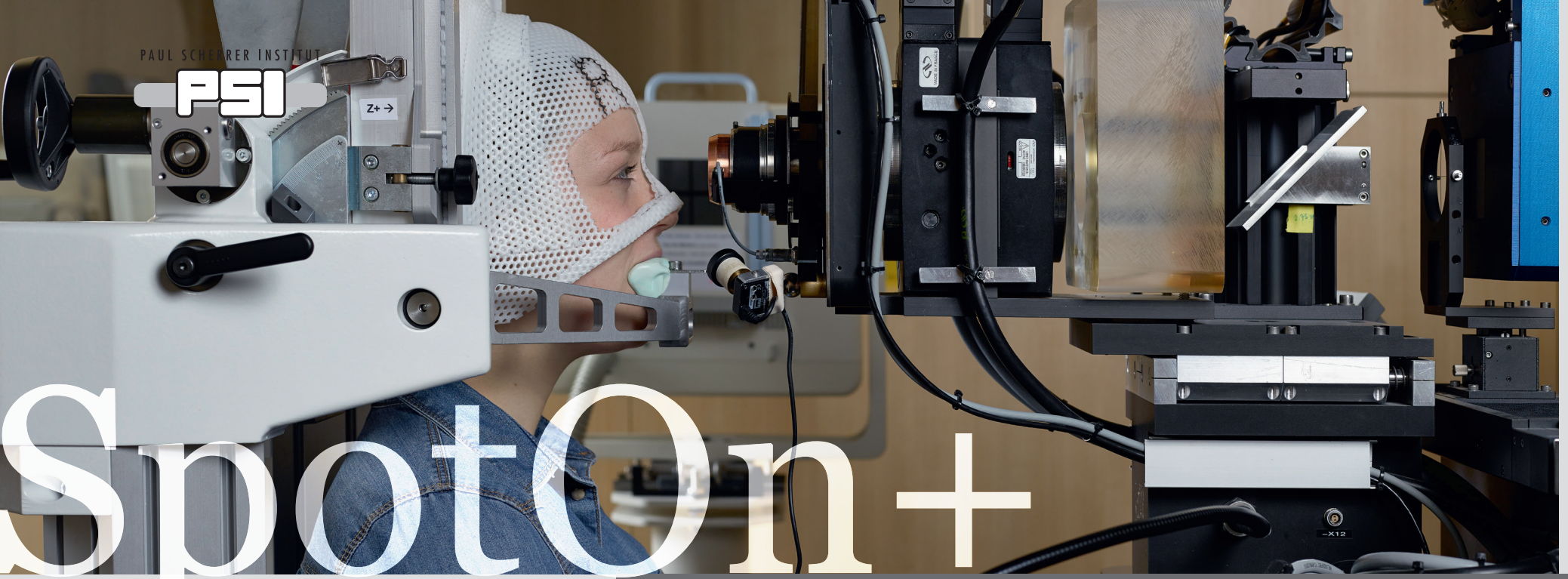



# SpotOn+

Center for Proton Therapy :: Paul Scherrer Institut :: #8_3/2016

Dear Colleagues

In this Q1 2016 edition of our SpotOn+ newsletter, Dr. Jan Hrbacek reports on the results of an international survey on ocular proton therapy that was initiated by PSI within the framework of the OPTIC working party of the PTCOG (www.ptcog.ch). It was initially discussed within this group that protons for ocular oncology needed some added visibility, as this treatment modality is indeed a highly effective treatment in terms of tumor control and eye-retention for uveal melanomas (UM) and other ocular tumors. PSI has treated over 6'000 patients, which represents 22% of all UM patients treated worldwide with protons. This remarkable achievement over many decades has been only possible with the clinical and scientific collaboration of the team of Dr. Ann Schalenbourg and Prof. L. Zografos in Lausanne (Hôpital Ophtalmique Jules-Gonin). It is interesting to note that the majority of centers (80%) uses a treatment planning system that is not supported by any vendors at the present time. This raises interesting questions so as how to support & upgrade such a planning platform in the future, with no support from industry and it is doubtful that we will find easy & quick answers to this challenge. The second article reports on the results of PBS proton therapy for extra-cranial chordomas and chondrosarcomas. This analysis was co-performed by Dr. J.W. Snider (University of Maryland, USA) and Dr. Ralf Schneider. The outcome of patients with these spinal tumors is good, with 2/3 of patients surviving at 5 years after the radiation therapy. For the first time, we have been able to show that patients with post-operative implants treated with protons have a significantly ($p<0.05$) lower overall survival than those without any metal implant. This is in line with the data from Boston and it is currently unclear if metal implants do compromise proton radiation or if it is merely a proxy of more aggressive disease. Simulation studies performed at PSI using dedicated phantoms suggest however