Hypofractionated Stereotactic Radiotherapy in brain metastasis using Nomostat® System

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Abstract

In metastatic brain lesions treatment, stereotactic radiation therapy represents a valid alternative to surgery, which indication is limited to single lesions, in accessible brain sites and in patients presenting an optimal performance status.
The aim of this study was to develop a novel method for delivering fractionated stereotactic intensity-modulated radiotherapy. We present treatment parameters, dosimetry analysis, and preliminary clinical outcome. The method incorporates high-precision invasive fixation and reduced dimension pencil beams.
In our hospital, since January 2008 Hypofractionated Stereotactic Radiation Therapy is performed using Serial Tomotherapy with Nomostat® System, connected to a 6 MV Linac. This system realizes an IMRT with dynamic gantry and a beam modulation by a binary multileaf collimator (MIMiC® multivane intensity-modulating collimator) attached to the Linac head. During gantry rotation, collimator automatically modifies its morphology following target shape. In treatment of lesion smaller than 1,5cm, a post-collimation device called Beak® provides leaves opening limitation to 4mm, allowing an high dose conformation around the target and an high dose fall-off in surrounding healthy tissues.
For stereotactic radiation therapy in brain malignancies, we use Talon® immobilization device, a minimally invasive system which consists in two titanium screws fixed in patient scalp; this device, making the patient in solidarity with the couch, provides high accuracy in his positioning during radiotherapy sessions.
In our experience, the technique has proven to be easy in implementation and highly reliable, allowing accurate repositioning in the hypofractionated treatments.

INTRODUCTION

Radiation therapy consists in therapeutic use of ionizing radiation in malignant disease. High radiation doses arise probability of disease care, but also toxicity, so treatment plans derive always from a compromise between curative and toxic doses.
Advanced radiation therapy techniques are required to allow delivering of higher and potentially curative doses to treatment volumes, respecting tolerance doses of organ at risk near the target.
Radiation therapy needs several steps: patient set-up definition, imaging acquisition for treatment planning (TC without contrast enhancement), contouring volumes of interest on TC slices (**P**lanning **T**arget **V**olume, **O**rgans **A**t **R**isk), also with imagine fusion between TC and contrasted TC or RM, treatment planning and, finally, treatment sessions.
Three-dimensional conformal radiation therapy (3DCRT) is the standard technique and consists in using multiple fields conformed on target geometry and dose contribution fixed for every beam. Treatment planning is defined forward planning because the operator provides beam modelling on PTV and OAR shape and prescription to a point dose (isocenter).
Intensity Modulated Radiation Therapy (IMRT) is an advanced technique which allows a conformal beam geometry and a fluence modulation of radiation beam geometric and dosimetric parameters (modulation of beam shape and intensity). The treatment plan is obtained with an inverse planning, because the operator defines PTV and OAR constraints and beam fluence optimization is automatically calculated by treatment planning system (TPS) (Fig. 1).
Stereotactic radiosurgery was introduced more than

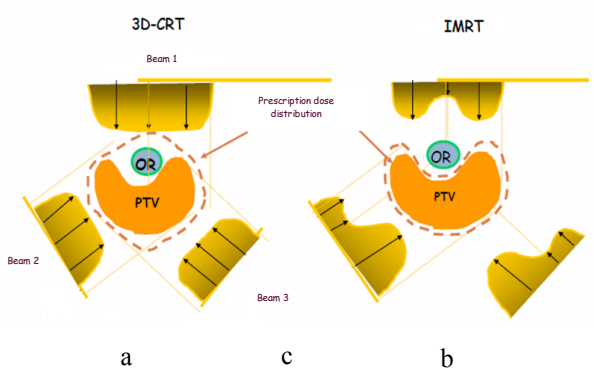


Fig.1: Differences between forward planning and invers planning. Beam fluente modulation allows concave dose distribution, which in not achievable with 3DCRT.

