UNIVERSITY OF PÉCS

DEPARTMENT OF HEALTH SCIENCES

DOCTORAL SCHOOL OF HEALTH SCIENCES

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Evaluation of treatment plan quality indices of linear accelerator based fractionated stereotactic radiotherapy treatment plans of patients with brain metastasis

Doctoral (Ph.D.) thesis

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Introduction

The risk of developing brain metastases in the adult tumour population is between 20% and 40%, given that the localization of primary tumours can be very diverse. In the past, whole brain radiotherapy (WBRT) played a leading role in the treatment of brain metastases, but nowadays the used therapy is determined more by the number of metastases, the general condition of the patient and the status of the primary tumour. In the presence of a small number (1-5) of metastases, radiosurgery (SRS) can be considered. During the procedure ablative dose is delivered with a very steep dose gradient in order to protect healthy tissues. Due to the ablative nature of this treatment, the size of treatable metastases is strictly limited (maximum 3.5 cm). The appearance of very high doses in both the surrounding healthy organs and healthy brain tissue carries a significant risk. The correlation between the volume of intact brain tissue that received 12 Gy (V12) and the cognitive deficit has already come to light. During fractionated stereotaxic radiation (FSRT), the goal is to achieve similar local control, so that toxicities remain acceptable. FSRT also delivers high doses, but not in one session, but in 3-5 fractions, for which it uses non-invasive patient fixation systems. The goal of FSRT is to maintain control while reducing toxicity. The accuracy falls short of SRS's, but it results in a reduced normal tissue dose and takes advantage of fractionation.

Research objectives

The purpose of my work is to present the FSRT introduced in our institute and through deriving quality indices examine their clinical suitability.

Hypotheses

Are the proposed and used metrics describe the plan quality sufficiently?

Is the current planning technique at the University of Debrecen results clinically acceptable plans?

Is the volume of the treated lesion affecting plan quality in FSRT treatments?

Can FSRT treatments represent similar healthy brain tissue dose as SRS treatments?

Description of research methods

In a group of patients with brain metastases, we evaluated the quality of completed treatment plans based on the indices used in the literature.

Materials and methods

Between May 2019 and May 2020, we produced treatment plans for 24 patients with one or more metastases treated with FSRT. Patients who underwent surgery but had additional body metastases were also included. The number of metastases treated within one treatment fraction ranged from 1 to 7, in each case several non-coplanar arcs from one isocenter was used.

Localization

The patients were positioned supine, in an open face thermoplastic mask system, which consists of a base plate, a moldable pillow and a thermoplastic mask. The masks are made of 2.4 mm thick material, reinforced with Kevlar, thereby ensuring the precision essential for stereotaxy. The open face masks leave a part of the face (eyes, nose) free, thus reducing the feeling of confinement of the patients and increasing their comfort. The use of Kevlar reinforcement and bite block can further reduce the rotational possibility of the head. We used knee supports and leg supports to stabilize the lower limbs. We prepared the planning CT series according to the institutional protocol, with a slice thickness of 2 mm.

Before the planning CT, preferably within 2 weeks, a contrast-enhanced magnetic resonance imaging (MRI) scan was performed on all patients.

Treatment planning, Dose Prescription

All patients were contoured and planned using Pinnacle (Philips, The Netherlands) radiation planning system version 9.8.

MRI examinations (T2 and Gd KA. T1 weighted series) were registered with rigid transformation to the planning CT series. The gross tumour volume (GTV) was contoured on the planning CT based on the MR information. According to the institutional protocol, GTV is the visible, contrast enhanced tumour volume on the T1 series. The GTV was the same as the clinical target volume (CTV). An isotopic margin of 3 mm was used between the CTV and the planning target volume (PTV). The organs at risk taken into account during the radiation planning were the brainstem, chiasma, inner ears, eye lenses, optic nerves and intact brain tissue. In each case, a mono isocenteric irradiation plan using several dynamic arcs was prepared. Depending on the localization of the PTV, the number of arcs could change, in the case of lateral tumour, the contralateral fields could be omitted. During the planning and treatments, it was allowed to use both traditional flattening filter (FF) and flattening filter free (FFF) energies. In all cases, the total dose prescription was 30 Gy in either 5 or 6 fractions. According to the stereotactic dose prescriptions, the

prescribed dose was 80% of the isocenter dose, and it was possible to deviate from this by 10%. In all cases, the treatments were carried out on an Elekta Versa HD linear accelerator, with a HexaPOD table top, which is capable of correcting not only translational but also rotational deviations in 3 directions up to ±3°. Correction of rotational deviations plays a particularly important role in irradiation plans with one isocenter.