that the former could not be a major detrimental factor on survivorship and other factors, such as delineation issues during the planning process, are possibly more relevant. In the last section of this newsletter, the interplay effect of motion on PBS protons is assessed using our LuCa phantom which is displayed in the summary. The figures show clearly that gating alone is probably not appropriate to treat mobile tumors with scanned protons. As such, the current PSI strategy to treat these challenging mobile tumors is to use a combined dose-disruption mitigation strategy, namely re-scanning and gating in the not too distant future. This would be possible using our up-graded treatment platform of Gantry 2 and Gantry 3, the latter being operational at the end of this year. It is the believe of PSI that protons should not be only reserved to 'niche' indications but could benefit a substantial number of cancer patients that have to be properly selected. This then will be clearly debated in our European radiation oncology community as a number of proton/carbon beam therapy centers will come on line between 2018 and 2020.

**Yours sincerely,**
**Prof. Damien Charles Weber,**
**Chairman of CPT**

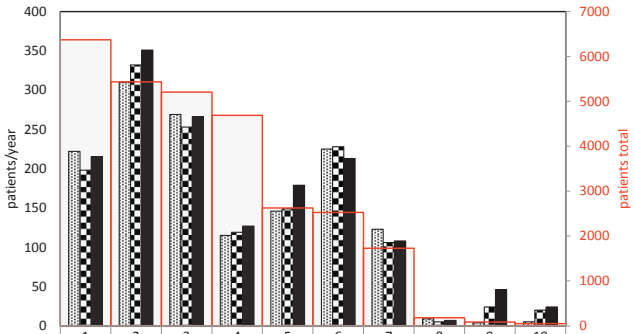
# Radio-Oncology News

## Ocular Proton Therapy International Community Survey

Ocular Proton Therapy International Community (OPTIC), a sub-committee of Particle Therapy Co-Operative Group (PTCOG), organized the questionnaire survey to carry out a comparative analysis of the treatment, human and technical resources allotment, QA program, and follow-up strategies of centers performing this highly specialized treatment.

**Patient numbers:** Ten centers participating in the survey (Table 1) treated a combined 28'891 patient by the end of 2014. This corresponds to 98.8 % of ocular proton therapy patients worldwide. Figure 1 details the number of patients treated by centers from 2012 to 2014 and in total. The yearly accrual of all centers is approx. 1'500 patients. CPT PSI, with the total of 6'369 patients (22 %), remains the center with the largest cohort of patients treated worldwide.

