Brain metastases: The magnitude of the problem and the struggle to improve outcomes

By May Tsao, MD, BSc, FRCPC

Brain metastases represent a significant health care problem. It is estimated that 10 to 30% of patients with cancer will develop metastatic cancer to the brain during the course of their illness. The burden of brain metastases impacts on quality and length of survival. Brain metastases may spread from any primary site. The most common primary site is lung followed by breast and gastrointestinal cancer. Eighty-five per cent of brain metastases are found in the cerebral hemispheres, 10 to 15% in the cerebellum and one to three per cent in the brainstem. At the TSRCC, brain metastases account for 20% of all referrals sent to the palliative clinic (the RRRP). (see Figure One)

The mainstay of treatment for brain metastases has been corticosteroids and whole brain radiotherapy. Although patients with good performance status and minimal or slowly progressive extracranial cancer may do better than average, the majority of patients seen in our palliative clinic fit into poorer prognostic categories. This issue of Hot Spot provides an insert which summarizes management of patients with brain metastases.

There have been numerous phase III randomized controlled trials which have examined varying altered whole brain radiotherapy dose fractionation...
Dignity-conserving care in palliative care

By Mary L.S. Vachon, RN, PhD

Dr. Harvey Chochinov is Professor of Psychiatry at the University of Manitoba and the recipient of the Queen’s Jubilee Medal for work in palliative care. He recently published *Dignity-conserving care – A new model for palliative care: Helping the patient feel valued.*

“When the preservation of dignity becomes the clear goal of palliation, care options expand well beyond the symptom management paradigm and encompass the physical, psychological, social, spiritual and existential aspects of the patient’s terminal experience. Systematically broaching these issues within discussions of end-of-life care could allow patients to make more informed choices, achieve better palliation of symptoms, and have more opportunity to work on issues of ‘life closure’.”

Fifty patients with advanced terminal cancer identified three major areas of influence on individual perceptions of dignity: *illness-related concerns,* i.e., those things that directly result from the illness – including *symptom distress* (physical, psychological, medical uncertainty, death anxiety) and *level of independence* (including cognitive acuity and functional capacity); the *dignity-conserving repertoire,* i.e., those influences related to the patient’s psychological and spiritual resources or makeup – including *dignity-conserving perspectives* (continuity of self, role preservation, maintenance of pride, hopefulness, autonomy/control, generativity/legacy, acceptance, resilience/fighting spirit) and *dignity-conserving practices,* (living in the moment, maintaining normalcy, and finding spiritual comfort); and the *social dignity inventory,* i.e., those environmental influences that can affect dignity (privacy boundaries, social support, care tenor, burden to others and aftermath concerns).

Mrs. B. was a 52-year-old, married mother of two children, and a fashion consultant. She was diagnosed with lymphoma, but continued to work throughout her treatment and relapses, choosing to keep her disease a secret from colleagues so as not to alter her relationships with them. At the initial interview for psychosocial assistance in dealing with her illness, she said that she felt she hadn’t finished what she was meant to do. She still had things that she wanted to accomplish, one of which was to find peace of mind. Her job helped her to get through the day, but she had to deal with the cancer at night.

Prior to her illness, she was the caretaker for everyone, including a daughter who had died in early childhood. She had considered herself to be independent and self-sufficient, but felt that, with her cancer, she needed love and care and was beginning to allow herself to be taken care of. She told her husband that it was his job to deal with the doctors, and she didn’t want any information that she didn’t ask to receive. Her daughter explored complementary therapies and Mrs. B. utilized several of these.

Initially, she said that she was spiritual, but didn’t believe in God. Over time, however, she began to use a prayer that “became like a mantra, I’m not a religious person, I’m an agnostic, but I’m praying. It gives me comfort and helps to overcome anxiety”.

