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FACULTY OF HEALTH SCIENCES
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CBCT verification of SRT for patients with brain metastases

Doctoral (Ph.D.) thesis

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Introduction

Brain metastases are considered a serious problem regarding the nature of oncological diseases, as they develop in 20-40% of cancer patients during the disease history. WBRT SRS and SRT could be an option of the treatment of brain metastases (Khuntia, 2015).

Brain stereotactic (SRT) is a type of external beam radiotherapy that uses special devices/equipment to position and immobilise the patient in order to deliver high fractional doses of radiation to a well-defined clinical target volume. This significantly reduces normal tissue exposure and subsequent side effects close to the target volume, thus improving the quality of life of patients. The delivery of hypofractionated radiotherapy requires the highest possible reliability and accuracy of equipment, devices and staff (Baliga *et al.*, 2017; Lamba *et al.*, 2017).

Given the efficacy and effectiveness of stereotactic radiosurgery, there is a growing demand for the use of adapted linear accelerators in the treatment of BM. State-of-the-art linear accelerators ensure increasingly conformal treatments, and have an FFF function, therefore increased intensity beam reduces treatment time, ensures that SRT treatments can be performed in 15 minutes or less, as well as door-to-door. At the same time, high-resolution, dynamic volumetric imaging together with an integrated positioning and position determining system, as well as a customisable fixation system are, essential for performing SRT to ensure sub-mm accuracy. In addition, non-invasive 4D imaging, continuous soft tissue monitoring without implanted markers, and protocol-driven interventions are also necessary (Soffietti *et al.*, 2017).

The aim of our work is to demonstrate the effectiveness of volumetric imaging by analysing CBCT scans per treatment fraction performed according to our image guidance protocol. We investigated the pre-treatment correction components to determine whether our fixation system is capable of achieving the desired high accuracy of immobilization. In addition, we used post-treatment CBCT scans to verify that the intrafractional displacements were also below the expected level.

Research objectives

The aim of my work is to present the role of image control and volumetric imaging in stereotaxic radiotherapy (SRT) of brain metastases.

Hypotheses

My hypothesis is that analyzing cone-beam CT scans per treatment fraction according to our image control protocol can increase the effectiveness of volumetric imaging.

The examination of the corrective components before radiotherapy confirms that the patient recording system we use is suitable for achieving the desired high-precision immobilization.

In addition, by examining the data of cone-beam CT performed after treatment, we can make sure that the degree of intrafractional displacement remains below the expected level.

Materials and methods

Patients

Our clinic has 2 adapted Elekta linear accelerators (Synergy, Versa HD), which are capable of performing the most advanced image-guided (IGRT), intensity-modulated (IMRT), dynamic-arc therapy intensity-modulated (VMAT) and stereotactic (SRT) techniques. Their functionality serves the needs of hypofractionated radiotherapy, so that SRT or SBRT techniques can be used to safely treat skull, head and neck, chest, abdomen and pelvis targets. The two regions most commonly treated with stereotactic radiotherapy are the skull and the lungs.

For this analysis, we selected a cohort of patients treated with SRT for BM to investigate the efficacy of a specific image guidance protocol. Considering the hypofractionated dosimetry scheme, it is of paramount importance to accurately (in millimeters) select, the target area with the help of image guidance. For each patient, 5x6 Gy were delivered every other working day, at a total dose of 30 Gy.

Between 2018 and 2020, 106 patients were treated with intracranial stereotactic radiotherapy as per indication, which resulted in. 1060 HR 3D CBCT series of images were registered and corrected based on our verification protocol. To verify our image guidance method, we randomly selected 10 patients from this database who had undergone brain SRT. Thus, our representative sample of 50 stereotaxic fractions contains the measurement results of 100 cone beam CT images. Demographic and clinical data of the patients are shown in Table 1.

Verification of SRTs was always performed according to an on-line protocol: each pre-treatment, a verification image was taken at the treatment position to determine the submillimetre accurate the patient's position by a submillimetre accuracy for correction. For image verification, a region-specific preset was used, according to our predefined methodology.