**Indication & fractionation regime:** The most common ocular treatment for all centers was uveal melanoma (UM). In addition, centers treated other primary ocular malignancies, benign ocular tumors, choroidal metastases, conjunctival tumors, and retinoblastomas. Half of the centers had treated also pediatric patients. For UM patients, all but one center deliver four fractions over a week, and the dose prescription was relatively homogeneous across centers (56–60 Gy RBE). Likewise, the dose prescription was 18–24 Gy RBE in 2–4 fractions for age-related macular degeneration. Dose prescription for conjunctival melanoma differed substantially, with dose and fraction number ranging from 20.4 to 70.0 Gy RBE in 4 to 8 fractions, respectively.




| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| 2012 | 222 | 310 | 269 | 115 | 146 | 225 | 123 | 9 | 4 | 5 |
| 2013 | 198 | 332 | 253 | 119 | 149 | 228 | 106 | 5 | 24 | 20 |
| 2014 | 215 | 351 | 266 | 127 | 179 | 213 | 108 | 7 | 46 | 24 |
| total | 6369 | 5433 | 5205 | 4689 | 2625 | 2525 | 1729 | 182 | 85 | 49 |

**Figure 1:** Number of eye patients treated with proton therapy by 10 centers in total and in last three years (sorted in descending order by number of total number of patients)

**Treatment planning:** The majority of centers (80 %) used EyePlan treatment planning system (TPS), software developed and maintained by a collaborative effort amongst several research centers for OPT (Massachusetts General Hospital, Paul Scherrer Institute, Clatterbridge Cancer Centre). All centers used a geometrical eye model. Parameters of the geometrical model were primarily based on ultrasound (8 centers), however, CT (5 centers) and MRI (4 centers) were used frequently as well. For intraocular tumors, all centers defined clinical target volume (CTV) based on transillumination during ophthalmic surgery in combination with ultrasound (A- and B-scan) examination. Most centers (90 %) verified the position of a CTV using a fundus photography registered to the fundus on the geometrical model.

**Technical:** All centers used a cyclotron to accelerate protons, in combination with dedicated horizontal beam lines only, and with robotic chairs. Protons were accelerated to energies of 60–520 MeV. All multi-room centers (50 %) accelerated to energy higher or equal to 230 MeV with subsequent degradation. Energy of protons entering into a nozzle was degraded to 58–105 MeV (mean, 68 MeV) for clinical treatment. All centers position patients using orthogonal x-ray imaging. Patient treatment time slots for set-up and delivery ranged from 20 to 90 minutes (median 30 minutes). Manual treatment gating was performed by a majority (90 %) of centers to carefully track intra-fractional motion of the eye.

**QA:** Most centers (90 %) would check on a daily basis the range and the dose (in water or other material) with the passing criteria ranging from ±0.1 mm to ±0.5 mm (median ±0.3 mm) and from ±0.5 % to ±3.0 % (median ±2 %), respectively. All centers required highly accurate coincidence of the imaging system with the treatment iso-center, ranging from ±0.1 mm to ±0.5 mm. While tolerance for other tests such as modulation, coincidence between imaging and treatment coordinate systems, and beam's flatness/symmetry was comparable, the frequency of these tests varied anywhere between daily to yearly. Patient specific verification was performed by 90 % of the centers checking dose, range, and modulation.

Additional details of the survey and discussion of the results may be found in http://dx.doi.org/10.1016/j.ijrobp.2016.01.040

For any further information, please refer to CPT,

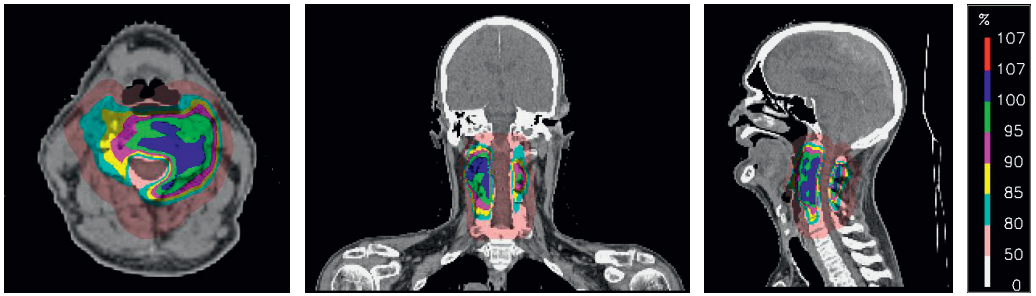
**Dr. Jan Hrbacek**
Tel. +41 56 310 37 36
jan.hrbacek.psi.ch