Through meditation and dreams, Mrs. B. began to come in touch with a light. In one dream, she said, “I felt so lost - then suddenly I saw the light”. She saw cancer as a transforming, healing experience and found herself consciously choosing to transform challenging experiences into positive ones. She became a happier person and experienced a new level of wisdom and compassion she had never previously known. She worked until a couple of weeks before a final hospitalization. A few days before this hospitalization, Mrs. B. said, “I’ve never been one to pray, now it’s come into my life. I am no longer worried about death. When I pray, I truly give my life to the Universe. I don’t hold back. I am more comfortable.” She wanted to live, but had begun to experience calmness about the possibility of dying. Nevertheless, she wished to continue chemotherapy with the possibility of one final remission to see her daughter marry. During her last few days, Mrs. B. was able to speak with her daughter about her hopes for her daughter’s future, and the family was able to share important memories and to explore the legacy that she would leave. Working collaboratively, the family and staff were able to maintain her dignity until the end of her life. Together, they cared for Mrs. B., nurturing her and maintaining hope. Four days before her death, Mrs. B. spoke of being emotionally calm and at peace. She spoke of seeing lights and stars that she felt were there to guide her on the next phase of her journey.

**Reference**


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*BRAIN METASTASES, FROM PAGE 1...*

...schedules, the use of radiosensitizers with whole brain radiotherapy, and the role of surgery and whole brain radiotherapy for patients with a single brain metastasis.

Key questions remain unanswered. Particularly for poor prognostic patients, the additional benefit of whole brain radiotherapy in addition to dexamethasone is unknown as compared to best supportive care alone. Quality of life outcomes with treatment in this group of patients remain difficult to measure. A prospective study of quality of life outcomes with proxy-ranked correlations in patients with brain metastases undergoing a course of whole brain radiotherapy is currently active at TSRCC. In addition, patient and physician expectations of brain metastases treatment have not been well-elucidated. A survey of physician expectation of whole brain radiotherapy for patients with a diagnosis of brain metastases who are seen in the RRRP is currently being conducted by Dr. Toni Barnes. Other key questions which remain unknown include determining the optimal use and timing of radiosurgery and the optimal use of systemic agents, including novel agents, in the management of patients with brain metastases. Furthermore, the possible sequelae of whole brain radiotherapy, such as fatigue and neurocognitive effects, may be attenuated with experimental agents and such issues are being investigated by other research groups.
When capacity fluctuates, what happens to consent?

By Karen Faith, MEd, MSc, RSW

Jonathan is a 72-year-old man with metastatic prostate cancer. He receives chemotherapy every three weeks. He had been doing well prior to his diagnosis, despite early signs of dementia. Normally good-natured and cooperative during treatment sessions, Jonathan began to resist his IV infusions and attempted on several occasions to leave the clinic. When asked if his wishes for treatment had changed, Jonathan expressed good will towards continued chemotherapy and his wife urged the oncologist to continue. The next day in clinic, Jonathan removed his IV and left the treatment centre appearing disoriented and confused.

This situation is sadly not uncommon in treating patients with dementia and chronic or life-threatening illnesses. Should behaviours or wishes from an incapable patient overrule previous capable consent? When patients show signs of cognitive impairment, health care providers assess capacity and consent while maintaining communication with a patient’s close friend or relative who participates in his/her care. Such measures help to determine if the treatment provided meets ethical obligations regarding capacity and consent. Consent requires that the patient is capable to understand treatment options and consequences, is given adequate information, and is free from undue pressure or coercion. But consent must also be seen as a process, evolving over time and thus subject to change.

In treating patients with dementia, care providers may find that capacity fluctuates and will at times bring consent for treatment into question. Careful assessment of capacity with patients like Jonathan is important in determining how treatment decisions ought to be made. In assessing capacity, the individual’s ability to understand the medical problem, proposed treatment, and available alternatives is evaluated (Etchells, Sharpe, Elliott & Singer, 1999). In determining capacity, neither cognitive impairment nor mental disorder should prevent the individual from understanding the proposed treatment, or in making an informed choice (Van Staden & Krüger, 2003). It is important, in treating patients like Jonathan, that health providers know the previously-stated capable wishes of the patient and have sustained interaction with him over time. Continued communication with family or friends who support and participate in the patient’s care is also essential. Although decisional authority regarding treatment should always rest on the capable individual, declining capacity and illness often require that substitute decisions be made on the patient’s behalf. Therefore, developing a caring circle of relationships that interconnect with the patient is essential to supporting good decision-making when capacity is compromised by cognitive impairment. Care providers and substitute decision-makers, whose obligation it is to pursue what is good and just for incapable patients like Jonathan, must consider the patient’s previously-stated capable wishes as important guides in any future treatment decisions.

