Spinal Radiosurgery Using the Synergy-S system

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Radiosurgery is defined as the delivery of high intensity radiation energy to a target while sparing the surrounding organs. Lars Leksell was the first to describe stereotactic radiosurgery for cranial targets in 1951 [1]. The transition to extracranial radiosurgery required technological advances such as practical non-invasive patient immobilization, precision targeting and radiation delivery using real-time image guidance, as well as the advent of high tech computer-intensive radiation delivery modalities such as intensity-modulated radiation therapy and rapid arc. These technologies made spinal radiosurgery a viable tool for the treatment of spinal tumors in recent years [1,2].

Strauss et al. [3], in this issue of *IMAJ*, report their experience with spinal radiosurgery using the Synergy-S linear accelerator system. Thirty-four patients harboring 41 spinal tumors of various pathologies were treated during the years 2007–2011. The tumors were delineated according to magnetic resonance imaging and computed tomography scans fused by the system software. Patients were immobilized by means of a bluebag or facial mask, and positioning was achieved using the cone beam CT included in the system. The authors do not report position verification performed during or after the treatment. Pain control was achieved in 80% and local tumor control in 87.5% of treated sites over a mean follow-up period of 10.8 months.

Current spinal radiosurgery systems have a different workflow: the procedure is initiated with a CT scan and MRI using special high resolution protocols and immobilization devices. The targets and organs at risk are contoured, treatment is planned, and quality assurance procedures are performed. The patient then undergoes the treatment with the same immobilization device in an outpatient setting. In the Novalis and Cyberknife systems, initial rough localization is done with external non-invasive fiducial markers usually affixed to the patient's skin or a fitting vest, isocenter markers or cone beam CT. Exact localization is performed with on-board X-ray cameras and flat X-ray detectors that allow instant image availability. X-rays acquired on-board are fused to digitally reconstructed radiographs from the pre-treatment CT, allowing for continued verification of patient position during treatment delivery. Furthermore, and most important, these systems use the actual image information for automated position correction relaying the coordinates of actual patient position to a computer-driven robotic coach which executes the necessary positional changes in 6 degrees of freedom (anterior-posterior, lateral, vertical, pitch, roll, tilt and swivel) to allow for precise and fast final patient-positioning correction. The real-time imaging is frequently activated during the actual irradiation to provide feedback on continuous mechanical accuracy.

Indications for spinal radiosurgery include oligometastatic spine tumors, radio-resistant spine tumors, progression after prior conventional radiation, residual or progression after surgery, difficult surgical approaches, and significant medical comorbidities. Similar to this Israeli study, multiple studies have reported a high rate of pain control ranging from 85% to 92% with the effect taking place a few days to weeks after the treatment [4-6]. In contrast to conventional radiation, spinal radiosurgery achieves high local control rates for spinal metastases [5,7], and even radio-resistant pathologies show high rates of local control [6,8]. The efficacy described by Strauss et al. is comparable to previously published studies [4,5,7,9] and prove once again the great value of spinal radiosurgery for the treatment of spine tumors. The authors describe the Synergy-S as unique owing to the on-board CBCT. However, the Novalis TX and the Novalis TrueBeam (both used by these reviewers) have on-board cone beam CT as well. CBCT, however, cannot be used during actual treatment to confirm stability of patient positioning and in this respect, for the purpose of precise positioning control, it is inferior to the combination of fiducials and on-board soft X-rays, which provide true real-time imaging with less radiation exposure and much faster acquisition.

To date, most reported studies on spinal radiosurgery safety and efficacy have come from the Cyberknife [5,7,10-14] or Novalis systems [2,4,9,15,16]. Both utilize real-time image guidance based on digitally reconstructed radiographs and a real-time image intensifier. The Synergy-S IGRT system relies on cone-beam CT only. CBCT is done *before* the radiation is delivered but cannot be used during the actual treatment. Gerszten et al. [17,18] described the treatment flow of spinal radiosurgery with the Synergy-S, scanning the patient with the CBCT for

CBCT = cone beam computed tomography
IGRT = real-time image guidance

position verification just before treatment initiation, after one-third of the treatment, and after two-thirds of the treatment, with a mean position deviation of 1.1 mm and 1.0 mm respectively. We have encountered position deviations greater than 2 mm with the Novalis TX for spinal radiosurgery, which were corrected using the Exact Trac system and the robotic coach. Strauss et al. do not report position verification or correction after initial positioning.

The delivery of high levels of radiation energy to tumors compressing the spinal cord yields good results in terms of rapid pain control and local tumor control rate. Obviously, these doses should be delivered accurately to avoid damage to the spinal cord. Sahgal and co-authors [19,20] demonstrated a rise in radiation myelopathy rates in patients exposed to a high point dose within the spinal cord. Yet, only nine patients were diagnosed with radiation myelopathy in this multicenter study that included spinal radiosurgery centers with a large volume of patients.

Strauss and team report no radiation toxicity or radiation myelopathy during the follow-up period. Since the rate of radiation myelopathy following spinal radiotherapy is very low and the study cohort very limited with a short follow-up, it is difficult to compare the safety properties of the current treatment. Potentially however, the lack of real-time continuous positioning verification in the Synergy-S could jeopardize patient safety.

Radiosurgery has revolutionized the management of intracranial pathology in the last 25 years. The newly acquired capability of radiosurgery to the spine promises to increase therapeutic yield while drastically reducing the cost in terms of both patient handicap and hospitalization time.

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Capsule

Cerebral organoids model human brain development and microcephaly

The complexity of the human brain has made it difficult to study many brain disorders in model organisms, highlighting the need for an in vitro model of human brain development. Lancaster et al. have developed a human pluripotent stem cell-derived three-dimensional organoid culture system, termed cerebral organoids, that develops various discrete, although interdependent, brain regions. These include a cerebral cortex containing progenitor populations that organize and produce mature cortical neuron subtypes. Furthermore, cerebral organoids are shown to recapitulate features of human cortical development, namely characteristic progenitor zone organization with abundant outer radial glial stem cells. Finally, the authors used RNA interference and patient-specific induced pluripotent stem cells to model microcephaly, a disorder that has been difficult to recapitulate in mice. They demonstrate premature neuronal differentiation in patient organoids, a defect that could help to explain the disease phenotype. Together, these data show that three-dimensional organoids can recapitulate development and disease even in this most complex human tissue.

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