**Table 1: Alphabetical list of ocular proton therapy centers participating in the survey**

- BC Cancer Agency – TRIUMF, Vancouver, Canada
- Center for Proton Therapy, Paul Scherrer Institut, Villigen, Switzerland
- Centre Antoine-Lacassagne, Nice, France
- Centre de Protonthérapie d'Orsay, Institut Curie, Orsay, France
- Clatterbridge Cancer Centre, UK
- F.H. Burr Proton Therapy Center, Massachusetts General Hospital, Boston, MA, USA
- Institute of Nuclear Physics, Polish Academy of Sciences, Krakow, Poland
- Protons for Therapy, Helmholtz-Zentrum Berlin, Berlin, Germany in cooperation with BerlinProtonen am HZB, Charité – Universitätsmedizin Berlin, Berlin, Germany
- UCSF Ocular Tumor Proton Therapy Program – University of California San Francisco at Davis, CA, USA
- University of Florida Proton Therapy Institute, Jacksonville, FL, USA

# Radio-Oncology News

## Long-term follow-up and clinical outcomes of patients treated for extracranial chordomas and chondrosarcomas with pencil beam scanning proton therapy at PSI




Axial, coronal, and sagittal images of a representative treatment plan to 74 Gy for a cervical chordoma.

Tumors of the spine and paraspinal regions remain a challenge for surgeons and oncologists alike. Chordomas and chondrosarcomas are rare, locally aggressive, and devastating tumors that commonly arise extracranially in close proximity to or involving the spinal column. For neurosurgeons, the juxtaposition of these tumors often necessitates subtotal or intralesional resection followed frequently by surgical stabilization. For radiation oncologists, the particular proximity to the spinal cord complicates the delivery of adequate adjuvant radiotherapy. For safely achieving the particularly high doses required (often 70–74 Gy) to sterilize these tumors, proton therapy, and in particular pencil beam scanning proton therapy, has proven particularly well-suited. Previous reports from our institution (Staab et al. 2011) have demonstrated the safety and efficacy of this approach in small sample sizes.

These initial outcomes also raised substantial concerns regarding worsened outcomes in patients with metal implant, surgical stabilization. Recently, we updated the center's experience utilizing pencil beam scanning therapy in these diseases, having treated now over 130 patients with extracranial chordoma or chondrosarcoma. Patients were only included in this new analysis if they had at least one year of follow-up and were adults. Spanning 18 years of treatment, from 1997 to 2015, 133 patients, including 3 patients that underwent radiotherapy a second time for new lesions (n=136), met the selection criteria.

This sample included 102 chordomas and 34 chondrosarcomas, distributed throughout the spinal column and pelvis: cervical (n=57), thoracic (n=24), lumbar (n=12), sacral (n=39) spine, and pelvis (n=4). Patients ranged in age from 22 to 81 (median=54). As expected, despite and due to the typically aggressive resections, 60 % of patients presented for proton therapy with gross residual disease, and 40% of patients required metal implant surgical stabilization prior to radiation. Though patients, during the early experience at PSI, were sometimes treated with mixed modality (photon-proton) techniques, 85 % (n=116) of the patients in this analysis received pencil beam scanning proton therapy exclusively. For the entire cohort, median follow-up was 63 months.

Despite historical controls reporting particularly poor local control in this disease, especially with lower dose, photon techniques, five year local control, progression-free survival, and overall survival in this study were an impressive 63 %, 57 %, and 77 %, respectively. Surgical stabilization remained an important prognostic factor in determining outcomes, especially in patients with chordoma, and overall survival was 49% versus 66 % at five years with and without metal implant ($p < 0.05$).