50 years ago as a way of treating various intracranial lesions without recourse to open-skull surgery. Since then, it has been extended both in terms of the radiation modalities that have been used and the types of lesions treated [1]. Stereotactic radiation therapy consists in the application of very high ionizing radiation doses in larger than conventional fractionation (2 Gy/die) to volumes smaller than conventional radiotherapy fields often with integration of advanced modalities for tumour imaging and devices for patient immobilization [2]. In particular, in stereotactic therapy of intracranial lesions, is mandatory to use bloody immobilization devices, such as Leksell helmet (Fig. 2).

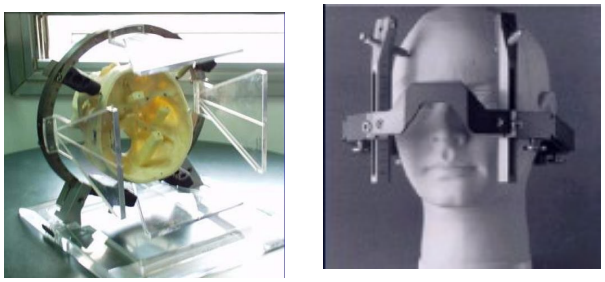


Fig 2: Leksell helmet: to align precisely the and the positioning of the isocentric site of linear accelerator.

It consists in four screws fixed to patient scalp and a ring fixed to the helmet. This device is useful only in single fraction stereotactic radiotherapy, because of its uncomfortableness.

The aim of this paper is to describe a cranial stereotactic radiation therapy technique using Serial Tomoherapy and Talon immobilization device as alternative to Leksell stereotactic helmet. The design of the system is intended to combine the accuracy of an invasive system while supporting fractionated stereotactic treatment regimens.

MATERIALS AND METHODS

The sequential tomotherapy system

Serial Tomotherapy (Nomostat® System) [3] is an advanced IMRT system which uses a standard linear accelerator (Linac) combined with several tools that allows a dynamic arc intensity modulation radiotherapy [4]. This system consists of an inverse planning system and multileaf collimator, that is attached to the Linac head and operates dynamically during an arc delivery. In short, by segmenting target treatment into sections, or slices, dose to each slice can be tailored to match target shape on that slice, thus leading to a truly 3D conformal distribution.

Nomostat® System consists in three units: MIMiC®, Autocrane® and Corvus®.

The MIMiC® (Multileaf Intensity-Modulatin Collimator) consists of two rows of 20 leaves governed by a binary system (open or close) and moved by a pneumatic mechanism. Collimator shape changes following target morphology every 5° along a gantry rotation of 340°, defining a pencil beam, so also 2560 pencil beam for an arch can be delivered. MIMiC® can be used in three modalities, in according to three different levels of leaves opening: 2cm , 1cm and beak (4mm).

Autocrane®, attached to the couch top hand rails, is useful system for precision indexing of the table. It is needful in case of target length superior to leaves maximum opening (maximum beam length: nominal 4cm, real 3.2cm). In facts, it provides to automatic couch movement at the end of an arch delivering to the next treatment slice. To limit slice-to-slice dosimetric junctioning errors to 5%, couch incrementation has to be accurate to about 0.2mm

Corvus® is an inverse planning system that provides to automatic calculation of dose distribution, in respect to target prescription and constraints to organ at risk near the target.

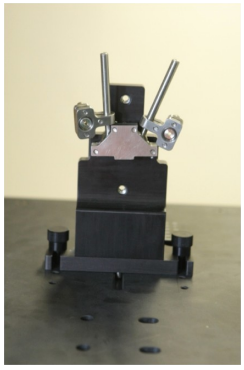
Serial Tomotherapy allows IMRT and Stereotactic treatments.

Talon® is a removable stereotactic head fixation and positioning device, characterized by accuracy of an invasive system while supporting fractionated stereotactic treatment regimens. It requires neurosurgical bicortical insertion of two self-tapping titanium base screws into patient's skull (20 min, local anesthesia). For imaging and treatment, Talon is attached to base screws.