Characteristics	No./median	Proportion (%)
Sex		
Male	2	20%
Female	8	80%
Age		
Min	24	
Max	84	
Median	55,5	
Primary site		
Lung	5	50%
Breast	3	30%
Skin (Melanoma)	1	10%
Ovarium	1	10%
Indication for SRT		
Intact met.	4	40%
Postop. tumour cavity	1	10%
Postop. tumour cavity+ met.	1	10%
Postop. rec.	2	20%
Postop.rec. + met.	2	20%

Table 1 Patients characteristics

Planning CT

The SRTs were prepared in the CT simulator, using a Philips Brilliance Big Bore device (Philips, The Netherlands) with a special 85 cm aperture. The scans were performed according to protocol, with a slice thickness of 2 mm and oncological settings.

In all cases, the immobilization system used was Qfix (QFix, Avondale, PA, USA). Patients were immobilized in the supine position with a carbon fibre head support and a Moldcare water-activated cushion placed under their head to maintain cervical lordosis. After positioning, an open, kevlar-reinforced 2.4 mm thick thermoplastic mask flap with eye and nose perforations was moulded onto the patients with a bite block bite fixation device. Kevlar reinforcement and bite block insertion can further reduce the potential dislocation of the head due to rotation.

Treatment planning, dose prescription

All patients were contoured and planned using Pinnacle (Philips, The Netherlands) irradiation planning system version 9.8. Imaging data from MRI scans performed before localization (T2 and Gd ka. T1 weighted sequences) were registered into the planning CT sequences by rigid transformation. Treatment target volumes and risk organs were defined based on the information from the MRI scans. In all cases, the dose was 30 Gy delivered in 5 fractions. Mobius 3D (Varian Medical Systems, Palo Alto, CA, USA) was used for the secondary verification of irradiation plans. Geometric verification during day zero was performed using Mobius 3D software.

Image guidance

Radiotherapy of all patients was image-guided and performed on an Elekta Versa HD linear accelerator (Elekta Oncology Systems Ltd, Crawley, UK). The equipment has an Agility MLC head, and uses Flattening Filter Free (FFF) technique, advanced 2D, 3D and 4D real-time imaging. Volumetric imaging is provided by the high resolution cone beam CT system integrated in the accelerator and its software XVI. The cone beam CT is a kilovolt (kV) imaging system with a beam perpendicular to the treatment beam, and it is possible to apply filters and collimators depending on body shape and the region treated. Another condition for stereotaxy is the positioning of the patient together with the individual patient positioning accessories based on image guidance. Image guidance is performed by the HexaPOD™ evo RT system and iGuide software, effectively correcting for in-plane and rotational misalignment during patient positioning. While conventional treatment tables allow for 3 directions translational correction, the HexaPod system ensures 3 directions rotational correction by tilting the table.

Cone-beam CT and XVI imaging technology

XVI 3D volumetric imaging allows you to visualize target volumes and critical organ positions without implanted markers. XVI is suitable for 3D matching/comparing CT and CBCT images taken in the treatment position on bone tissue and soft tissue basis.

CBCT scans a region in 2 to 4 minutes, depending on how data is collected, before/after each treatment fraction. For the acquisition, a single turn of the gantry is enough, the scanning range is a full arc. Meanwhile, the CBCT X-ray beam on the detector captures a series of two-dimensional summation images of the entire target volume. The summation images are used by a special algorithm to create a 3D reconstruction image database. There is no movement between slices, so no information is lost.

The image quality of CBCT scans differs from traditional CT scans. The main purpose of CBCT images is to determine the patient's position. The optimized image quality allows correct image registration with planned CT with minimal patient dose. XVI collects volumetric 3D data series and simultaneously reconstructs them. Imaging is performed at a low dose with submillimeter isotropic resolution in a treatment setting.

HexaPOD ™ evo RT system and iGuide

HexaPod is a unique, fully robotic patient positioning system. The computer-controlled control table is capable of independent movement in 6 directions: translation (along x, y, z axis) and rotation (pitch, roll, yaw) up to ±3°.

Patient positioning devices and a reference frame with an optical marker are recorded. A high-precision ceiling-mounted infrared camera tracks 6 optical markers on the reference frame in real time.

