | 50 | 40 | 30 | 30 | 30 | 30 | 40 | 30 | NA | NA | |
| SAQ Angina stability | P1 | 30 | 40 | 50 | 60 | 40 | 50 | 60 | 80 | 80 | 80 | 80 | 80 | 0,033 |
| | P2 | 35 | 40 | 55 | 60 | 40 | 50 | 65 | 70 | 80 | 80 | 80 | NA | |
| | P3 | 30 | 40 | 50 | 40 | 30 | 30 | 30 | 30 | 30 | 30 | NA | NA | |
| SAQ Angina frequency | P1 | 20 | 30 | 40 | 50 | 40 | 55 | 65 | 70 | 80 | 80 | 80 | 80 | 0,090 |
| | P2 | 25 | 30 | 45 | 50 | 50 | 55 | 70 | 70 | 75 | 70 | 70 | NA | |
| | P3 | 20 | 25 | 40 | 40 | 35 | 35 | 30 | 30 | 30 | 30 | NA | NA | |
| SAQ Treatment satisfaction | P1 | 50 | 60 | 80 | 85 | 50 | 80 | 85 | 80 | 80 | 80 | 90 | 80 | 0,144 |
| | P2 | 55 | 60 | 85 | 70 | 70 | 80 | 85 | 90 | 90 | 80 | 80 | NA | |
| | P3 | 50 | 55 | 70 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | NA | NA | |
| SAQ Quality of life | P1 | 20 | 35 | 45 | 55 | 45 | 45 | 60 | 55 | 60 | 70 | 60 | 70 | 0,037 |
| | P2 | 25 | 35 | 50 | 55 | 45 | 45 | 60 | 60 | 65 | 70 | 70 | NA | |
| | P3 | 20 | 30 | 40 | 40 | 25 | 20 | 20 | 20 | 20 | 30 | NA | NA | |

SAQ: Seattle Angina Questionnaire; EQ-5D: EuroQol Five-Dimensional Questionnaire; P1, P2, P3: Patient 1, Patient 2, Patient 3, respectively. Months are relative to the first SRS procedure, with negative values indicating months before the procedure and positive values indicating months after the procedure. Month 12 corresponds to the second SRS procedure (SRS 2) for Patients 1 and 2.

months, and after some fluctuations around the time of second SRS, further improved and stabilized at 200–300 m through 48–60 months. The EQ-5D index value increased from 0.50 to 0.55 at baseline to 0.7–0.8 after first SRS and reached 0.9 after the second SRS, maintaining this improvement through the entire follow-up. All five SAQ subscales showed sustained improvement: Physical limitation (from 30 to 35 to 80), Angina stability (from 30 to 35 to 80), Angina frequency (from 20 to 25 to 70–80), Treatment satisfaction (from 50 to 55 to 80–90), and Quality of life (from 20 to 25 to 70) at last follow-up, with improvements maintained after 36–48 months.

#### Case with incomplete treatment

The third patient underwent left-sided SRS only. When evaluated for right-sided treatment at 12 months, the patient experienced a prolonged (24-hour) brachial plexus block during the diagnostic SG anesthetic procedure, attributed to challenging ultrasound visualization due to prior thoracic injury. This complication led to the patient's withdrawal from further study participation, precluding the planned bilateral treatment.

The patient's outcomes after unilateral SRS showed a transient response at 6 months. Prescribed nitrates temporarily decreased from 6 to 5 packages, daily emergency nitrates fell from 20 to 5 applications, walking distance improved from 10 to 40 m, and EQ-5D increased from 0.5 to 0.6. All five SAQ subscales showed similar temporary improvements during months 3–6. However, without bilateral treatment, these improvements were not sustained, and all parameters had returned to baseline levels by 9 months. The patient died 42 months after the radiosurgery of the left SG.

## Discussion

This case series is the first of its kind, detailing the feasibility of radiosurgical neuromodulation of SG. The reason for bailout radiosurgery was RAP with good response to SG anesthetic block and no other tenable treatment interventions, including open sympathectomy. We report that noninvasive stellate radiosurgical neuromodulation is feasible, with no acute or late radiation-related toxicity and with promising efficacy if bilateral irradiation is administered. In the case involving left-sided radiosurgery only, outcomes were poor.