The assembly has adjustable locking ball joints and extension rods to allow for minute adjustment of cranium position. The variability of possible fixation positions allows for patient comfort while rigidly im-

mobilizing the patient's head. Once all the degrees of freedom of the Talon® device are tightened and, thereby, locked into a patient-specific position, the device remains unaltered for all subsequent imaging and treatment of the patient. The particular Talon® device used belongs to that patient for the entire course of treatment and specifically defines the patient's treatment position. The Talon® assembly and patient were subsequently attached to the Nomogrip, a rigid perpendicular extension to the radiotherapy treatment table. Essentially, the Talon® system uses a one-time invasive placement of two titanium base screws combined with a non-invasive daily application of talon device to facilitate a removable stereotactic immobilization and alignment system (Fig.3) [5].

To treat smaller intracranial lesions, Nomostat® System includes beak (Fig.4), a post-collimation attachment to MIMiC® that allows the target to be segmented into even more and even thinner treatment slices, limiting the leaves' opening lenght to 4mm, resulting in significant improvements in dose conformity and reduction of inferior/superior spillover of dose [3,8].



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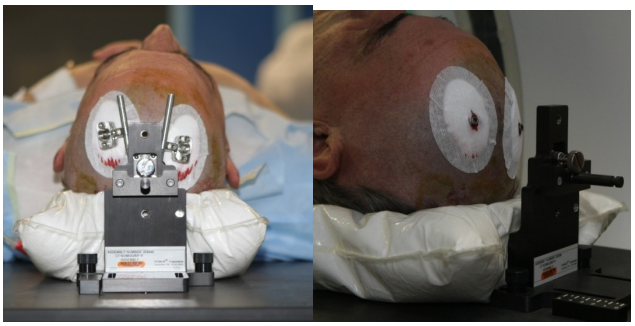

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Fig. 3.: a) Talon system: a unit with 2 head screws for precise localization. It is less invasive than competing technology. b, c) Talon® and titanium screws inserted in patient scalp.

Fig. 4: Beak: a post-collimation device that was inserted into the opening of the MlMiC for fine detail stereotactic IMRS delivery with a beamlet size of 4x8mm.

Patient and tumor characteristics

In our hospital, from January 2009 to May 2010, 36 patients (17 male and 19 female; median age 61 years; range 34-84 years) with 1-4 brain metastatic lesions (Ø max 3-4cm) underwent to Intensity Modulated Hypofractionated Stereotactic treatment using

Primary	lung	breast	colon	melanoma	kidney	ovary
n° patients	17	12	4	1	1	1

Table 1: Stratification of patients treated in our institution on basis of primary tumours generating brain metastasis

Serial Tomotherapy and Talon immobilization device. The total number of irradiated lesions is 63 (Table 1). In every patient, a pre-treatment brain RM was performed. Post-radiation therapy RM was performed after 3 and 6 months.

Treatment planning and delivery

CT images of the patient immobilized in the treatment position were acquired using the TALON system.

Image acquisition was performed on a Siemens Emocion 6 (Siemens Medical Solutions) in 3-mm contiguous slices, covering the entire patient head, from the base of skull upward. The thinner section CT slices were acquired to cover the target region and the stereotactic localizer.

MR imaging was performed without the TALON attached, because the metallic composite would have caused major image distortion. Typically, T1- and T2 - weighted MR images, as well as T1 post-contrast images, were acquired in contiguous slices using a 512x512 image matrix.

CT and MRI data sets were imported into a computerized intensity-modulated treatment planning program (Corvus 3, Nomos Corp.). Image registration/ fusion for CT and MRI was based on anatomical landmark registration.

The target was delineated as planning target volume (PTV) that encompassed the gross tumor volume (as identified in CT and MRI contrast-enhanced imag-