Analysis

The following indices were derived from the irradiation plans: RTOG Conformity Index (RTOG CI), Paddick Conformity Index (Paddick CI), Gradient Index (GI), Homogeneity Index (HI) and Quality Index (Q).

The RTOG CI is the ratio of the reference dose volume (PIV) to the target volume (TV):

$$CI_{RTOG} = \frac{PIV}{TV}$$

Paddick CI is the ratio of the square of the volume covered by the reference dose of the target volume (TVPIV) to the product of the target volume (TV) and the volume of the reference dose (VRI):

$$CI\ _{Paddick} = \frac{TV_{PIV}^{2}}{(TV * V_{RI})}$$

The Gradient Index is the ratio of the volume of the 50% isodose curve (V50) to the volume of the 100% isodose curve (PIV).

$$GI = \frac{V_{50}}{P_{IV}}$$

The Homogeneity Index is the ratio of the maximum dose within the target volume (max) to the reference dose (PIV)

$$HI = \frac{I_{max}}{P_{IV}}$$

The Q index is the ratio of the minimum dose within the target volume (Imin) and the reference dose (PIV).

$$Q = \frac{I_{min}}{P_{IV}}$$

In addition to those mentioned above, the parameter V24.4Gy was also derived, V24.4 Gy is the volume of the intact brain tissue that receives at least 24.4 Gy. V24.4 Gy was derived as an alternative to the V12 index used during FSRT based on the following equation:

$$BED = nd\left(\frac{1+d}{\alpha/\beta}\right)$$

Where $\alpha/\beta = 2$, n is the number of fractions and d is the fractional dose.

PTV volumes were binned into 10cm² or 15cm3 groups for further analysis.

Results

In the case of 24 treated patients, we derived the listed quality metrics. 4 patients previously received some form of radiation therapy (1 WBRT, 2 SRS, 1 SRT). Surgical resection was performed in 4 patients, 7 patients had solitary, and 17 patients had oligo-metastatic disease. We treated a total of 65 lesions, of which 32 were left-sided, 32 were right-sided, while in one case the laterality could not be interpreted. The most common primary tumour types were non-small cell lung cancer (NSCLC) in 46%, breast cancer in 17% and melanoma in 13%. The mean number of treated lesions was 2.7 (SD ± 1.7).

The mean value of the RTOG CI was 0.942, the standard deviation (SD) was ±0.153. The average value of the Paddick CI was 0.824, SD of ±0.090. GI mean 6.146±3.085 (SD). The mean of Q was 0.940 and the SD was 0.118. The mean value of HI is 1.263, SD 0.103. The average of V24.4Gy was 33.434 cm3.

Discussion

The gold standard treatment for brain metastases is still SRS, although size restrictions and the risk of radionecrosis limits its use. However, some comparative studies between SRS and FSRT suggest that FSRT may serve as an alternative. The FSRT protocol implemented by us results in clinically acceptable plans with a non-invasive patient fixation method and treatment planning. Accelerator-based FSRT treatments for large lesions provide better compliance than gamma knife (GK) and are comparable to the results of GK in terms of V12. Our goal was to derive quality characteristics from the irradiation

plans, with the help of which the quality of the plans can be assessed objectively. The main limiting factor was the lack of different modalities, so we compared our results with data published in the literature.

The method we use creates the opportunity for the fractional treatment of several brain metastases from one isocenter and, based on literature data, results in clinically acceptable irradiation plans regardless of the number or size of the target volumes.

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Published work written during the course of this thesis.

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

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 | https://doi.org/10.3389/fonc.2021.745140

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

Papp Judit, Simon Mihály, Csiki Emese

A tumor amplitúdóváltozás 4D CBCT alapú meghatározása a tüdőrák sztereotaxiás sugárkezelése során Egészség Akadémia, 2020.

MTMT közlemény és idéző összefoglaló táblázat				
Simon Mihály adatai (2023.05.18.)				
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, szerkesztőként2	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
Absztrakt3	14	---	1	1
Kutatási adat	0		0	0
További tudományos művek4	19	---	0	0
Összes tudományos közlemény	35	---	3	3
Hirsch index5	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 művek6	0	---	0	0
További közlemények7	0		0	0
Egyéb szerzőség8	0	---	0	0
Idézők szerkesztett művekre	---	---	0	0
Idézők disszertációban, egyéb típusban	---	---	0	0
Összes közlemény és összes idézőik	35	---	3	3
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.