For the two patients who underwent bilateral procedures and had a good response, nitrate prescriptions declined from 5.5 to 2.5 at 12 months and to 0 at 24 months. Average daily emergency nitrates decreased from 20 to 30 applications at baseline to 5, which is similar to results with other strategies. In a case series of 43 patients undergoing bilateral thoracoscopic sympathectomy, Claes et al. reported that 93% had symptomatic improvement and that the mean glyceryl trinitrate consumption declined from 20 to 6 tablets per week [23]. Yoshida et al. described bilateral endoscopic thoracic sympathectomy in five patients and reported successful reductions in medication use for four of them, on average from 6.6 to 2.2 times [8]. A meta-analysis of SCS that included 14 studies (518 patients) showed that the procedure led to decreased nitrate consumption from 2.0 to 1.3 applications per day [24]. Our case series is smaller than that dealing with spinal cord stimulation or open sympathectomy, however, one could expect feasibility of SRS for patients with severe intercurrent diseases as well.

In the two response cases in our series, walking distance improved from 10 to 20 m at baseline to 200 m at 6–9 months after the first SRS. Despite some fluctuations from 9 to 18 months, walking distance remained stable or slowly improved during follow-up. Stritesky et al. similarly reported a significant increase in walking distance from 110 to 220 m among patients who had undergone bilateral endoscopic thoracic sympathectomy [25]. Studies investigating the effect of walking distance after SCS reported a mean increase from baseline of 53.8 m after 12 months [26], and an increase of 890 m after 5 years [27].

In keeping with walking distance improvements in the two responder cases, the scores for the SAQ Physical Limitation, Angina Stability, and Angina Frequency subscales increased after 1 year from 32.5, 32.5, and 22.5 to 45, 45, and 40, respectively. Improvements at 2 years were even more pronounced, with scores reaching 75, 80, and 77.5, respectively. Lanza et al., in their series of 10 patients who had been randomized to continue or withdraw SCS for 3 weeks, also reported significant improvements during the SCS-ON phase in the SAQ Physical Limitation, Angina Stability, and Angina Frequency subscales, from 36, 10, and 33 to 57, 80, and 67, respectively [28].

Quality of life also improved in the two cases involving a response. The EQ-5D index value increased from 0.50 to 0.55 at baseline to 0.80 and 0.90 after the first and second SRS procedures, respectively. These quality-of-life improvements after SRS seem to be comparable to those seen with other strategies. However, comparison with other findings is difficult because different measures have been used in other studies, such as the visual analogue scale applied in a series of patients undergoing endoscopic sympathectomy, in which self-reported pain fell from 4 to 2.4. In their series of 10 patients who underwent video-assisted thoracoscopic surgery, Khogali et al. reported that six patients were pain free and four had less pain after the procedure [29]. Rathinam et al. described outcomes for 26 patients who underwent bilateral video-assisted thoracoscopic surgery, including a 92% symptomatic improvement at 6 months [30]. A visual analogue scale for quality-of-life assessment was used in a case series of patients undergoing SCS, with

significant improvement in scores from 30 to 80 after the intervention.

No acute or late radiation-related toxicity was seen in any of the three cases. The safety of SRS neuromodulation seems to be higher compared to invasive strategies. Typical chest pain related to sympathectomy has been reported [31], and SCS implantation is also not a risk-free procedure, with a reported incidence of postimplant complications of around 30–40% [7]. Adverse events may be hardware-related (lead migration, device failure, lead fracture) or biological (infection and pain over the implant site, dural puncture headache, infection, and neurological injury). Moreover, discontinuation of antithrombotic therapy is required during implantation.

The effect of radiosurgical neuromodulation in this case series was continuous, with slow pain relief compared to other procedures. The nadir of nitrate consumption, improvement in the walking test, and improvement in questionnaire measurements were noted at 6–9 months after irradiation. Also, in the incompletely treated case, some effect was seen after the symptomatic period of 6 months. The effect was a bit more rapid after the second, right-sided irradiation was administered to the patients experiencing a response, emerging at 3–6 months after the second procedure. The delay between procedures is a significant drawback of SRS compared to sympathectomy, which entails immediate pain relief, especially when less-invasive techniques are used for minimizing postoperative pain and length of hospital stay. Similarly, SCS is associated with fast pain relief, with only 3 weeks of stimulations enough to bring on significant improvements in one randomized study [28].