The reference frame can be attached to the table top so that the position of the table or the patient can be calculated.
HexaPOD's software unit, iGuide, controls the HexaPod and registers the table position. During verification imaging, the cone beam's CT software, XVI, determines the translational and rotation vectors and transmits them to the iGuide software, which moves the HexaPod and the patient along with the specified values and directions.

Verification

Patient positioning and immobilisation is followed by the registration of the patient's position. In iGuide, we record the location of the reference frame and the current position of the table along the X, Y and Z axes. Based on this, iGuide generates a relative table position, which the system will use as a starting point during the correction process.
The verification of patients treated with SRT for brain met will be performed according to an image guidance protocol we have defined. For this method, we have created a region-specific preset. This preset consists of 2 series of HR 3D CBCT and 1 series of 3D CBCT.
The first pre-treatment high-resolution 3D CBCT is taken in the initial table position. This is used to determine the translational and rotational deviations; during this we register the CBCT images taken in the treatment position to the planning reference CT done in the CT simulator. The XVI software determines the required translational and rotational movements and transmits them to iGuide. Based on the values obtained, medical approval is required to perform the

correction. Rotation values can be corrected up to 2.9°, and for values above 3° the patient must be repositioned and reclamped. Based on the approved correction values, iGuide will guide the HexaPod to the desired coordinates.

As this process takes several minutes, a 3D CBCT is taken immediately before the treatment to check for displacements during the registration process, and the scan is designed to exclude gross error.

Once accepted, the SRT fraction can be delivered. The daily fractions are designed from 2 coplanar and 3 non-coplanar half-arc (180°). To cast the 3 non-coplanar arcs, it is necessary to rotate the table from 0°, ± 45°, + 90° isocentre.

Immediately post-treatment, another HR 3D CBCT is performed to assess the intrafractional displacements.

Results

Our analysis compared the results of 50 pre-treatment and 50 post-treatment verification HR 3D CBCT measurements in 10 patients.

For each patient, 5 fractions were delivered with a fraction dose of 6 Gy on each occasion.

All patients' treatments were complete, with no interrupted SRT.

The same bed anchoring system was used in all treatment set-ups (carbon fibre baseplate, Q2 head support plexi, Moldcare mask pad, SRT 2.4 mm mask, bite block, knee support, foot support).

All treatments were performed using on-line image-guided patient positioning with HexaPod.

All cone beam CTs were performed under identical technical conditions (collimator: S20, 100 kV, 39.8 mAs, filter: F0).

The measurement results of 50 HR 3D CBCTs before treatment are shown in Figures 1 and 2.