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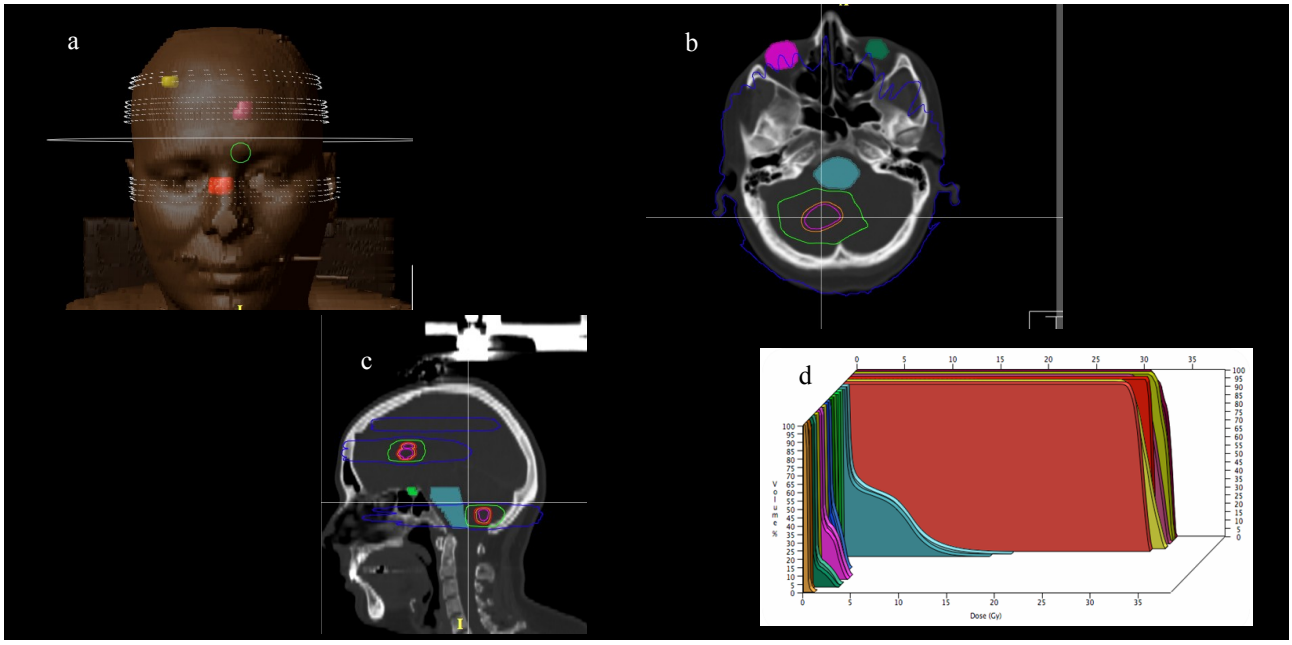

Fig. 6. : a) Treatment plan view in a 3D reconstruction of contoured structures. b, c): dose distribution around brain lesions: axial and coronal dose distribution for three small intracranical lesions, with a display of the planning target volume (red, violet and yellow) and the brain stem (blue). The 100% isodose line (pink) as well as the 90% (red), 80% (orange), 50% (green) and 10% (blue) isodose lines are displayed. The dose-surface rendering displays that the entire target volume is covered by the 100% isodose, while only a small surface fraction of the brain stem is exposed to potentially clinically relevant doses (50%). d) The DVH documents 99% targets volume coverage by the prescription isodose and excellent dose sparing regarding the healthy tissue

ing) and a safety margin of 2 mm. In addition, the brain stem, optic chiasm, optic nerves, and the eyes were delineated.

For the present treatment plans, the goal was always 30 Gy in 5 daily fractions. Every treatment started on Monday and ended on Friday. Plan

optimization was performed to obtain that 100% of tumor volume receive at least 95% of prescription dose and hot spots of 150% of dose within the target were accepted.

Patients received IMRT treatment using one couch angle (0 degrees) and the rotational arc ranged from 215° to 145° (290 arcing degrees).

The dose-volume histogram (DVH)-driven objective function of the planning system computed an optimized dose distribution (Fig. 6). An example of dose distribution in axial, coronal and sagittal plan is shown in fig. 6A. A representation of treatment view is shown in fig. 6B. An example of stereotactic treatment DVH is shown in Fig. 5.

Treatment was delivered using a 6-MV linear accelerator (Primus, Siemens) and the attached MlMiC binary collimator (Nomos Corp.). The pencil-beam size for the 1-cm mode was automatically delivered by the MlMiC and the BEAK post-collimation device was inserted into the opening of the MlMiC. The patients were precisely repositioned on the treatment couch using the TALON system. The target isocenter was adjusted according to stereotactic coordinates calculated during treatment planning. Duration of a typical treatment was 20 to 25 minutes, requiring 1 or 2 serial arcs. Daily set-up control was performed using a portal imaging system.

