Surgery in neuro-oncology with a focus on stereotactic radiosurgery

Veronica Chiang*

VERONICA CHIANG is jointly appointed as Associate Professor in Neurosurgery and Therapeutic Radiology at the Yale School of Medicine. Dr Chiang became the Medical Director of the Yale New Haven Hospital Gamma Knife Center in 2006 where currently over 300 patients are treated each year. She is predominantly interested in the management of brain metastases and now works closely with Medical Oncologists, Radiation Oncologists, Pathologists and Radiologists in the development of new treatment paradigms for patients with brain metastases as well as understanding the effects of these treatments on the normal brain.

Q You earned your medical degree at the University of Western Australia – what sparked your interest in neurosurgery and neuro-oncology?

All Australian medical students have the opportunity to do an away rotation in their final year. For personal reasons, and because I had never had the opportunity to see this subspecialty in Australia, I did a subinternship in neurosurgery in the USA. I was captivated by the unique cross between the neurosciences and the possibility of treating patients surgically. During my residency, I saw the morbidities associated with delayed recognition of brain metastases and then surgical management followed by whole-brain radiation therapy – standard of care at the time. After my residency, the use of Gamma Knife stereotactic radiosurgery, as a minimally invasive option, paired with the use of surveillance imaging provided an opportunity for neurosurgeons to prophylactically treat brain metastases before they became troublesome. As a junior attending, this common sense concept was an appealing paradigm, as well as being an opportunity to grow a career.

Q As Director of the Yale New Haven Gamma Knife Center, could you tell us a little about the research being undertaken there?

Research at the Yale Gamma Knife Center is divided mainly into three areas:

• Outcomes after radiosurgery

In the past, we have studied the efficacy of radiosurgery on local control of brain metastases and its effect on overall patient survival. We then studied the patient factors and associated treatments that affected outcome. Our research suggests that patient with certain tumor genetic mutations such as *EGFR* or *ALK* mutations in lung cancer and *NRAS* mutations in melanoma may make these tumors more susceptible to radiation. More recently we have developed a rationalized radiation dose protocol based on lesion size to standardize the dose administered across all patients in order to establish standardized outcomes. Based on this, we may then consider clinical trials to de-escalate radiation dose if patients are found to have susceptible tumor genetics thereby hopefully decreasing their toxicity risks;

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• **Exploring the rational use of radiosurgery in conjunction with systemic targeted or immunotherapies**

The use of these newer agents for systemic therapy are increasing and there is evidence that unlike chemotherapy, these agents can penetrate the CNS. What remains unknown is the efficacy of these agents in the CNS and their interaction with the effect of radiosurgery. There is preliminary evidence to suggest that these agents can be effective alone in the brain, at least transiently, and this may ultimately change the timing or indications for use of radiosurgery particularly with regard to micrometastatic disease. In addition, single lesions that may be too large for upfront radiosurgery (usually requiring that the patient undergo surgery or whole-brain therapy only) may be able to have their lesions shrunk by these systemic agents in order to bring them down to a size amenable to radiosurgery. Studies looking at the efficacy of immunotherapy and targeted therapies alone or in conjunction with radiosurgery for brain metastases are currently being conducted;

• **The diagnosis and management of radiosurgical complications**

The most common complications of radiosurgery include seizures and an entity misnamed as radiation necrosis. We are currently studying factors in cancer patients with brain metastases treated with radiosurgery that may increase their chances of seizures. In addition, we continue to study radiation necrosis. It is well known now that lesional regrowth on MRI after radiosurgery can be explained histologically by either tumor regrowth or a delayed inflammatory response of the brain to the high-dose radiation that was delivered (called radiation necrosis). The management of tumor regrowth is very different from the management of post-radiation inflammation but the ability currently to differentiate the two diagnoses using imaging alone is poor. We are currently working on trying to develop new imaging tools for this purpose. In addition, since biopsy is often required for diagnosis, the addition of a minimally invasive laser procedure to treat both tumor and radiation necrosis at the same time is being developed.

Q **Could you briefly describe the procedure for stereotactic radiosurgery?**

Stereotactic radiosurgery is the delivery of high-dose radiation in a single fraction aimed using

3D imaging at a target in the brain. There are two main types of machines capable of delivering radiosurgery – the Gamma Knife and the LINAC-based machine such as the Cyberknife, Truebeam, Synergy and Edge.