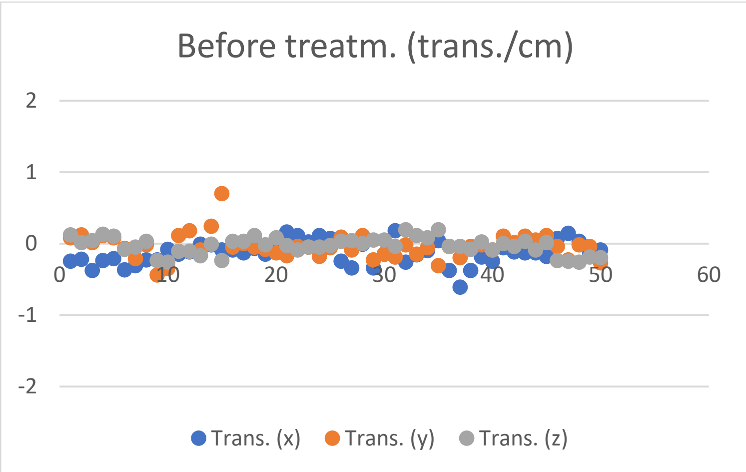

Figure 1 Translational CBCT values recorded in 50 cases before treatment

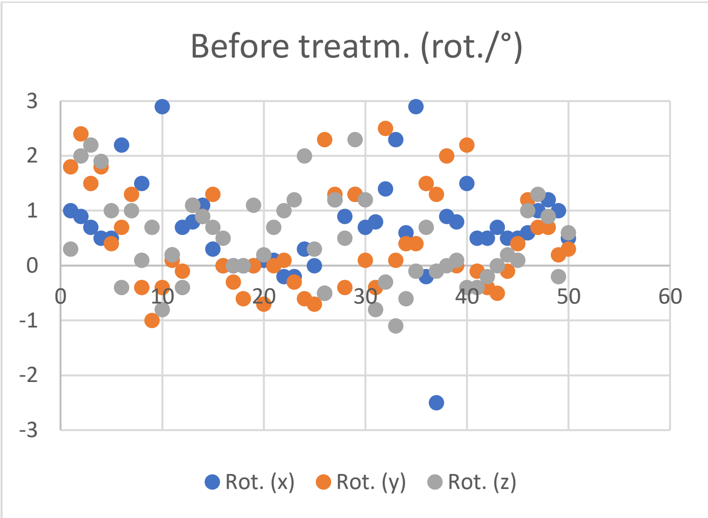

Figure 2 Rotational CBCT values recorded in 50 cases before treatment

Based on the registration of HR 3D CBCTs performed during patient set-ups before the treatments, 2 out of 50 fractions required patient repositioning (Figures 1 and 2) and re-registration.

On 48 occasions, patients were positioned without gross error using reference signals on the thermoplastic mask.

From the error components established and corrected before the treatment, we calculated the average and standard deviation for each patient.

Population mean X, Y and Z values derived from translational components (-0.1334 cm, -0.0396 cm, -0.0324 cm - respectively), rotation values (0.806°, 0.506°, 0.458°- respectively).

Systematic error components for translational displacements before corrections: 0.14 cm for X, 0.13 cm for Y and 0.1 cm for Z.

The post-treatment measurement results of 50 HR 3D CBCTs are shown in Figures 3 and 4.

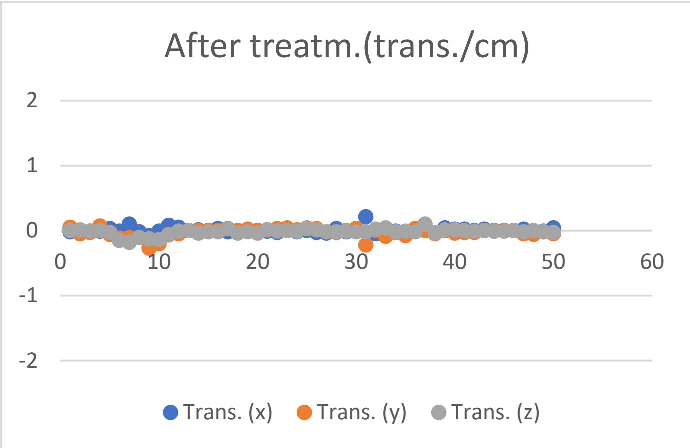

Figure 3 Translational CBCT values recorded in 50 cases post-treatment

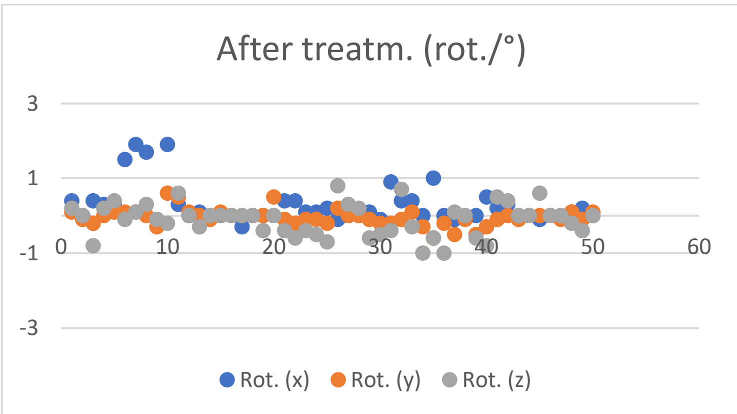

Figure 4 Post-treatment rotational CBCT values recorded in 50 cases

Based on the registration of HR 3D CBCTs during patient set-ups after the treatments, the translational measurement data of the 50 fractions show no significant residual error or intrafractional displacement (Figure 3).