Pretreatment patient quality assurance

Stereotacic Radiotherpy requires a dedicates quality assurance (QA) procedure for each treatment patient. The aim of patient QA is to check the agreement between the dose distribution calculated by the TPS and the effective one.

In our hospital, patient specific Stereotacic Radiotherpy treatment plan QA is based on a so-called hybrid plan verification, i.e. an accepted treatment plan is recalculated with unmodified fluence maps in a verification phantom. The resulting dose distribution of such a composite treatment plan is measured with film and compared to the calculated one. The phantom consists of plates which allow inserting films in axial planes. The dimensions of the phantom is 17cm x17cmx18cm high. Additionally, a dedicated

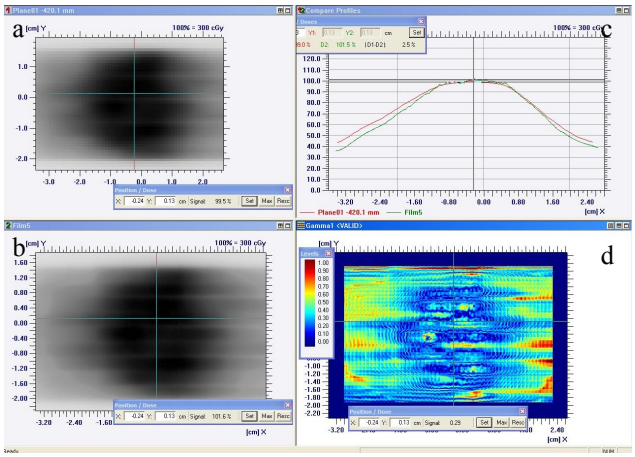

Fig.7: The treatment plan slice to be validated with film dosimetry as used in the initial quantitative quality assurance system. a) The film from the isocentric plane in TPS modelling. b)The film from the phantom . c) the line dose profile obtained from planned dose data (red line) and from measured data (green line) d) γ index method to check the agreement between the dose distribution calculated by the TPS and the effective one: blue color represents regions where the gamma index criterion is complied with and red for the other regions where the gamma index criterion fails.

ionization chamber insert is an integral part of the respective phantom, which can be filled with pure polystyrene if film measurements are carried out.
For film measurements EDR-2 film (Eastman Kodak Company, New York, US) is used in a plane as it allows verifying a typical daily fraction dose of 2 Gy. The film is processed using a computer controlled film processor (KodakM35 X-Omat processor). After processing, the film is scanned with a Vidar VXR-12 plus scanner (Vidar Systems Corp, Herndon, VA) connected to a PC. All scans are performed with a resolution of 300 dpi. Film analysis is performed using OmniPro- I'mRT software package. After selecting a region of interest and using a low pass filter for noise reduction purposes, the resolution is reduced to 1 mm. A 1 mm grid size is also used to compute dose distributions with the TPS. For the conversion of optical density to dose a so-called normalized sensitometric curve is used [10]. With this method a relative dose distribution can be obtained.
For absolute dosimetry ionization chamber measurements are performed in regions of shallow dose gradient using a calibrated cylindrical ionization chamber (Room Exradin A1, volume sensitive: 0,0056 cm^3) connected to an appropriate electrometer (type NE 2620, Nuclear Enterprise).
The two dose distributions, calculated and measured, are evaluated by γ method [11-14]. This concept combines a dose difference criterion with a distance-to-agreement (DTA) criterion for each point of interest. For the present work, all γ vector calculations are based on 3% dose criteria and 3 mm DTA acceptance criteria, where the 3% dose deviation is relative to the dose at the normalization point (Fig. 8).

RESULTS

Re-position accuracy was high in every patient and in every radiation fraction. Median set-up error was 1mm (range 0-2). On post-treatment RM, tumour response was classified as complete response (RC) when a reduction of tumour volume was at least 75% was observed, partial response (RP) if reduction was between 50 % and 75%, stable disease (SD) if tumour reduction was less than 50% and progression of disease for arising tumour volume.
The results in our series are shown in Table 2. After three months from treatment, we observed a complete or partial response in 69% of cases.