Radiosurgery itself has not shown any periprocedural side effects. Introduces two-period design allows better identification of patients with a good response to the first radiosurgical neuromodulation. In our series, the third patient underwent SRS of the left SG only, having declined the right-sided SRS procedure because of a complication during the probatory right-sided stellate anesthetic block. The non-invasiveness of SRS is a significant advantage compared to more invasive procedures. Moreover, the workflow of SRS is well described, computed tomography is suitable for identifying the bony structure of the C6 and C7 transverse processes together with soft tissues such as the longus coli muscle and vertebral artery, and pain relief after anesthetic block of the SG seems to have predictive value for SRS efficacy [32]. To reduce the risk of radiation-related atherosclerosis, however, the dose to the vertebral artery needs to be minimized. Another major challenge is meeting the dose-volume limits because bilateral irradiation is involved, and the consistent reconstruction of dose distribution from the left ganglion radiosurgery is crucial to optimize the dose for the right ganglion radiosurgery.

Although these three patients represent the largest group described as having undergone radiosurgical SG neuromodulation, the number of cases is quite low. The screening failure log file included 7 patients (Three patients declined the experimental method and four patients were ultimately deemed ineligible due to various contraindications). Moreover, bilateral treatment could not be completed in one patient because of the technical complication during the diagnostic right-sided SG block, limiting our ability to evaluate the full treatment protocol in all three patients. Recruitment was also influenced by the COVID-19 pandemic, and we decided to interrupt accrual until a reasonable long-term follow-up (up to 60 months) would allow for evaluation of any late radiation-related side effects. Additionally, the feasibility study is unable to answer the question of what dose might be optimal for SRS neuromodulation. Unfortunately, there is still a paucity of data describing the neuromodulatory effects of radiation on peripheral tissue and therefore 40 Gy is mainly a question of a trade-off between efficacy and safety. And finally, we did not consider other non-neural treatment options such as enhanced external counter-pulsation, transmyocardial laser revascularization [33, 34], or a COSIRA (coronary sinus reducer for treatment of refractory angina) device [35]. In line with current guidelines, however, our patients were referred for psychological intervention to reduce anxiety and depression [3]. Despite these limitations, we believe that our data support the possibility of considering SRS neuromodulation as another bail-out procedure for patients with RAP. Apparently, further research is necessary and besides others a prospective study with dose (de)escalation would be desirable.

## Conclusions

The management of RA remains complex, requiring a multidisciplinary approach to optimize symptom control and improve quality of life. Bilateral radiosurgical neuromodulation at 40 Gy appears to be feasible, safe, and effective as a bailout procedure for RAP, with sustained improvements in quality of life, exercise capacity, and nitrate consumption maintained through 4–5 years of follow-up. For a sustained positive response to diagnostic SG block, a bilateral treatment seems to be required.

**Abbreviations**

| | |
|---|---|
| CABG | Coronary artery bypass grafting |
| CAD | Coronary artery disease |
| COSIRA | Coronary sinus reducer for treatment of refractory angina |
| CSS | Canadian Cardiovascular Society |
| EQ-5D | EuroQol Five-Dimensional Questionnaire |
| RAP | Refractory angina pectoris |
| SAQ | Seattle Angina Questionnaire |
| SCS | Spinal cord stimulation |
| SG | Stellate ganglion |
| SRS | Stereotactic radiosurgery |

**Acknowledgements**
Jakub Cvek and Otakar Jiravsky have equal contribution. Manuscript was edited by San Francisco Edit.

**Author contributions**
JC and OJ design the study and wrote article. LK and JH analysed data and wrote article. MH and AR provided patients selection and follow them up. RN and RS prepared methology related to the treatment, LK collected data for analysis and participated in study design, JK carried out a critical review of the manuscript. All authors read and approved the final manuscript.

**Funding**
Supported by Ministry of Health, Czech Republic - conceptual development of research organization (RVO-FNOs/2021).

**Data availability**
The datasets used during the current study are available from the corresponding author on reasonable request.

## Declarations

**Ethics approval and consent to participate**
This project has been approved by IRB University Hospital Ostrava.

**Consent for publication**
Not Applicable.

**Competing interests**
Dr. Knybel and Dr.Cvek reports grants from Ministry of Health, Czech Republic, during the conduct of the study. Dr. Knybel and Dr. Cvek received honoraria for presentations from Accuray, Sunnyvale, CA, USA.

**Conflict of interest**
Dr. Knybel and Dr.Cvek reports grants from Ministry of Health, Czech Republic, during the conduct of the study. Dr. Knybel and Dr. Cvek received honoraria for presentations from Accuray, Sunnyvale, CA, USA.

Received: 24 January 2025 / Accepted: 23 February 2025
Published online: 10 March 2025

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