We also calculated the average and standard deviation per patient from the established and corrected error components of the HR 3D CBCTs taken after the treatment.

Systematic error components derived from the standard deviation of the mean of the translational components at post-treatments CBCT: 0.01 cm for X, 0.06 cm for Y, and 0.04 cm for Z.

Discussion

Brain metastases are the most common adult brain tumours, with an incidence in Hungary by origin of: lung 40%, skin (melanoma) 30%, breast 25%, gastrointestinal and renal 5-10%. Radiotherapy, either alone or after surgery, remains the mainstay of treatment for brain metastases. Radiotherapy treatment options include: whole brain radiation therapy (WBRT), fractionated stereotaxy (SRT) or radiosurgical stereotaxy (SRS). SRT can be performed with Gamma knife, Cyberknife, tomotherapy and linear accelerator. Gamma knife SRS is a single session, high dose, focused irradiation. It is used for non-infiltrative intracranial tumours smaller than 3 cm. SRT-stereotactic fractional stereotaxy ususally performed on a dedicated linear accelerator, which allows larger lesions to be treated in critical areas of the brain (Mehta *et al.*, 2005; Kwon *et al.*, 2009; Marcrom *et al.*, 2017; Mazzola *et al.*, 2019).

Modern linear accelerators with integrated IGRT solutions such as CBCT enabled the extensive use of SRT in the management of BMs. Non-invasive patient positioning approaches like thermoplastic masks are suitable for fractionated stereotactic treatments of the brain (Kamath *et al.*, 2005; Clark *et al.*, 2010; Tarnavski, Engelholm and Af Rosenschold, 2016). Cone-beam CT imaging allowed the detection of translational and rotational alignment errors. Furthermore, the six-degrees-of-freedom (6-DOF) robotic couch allowed the correction of rotational alignment errors (Nielsen *et al.*, 2016).

3D volumetric imaging of the XVI device allows visualisation of target volumes and critical organ positions without the need for implanted markers. The XVI is suitable for 3D matching/comparison of planning CT and CBCT images acquired in the treatment position on a bone and soft tissue basis.

CBCT scans a region in 2-4 minutes, depending on the data collection method, which is done before/after each treatment fraction. A single turn of the gantry is sufficient for acquisition, the scan range is one full arc. Meanwhile, the cone-shaped X-ray beam on the detector captures a series of two-dimensional summation images of the entire target volume. From the summation images, a 3D reconstruction image database is generated using a special algorithm, due to which no information is lost.

The image quality of CBCT scans differs from that of conventional CT scans. The main purpose of CBCT images is to determine the position of the patient. Optimized image quality allows correct image registration using planned CT with minimal patient dose (Haertl *et al.*, 2013).

The XVI collects volumetric 3D data series and reconstructs them simultaneously. Imaging is performed at low dose, sub-millimeter isotropic resolution in the treatment setting.

HexaPod is an unique, fully robotic patient positioning system. The computer-controlled operating table is capable of independent movements in 6 directions of which are a combination of: translation (along x, y and z axes) and rotation (pitch, roll and yaw) of up to ±3°. The patient positioning devices and the reference frame containing an optical marker are fixed. A high-precision ceiling-mounted infrared camera tracks the 6 optical markers on the reference frame in real time. The reference frame can be dedicatedly fixed to the table top, so that the position of the table and the patient can be calculated.

The HexaPOD software unit, which is the iGuide, controls the HexaPod and registers the position of the table. During verification imaging XVI, the cone beam CT software, determines the translation and rotation vectors and transmits them to the iGuide software, which moves the HexaPod and the patient fixed to it in the specified values and directions.