Response	N° of lesions
RC	30
RP	14
SD	16
PD	3
Total irradiated lesions **63**	

Table 2: description of tumor response 3 months after treatment.

DISCUSSION

Stereotactic treatment are delivered in single fraction because of uncomfortable bloody immobilization system such as Leksell helmet. It allows high accurancy in patient positioning, lesion treatment and OARs sparing, considering the complex interplay between time-dose-fractionation, partial volume effect, physical dose distribution, and set-up uncertainties in influencing treatment outcome. The radiobiological advantage of dose-fractionation for normal tissue sparing is estimated using the linear-quadratic model and

viewed in the context of clinical situations and results.

Instead, multiple fraction treatment is characterized by larger geometrical uncertainty which would require increased treatment volume and an associated decrease in treatment dose [6].

An evaluation of Talon® repositioning accuracy, using a system based on sets of anatomic landmarks coordinates, evaluated in repeated CT scans, concluded that the device is very well suited for immobilization and alignment of single-fraction stereotactic radiosurgical applications.

Furthermore, the unique removable design of the system was also seen to facilitate the use of the device for extremely accurate and reproducible alignment of the patient for fractionated stereotactic treatment courses. The excellent accuracy of the system for single-fraction applications was seen to deteriorate only slightly over a 6-week course of treatment, so Talon® repositioning accuracy is greatest in hypofractionated treatment. Lastly, the removable design of the system was also seen to make possible the separation of the image acquisition, treatment planning, and treatment phases of the process into separate days, an option seen as desirable by our radiosurgery team [5]. Fractionation of dose is an important principle of radiation therapy. It allows dose escalation to tumour volume, because after every fraction healthy tissue can repair lethal and sublethal DNA risk. Using Nomostat® System, patient is positioned in an alignment point automatically derived from Talon position and Autocrane® provide to automatic movement of the couch, with an accuracy of 0,2mm, reducing risk of positioning errors. Furthermore, using multiple isocenters in treatment of multiple brain lesions, can produce dose overlap in several regions. Inverse planning allows dose prescription to a reference isodose and exclude risk of overlapping dose in healthy brain. In practise, IMRT treatment planning improves Conformity Index (CI: ratio of tissue volume covered by the prescribed dose to the target volume). Homogeneity Index (HI: ratio of the maximum isodose within PTV to the reference isodose) depends on isocenters number. IMRT allows high dose homogeneity within the target also in irregularly shaped lesions, while disomogeneity grade in radiosurgery is higher than 30%. This date is proportional to late toxicity.In regarding to OARs sparing, radiosurgery seems to provide to a better Brainstem sparing than IMRT, but IMRT improves OAR sparing in large and irregular target. Tissue around target receives minor doses using radiosurgery with circular collimators, so radiosurgery seems to be better in single fraction treatments. However, results show that IMRT treatment modality produces similar results as radiosurgery for small, spherical lesions, whereas it is found to be superior to SRS for irregular lesions in terms of critical structure sparing and better dose homogeneity [7].

The use of Beak® in lesions smaller than 1,5cm, further improves conformation of dose around the target. A study comparing dose distribution using Beak® or 1cm- MIMiC® collimator, demonstrate that Beak® allows better CI without homogeneity reduction and better dose fall-off in the healthy tissues around the target. This advantage is superior in small lesions, in irregularly shaped lesions and in high dose fractions. The Authors concluded that Beak stereotactic radiation therapy can be considered as an alternative to gamma Knife [8].

Another important advantage of IMRS (Intensity Modulated RadioSurgery) is the possibility to perform a set-up control throughout portal image acquisition on Linac, which are confronted with DRR deriving from TC slice, allowing a safe patient repositioning during every radiation fraction.

CONCLUSIONS

In our experience, the use of Serial Tomotherapy in the treatment of brain malignancies demonstrates easy implementation and high accuracy. The repositioning, checked daily through the portal images, was safe. This is also demonstrated by the high percentage of radiation necrosis found in the brain lesions sites at RM after at least 6 months.

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