For the Gamma Knife, a single day procedure, a frame-based Cartesian coordinate targeting device needs to be attached to the skull at the start of the procedure. This frame, when placed around the head, turns every point in the brain into an X,Y,Z coordinate guaranteeing accuracy of treatment and simplifying the calculations required for radiation dosing. With the frame in place, the patient undergoes a CT and/or MRI on the day of treatment and based on the findings on this scan, an individualized radiation plan is created for each identified lesion. The patient then lies down in the machine, and the head is locked in position in order to guarantee immobility and to ensure that the machine delivers accurate treatment. When treatment is completed, the frame is removed and the patient is able to go home that day. All lesions seen on the day of treatment are treated altogether on the one day.

For LINAC radiosurgery, an initial planning CT and/or MRI of the brain is obtained and an immobilization mask is made for the patient's head. Planning usually takes at least a few days to weeks. When ready, the patient is brought back to the center, repositioned on the treatment table using the mask and the patient's treatment plan is merged with a new treatment day CT scan. Depending on the radiation plan created, typically only one lesion is treated per day and therefore if multiple lesions are present on the planning scans, often multiple sessions are required to complete treatment. It is also possible that if the lesion is larger, that multiple treatment sessions may be required to increase the safety of the dose delivered.

For both treatment types, there is typically few side effects immediately after treatment.

Q **How does this option compare with standard radiotherapy?**

Standard radiation therapy is typically used to treat larger areas of the body and its target includes both normal and abnormal cells. In order to protect the normal cells, the total dose of radiation is divided into small fractions that the normal cells can tolerate. The effectiveness of standard fractionated radiation is therefore dependent on the increased susceptibility of

cancer cells to radiation compared with normal cells. It is the reason why whole-brain radiation therapy is associated with hair loss, scalp irritation and long-term potential neurocognitive side effects.

Standard whole-brain radiation therapy is therefore administered typically over a 10–15-day period. An immobilization mask is made at start of treatment, a radiation plan can usually be generated within 24 h and then the patient comes in every day for a few minutes, is placed on the treatment table in the mask and a small part of the radiation is delivered each time.

Q Have you seen improved outcomes using stereotactic radiosurgery compared with more traditional therapies?

Whole-brain radiotherapy is typically only prescribed once in a lifetime due to the fact that the radiation dose being administered is what is thought to be the maximum that the brain cells can tolerate. Because of the lower dose of radiation being delivered with WBRT compared with SRS, the local lesional control rate at 1 year is significantly better with SRS than with WBRT. Patients typically also tolerate SRS better due to the lower side effect profile. Lastly, in theory, due to the shortened treatment time required for SRS, systemic therapies often only need to be stopped for a maximum of a few days for SRS compared with 3–4 weeks for WBRT. Whether this translates into better overall outcome however is not known at this time. Also not known is whether first line radiosurgery followed by salvage SRS and/or WBRT results in overall better neurocognitive outcome than first line WBRT salvaged by SRS.

Certainly it is known that survival is no different between first line WBRT versus SRS.

Q Where do you see the field of surgery in neuro-oncology in 5–10 years?

The next 5–10 years will likely be busy for neurosurgery in neuro-oncology. Not only are cancer patients living longer and therefore more likely to develop delayed brain metastases but due to the need to limit healthcare costs, the use of screening MRIs are likely to be limited. Already in my practice I am seeing these patients, in remission from their primary disease, present with large

symptomatic brain metastases often for which surgical resection is the most effective treatment. I also believe that in the next 5–10 years, surgery will be essential in the understanding of the effect of the varying newer therapies on the brain by providing the histological confirmation required to understand the diagnostic changes seen after treatment. Tissue obtained after treatment may also provide insight into the normal and adverse CNS responses to injury.

Q Finally, are there any emerging or cutting-edge therapies you believe will be significant in the future?

I believe that nanoparticles will play an important role in the future of treatment of brain metastases. The current limitation of systemic therapy is the ability to penetrate into the brain in sufficient dose. The limitations of radiation and surgery are that focal treatments do not address the concept of micrometastatic disease without significant morbidity. What is needed are particles that will be able to diffuse through the brain due to their small size, carrying effective therapies to their target cancer cells wherever they are.

Alternatively, CNS-penetrating viruses modified to target specific surface markers unique to cancer cells are being developed. Viruses are uniquely suited to fighting cancer because they can change their DNA expression just like cancer cells can. The need for these viruses to be benign and self-limiting in the CNS environment however needs to be well tested to avoid virus-induced complications.

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