The performance of the CBCT scans recorded in our image acquisition protocol fully supported our medical decision making, both in terms of gross error exclusion and target volume localization. HR 3D CBCT scans before brain stereotaxy treatments greatly help to verify the patient's position, accurately adjust the target volume mm for high-dose radiation treatments. The optimal bone-soft tissue contrast and image quality of diagnostic image verification in the kV range allows for more accurate and safer positioning. This reduces the treatment margins for SRTs, resulting in reduced dose to the tissue and risk organs, which also reduces the incidence of region-specific side effects. HR 3D CBCT values obtained after treatment provide information on the extent of intra-fractional displacements, and body position changes due to organ movements/unintended movements during the treatment period. In the group of patients we studied, intrafractional displacements can be minimised with the used fixation system, as shown by the results derived from the data measured during post-treatment CBCTs.

Measurement results from CBCTs before and after SRTs have demonstrated that our verification protocol and the fixation systems we use are capable of achieving the positioning accuracy required during SRT treatments. The advantages of volumetric imaging techniques for the verification of stereotactic radiotherapy are the following:

Changes and deviations in the patient's irradiation position can be accurately tracked and quantified during the treatment.

Deviations can be corrected immediately in all directions, along all the axes of rotation. This is of paramount importance for tumours located close to critical organs, such as intracranial tumours, where visualisation of the tumour and its surroundings plays a huge role in medical decision-making (Haertl *et al.*, 2013). Image registration, the HR 3D CBCT technique and the coordinated image guidance system create safe conditions for performing SRTs.

Conclusion

The absence of gross errors means that correct patient positioning was achieved during the planning CT, which could be successfully reproduced before treatment fractions, without the need for frequent repositioning. The desirable value of the population averages should be close to 0, so that there be no hidden systematic error in the system. In our case, the results obtained show that we have no systematic error during either preparation or execution.

Publications related to the topic

Scientific journals

Judit Papp, Mihály Simon, Emese Csiki, Árpád Kovács
CBCT verification of SRT for patients with brain metastases
Frontiers in Oncology, section Radiation Oncology, 2022. IF:6,244
Front. Oncol., 19 January 2022, ttps://doi.org/10.3389/fonc.2021.745140

Mihály Simon, **Judit Papp**, Emese Csiki, Árpád Kovács
Plan quality assessment of Fractionated Stereotactic Radiotherapy treatment plans in patients with brain metastases
Frontiers in Oncology, section Radiation Oncology, 2022. IF:6,244
Front. Oncol., 08 March 2022 https://doi.org/10.3389/fonc.2022.846609

Papp Judit, Simon Mihály, Csiki Emese
A tumor amplitúdóváltozás 4D CBCT alapú meghatározása a tüdőrák sztereotaxiás sugárkezelése során,
Egészség Akadémia, 2020.

Simon Mihály, **Papp Judit**, Csiki Emese
Kezelési margók meghatározása frakcionált agyi sztereotaxiás kezelések nem-invazív technikával való rögzítése során
Egészség Akadémia, 2020.

Posters

Judit Papp, M. Simon, E. Csiki, Á. Kovács
Cone-beam CT verification of mask based immobilization of stereotactic radiotherapy treatments
Copenhagen, Denmark, 6- 10 May 2022, ESTRO 41 Conference

Judit Papp, M. Simon, E. Csiki, E. Á. Kovács
Manufactured 3D imaging treatment table for image-guided brachyterapy
Vienna, Austria, 3- 7 April 2020, ESTRO 39 Conference

Judit Papp, M. Simon, E. Csiki, E. Csobán, A. Molnár, P. Árkosy, Á. Kovács
4D CBCT based determination of tumor amplitude variation in lung cancer SBRT
Milan, Italy, 26- 30 April 2019, ESTRO 38 Conference

Csobán Eszter, Molnár Anett, Simon Mihály, **Papp Judit**, Jánváry Zsolt Levente, Horváth Zsolt
HexaPodTM evo RT rendszer használata a Sugárterápián
Debrecen, 2017. november 16-18. Magyar Onkológusok Társasága XXXII. Kongresszusa

Balogh Zoltán, Géhlné Kaulák Ágota, Derján Brigitta, **Papp Judit**, Simon Mihály
Az extrakraniális sztereotaxiás sugárkezelés előkészítése a CT-szimulátorban
Győr, 2017. május 18-20. Magyar Sugárterápiás Társaság XIII. Kongresszusa