The cause for this correlation remains unclear as in vitro measurements at PSI have demonstrated impressively reliable delivery of therapy despite the presence of such material (Dietlicher et al. 2014). It is conceivable that worse/larger initial disease or more complicated lesions necessitate such stabilization and that patients with such disease will, on average, fail more often. However, further investigation is required and underway to clarify this issue. Encouragingly, the toxicity of adjuvant proton radiotherapy remained exceedingly low despite the high doses delivered. Grade 3 or higher toxicity was experienced in only 6 % and 5 % of cases in the acute and late settings, respectively.

With long-term follow-up and a much larger patient sample, pencil beam scanning proton therapy has once again proven an effective and safe method for controlling these insidious tumors. Promising further analysis is ongoing in an attempt to identify patients with higher-risk disease that may benefit from further intensified therapy and to evaluate strategies for mitigating issues surrounding surgical stabilization. We are currently also investigating alternative stabilization materials and their effects on proton treatment planning in conjunction with corporate partners. Results have been submitted to the 55th Annual Conference of the Particle Therapy Co-Operative Group, which will be held in May in Prague.

**Reference:** Dietlicher et al: *The effect of surgical titanium rods on proton therapy delivered for cervical bone tumors: experimental validation using an anthropomorphic phantom;* http://dx.doi.org/10.1088/0031-9155/59/23/7181

Staab et al: *Spot-scanning based proton therapy for extracranial chordoma;* http://dx.doi.org/10.1016/j.ijrobp.2011.02.018

For any further information, please refer to CPT,

**Dr. Ralf Schneider**
Tel. +41 56 310 3789
ralf.schneider@psi.ch

# Medical-Physics News

## Optical tracking of breathing motion for gated treatment with PBS proton therapy

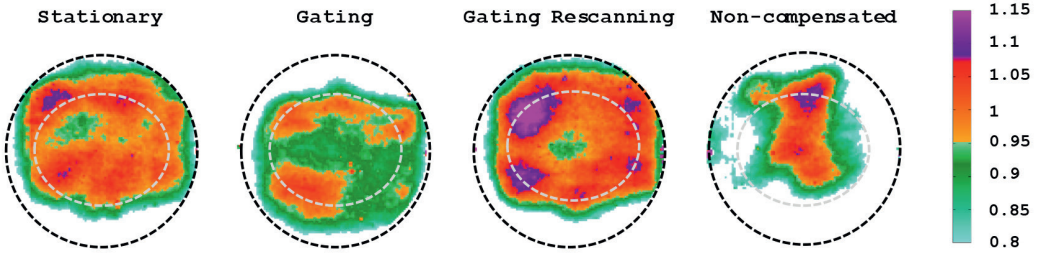
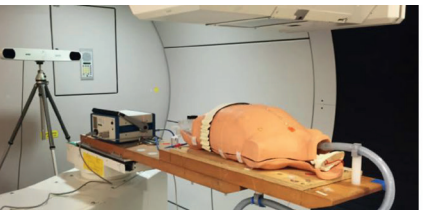



**Figure 2:** measured film dose distributions (normalised to the mean ITV dose 'Stationary') in the central plane of the tumour. Film edge and ITV delineated in black, and white dashed contours, respectively.

Intra-fractional motion is a major issue for proton therapy delivered using pencil beam scanning, limiting its precision for certain clinical indications. The problem is of critical importance in the treatment of patients with thoracic and abdominal tumours, where the breathing induced motion of anatomical structures is large and interplays with the dynamics of treatment delivery.