Szilágyi Csaba, Mihály E., **Papp J**., Simon M., Jánváry L.
A tüdő sztereotaxiás sugárkezelése klinikánkon
Győr, 2017. május 18-20. Magyar Sugárterápiás Társaság XIII. Kongresszusa

MTMT közlemény és idéző összefoglaló táblázat				
Papp Judit adatai (2023.05.23)				
Közlemény típusok	**Száma**		**Hivatkozások**[1]	
Tudományos közlemények	Összes	Részletezve	Független	Összes
I. Tudományos folyóiratcikk	2	---	---	---
külföldi kiadású szakfolyóiratban idegen nyelven	---	2	2	2
külföldi kiadású szakfolyóiratban magyar nyelven	---	0	0	0
hazai kiadású szakfolyóiratban idegen nyelven	---	0	0	0
hazai kiadású szakfolyóiratban magyar nyelven	---	0	0	0
II. Könyvek	0	---	---	---
a) Könyv, szerzőként	0	---	---	---
idegen nyelvű	---	0	0	0
magyar nyelvű	---	0	0	0
b) Könyv, szerkesztőként[2]	0	---	---	---
idegen nyelvű	---	0	---	---
magyar nyelvű	---	0	---	---
III. Könyvrészlet	0	---	---	---
idegen nyelvű	---	0	0	0
magyar nyelvű	---	0	0	0
IV. Konferenciaközlemény folyóiratban vagy konferenciakötetben	0	---	---	---
idegen nyelvű	---	0	0	0
magyar nyelvű	---	0	0	0

Közlemények összesen (I.-IV.)	2	---	2	2
Absztrakt[3]	10	---	0	0
Kutatási adat	0		0	0
További tudományos művek[4]	44	---	0	0
Összes tudományos közlemény	56	---	2	2
Hirsch index[5]	1	---	---	---
Oktatási művek	0	---	---	---
Felsőoktatási művek	0	---	---	---
Felsőoktatási tankönyv idegen nyelvű	---	0	0	0
Felsőoktatási tankönyv magyar nyelvű	---	0	0	0
Felsőoktatási tankönyv része idegen nyelven	---	0	0	0
Felsőoktatási tankönyv része magyar nyelven	---	0	0	0
Oktatási anyag	0	---	0	0
Oltalmi formák	0	---	0	0
Alkotás	0	---	0	0
Ismeretterjesztő művek	0	---	---	---
Folyóiratcikk		0	0	0
Könyvek	---	0	0	0
További ismeretterjesztő művek	---	0	0	0

Közérdekű vagy nem besorolt művek[6]	0	---	0	0
További közlemények[7]	0		0	0
Egyéb szerzőség[8]	0	---	0	0
Idézők szerkesztett művekre	---	---	0	0
Idézők disszertációban, egyéb típusban	---	---	0	0
Összes közlemény és összes idézőik	56	---	2	2

Megjegyzések
A táblázat számai hivatkozások is. A számra kattintva a program listázza azokat a műveket, amelyeket a cellában összeszámlált.
--- : Nem kitölthető cella
[1] A hivatkozások a disszertáció és egyéb típusú idézők nélkül számolva. A disszertáció és egyéb típusú idézők összesítve a táblázat végén találhatók.
[2] Szerkesztőként nem részesedik a könyv idézéséből
[3] Csak a tudományos jellegű absztraktok.
[4] Minden további még el nem számolt tudományos mű (kivéve alkotás vagy oltalmi forma), ahol a szerző: szerző, szerkesztő, kritikai vagy forráskiadás készítője szerzőségű.
[5] A disszertációk és egyéb típusú idézők nélkül számolva. A sor értéke az "Összes tudományos közlemény" sor idézettségi adatait veszi alapul.
[6] Minden Közérdekű, Nem besorolt jellegű közlemény, ahol a szerző nem egyéb szerzőségű szerző.
[7] Ide értve minden olyan művet, mely a táblázat más, nevesített soraiban nem került összeszámlálásra.
[8] Minden olyan egyéb szerzőségű mű, ahol a szerző nem: szerző, szerkesztő, kritikai vagy forráskiadás készítője szerzőségű.

2023. máj. 23.

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