In conventional radiotherapy, dedicated strategies for breathing synchronized treatments are well established and involve either the limitation of target motion during irradiation by means of gating, breath-hold or by direct tumours tracking. The transfer of such knowledge to proton therapy, however, requires additional efforts to take into account residual motion-induced range uncertainties and daily deviations in the motion pattern. In this direction, we have developed a customised solution for real-time monitoring of breathing motion using optical tracking technology. The Polaris SPECTRA position sensor (Northern Digital Inc. (Waterloo, CA)) has been integrated in the Gantry 2 facility and, mounted on the treatment couch, is used to precisely localize infrared reflective spheres (Fig. 1). Relying on the correlation between target motion and the displacement of the patient surface, a configuration of external markers is used to pause the beam delivery until the correct geometry is detected. The delivery of gated treatments has been verified in an experimental environment close to the clinical scenario that uses an anthropomorphic breathing phantom. A programmable ventilator was used to generate a realistic pressure curve, resulting in 10 mm and 2 mm peak-to-peak amplitudes for the tumour and skin surface respectively.



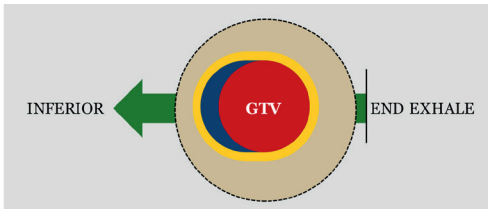



**Figure 1:** (left panel) experimental setup; (right panel) definition of PTV (yellow) from ITV (blue) and GTV (red).

A spherical GTV (3 cm diameter) was contoured on the end-exhale phase of a 4D-CT scan, acquired for treatment planning. The internal target volume (ITV) was then the GTV extended by 5 mm towards the peak-inhale phase, and the ITV was extended isotropically by another 5 mm to produce the PTV. The average-image computed from all the 4D-CT phases was used to optimize a single anterior-posterior field to give a uniform dose of 1 Gy to the PTV. Before irradiation, the phantom positioning was verified matching the end-exhale anatomy in the planning images with a stationary 3D scan acquired in-room by means of 3D volumetric image registration. Phantom motions were monitored by tracking a single marker position on the skin surface to selectively deliver beam at the end-exhale phase. Moreover, to mitigate the target residual motion in the gating window, limited to maximum 4 mm in our experimental setup, and the physiological instability of internal-external correlation expected in the clinical scenario, beam gating was coupled with rescanning. Four motion mitigation strategies were tested: gated, gated-plus-rescanning (3 rescans), no motion mitigation and stationary delivery, holding the phantom at the end-exhale position.

Dose distortions found in the non-compensated case (V95 = 49 %; D5-D95 = 33 %, γ3 % / 3 mm = 40 %) are partially mitigated by beam gating (V95 = 62 %; D5-D95 = 13.5 %, γ3 % / 3 mm = 60 %). Furthermore, target coverage is almost restored when coupled with rescanning (V95 = 95 %; D5-D95 = 17 %, γ3 % / 3 mm = 82 %). In the latter case however, homogeneity was worse than for the stationary case (V95 = 86 %; D5-D95 = 12 %, γ3 % / 3 mm = 79 %), indicating some residual motion effects.

Experimental film measurements showed that gating-plus-rescanning could recover the dose coverage at 95 % prescribed dose (Figure 2) and provide improved correspondence to the static case when evaluated using 3 % / 3 mm gamma analysis. In the perspective of the clinical use of gating, future activities will focus on robust breathing phase detection and synchronized x-ray imaging to verify the internal-external motion correlation on a daily basis.

For any further information, please refer to CPT,

**Dr. Giovanni Fattori**
Tel. +41 56 310 36 85
giovanni.fattori@psi.ch

**Dr. Rosalind Perrin**
Tel. +41 56 310 50 24
rosalind.perrin@psi.ch

## Imprint

**Editor**
Dr. Ulrike Kliebsch

**Chairman**
Prof. Damien C. Weber

**Chief Medical Physicist**
Prof. Tony Lomax

**Design and Layout**
Monika Blétry

## Contact

**Center for Proton Therapy**
CH-5232 Villigen PSI
protonentherapie@psi.ch
www.protonentherapie.ch
Tel. +41 56 310 35 24
Fax +41 56 310 35 15

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