References


Historical Vignette:

The Montréal Neurological Institute

By Charles Hayter, MA, MD, FRCPC

The insert in this issue of Hot Spot focuses on the management of brain metastases. Canada has played a leading role in research and treatment of brain tumours, largely due to activities at The Montréal Neurological Institute (MNI) which was created in 1934 thanks to several large donations, including a major gift of $1,232,652 from the Rockefeller Foundation. Neurosurgeon Dr. Wilder Penfield (1891-1976) was the moving spirit of the institute and pioneered many new areas of neurological research.

Penfield was a pioneer in seeking to understand the brain and nervous system and in helping patients with intractable neurological disorders. He investigated such conditions as epilepsy, brain edema and neuromuscular disease. Through the 1930s and 1940s, researchers at the institute made a name for themselves and the hospital with groundbreaking research in neurosurgery, electroencephalography and neurophysiology. Through its affiliation with the McGill University Medical School, the MNI excelled in the education of doctors and nurses specializing in neurology.

Though affiliated with the Royal Victoria Hospital, the Montréal Neurological Institute was incorporated as a separate institution in 1963. In the following year, Dr. Jean L. Bouchard (1910-1979) became the professor and chair of the newly-created department of radiation therapy at McGill University. Bouchard received his MD from Laval in 1934 and undertook postgraduate training in Europe. His major interest was in radiotherapy of tumours of the central nervous system, and his textbook Radiation Therapy in Tumors and Diseases of the Nervous System (1968) remains a classic today. Some of the other accomplishments of the MNI included the first positron images of a brain tumour (1975), Canada’s first CT scanner (1973) and North America’s first mini cyclotron (1981).
What is the optimal dose of steroids in patients with brain metastases receiving radiation?

Brain metastases (BM) develop in approximately 10% to 30% of adults with cancer. They produce major morbidity, a decrease in functioning, deterioration of performance status and quality of life (QOL), and a greatly shortened life expectancy.

The treatment consists of surgery or stereotactic radiation therapy (RT) (for solitary BM), palliative whole brain radiation therapy (WBRT), and steroids. Steroids in patients with neurological symptoms usually lead to quick responses, with improvement within 24 to 48 hours. However, long-term steroid use, especially in high doses, could lead to a number of side effects, adversely affecting patients’ QOL. WBRT is frequently employed, not to improve the patients’ neurological condition, but to allow steroid tapering and, hopefully, maintenance of neurological well-being without the steroid side effects.

In our radiation oncology practice (as documented in a retrospective review of 88 patients treated with WBRT by the Palliative Radiation Oncology Program [PROP] at the Princess Margaret Hospital over a six-month period [November 2002 to April 2003]), half of the patients are on dexamethasone (DXM) 4 mg PO QID prior to and during RT. The median duration of DXM therapy is two months; tapering schedules are recommended, but vary greatly, with no standardization.

The literature documents that lower doses of DXM (e.g., 4 or 8 mg) may be equally as effective as higher doses (e.g., 16 mg) Vecht et al., 1994), and that steroid side effects are common, and related to dose and length of treatment (Hempen et al., 2002). Some of the steroid side effects, such as insomnia, may be avoided by administration of DXM in the morning.

Given this information, we have embarked on a phase II clinical trial to determine whether DXM 8 mg qAM for symptomatic patients (or DXM 4 mg qAM for asymptomatic patients) prior to and during WBRT, with fixed taper following RT (see Figure One) is effective in maintaining symptom control in patients with brain metastases, without neurological deterioration. The primary endpoint of the study will be the percentage of patients who need a higher steroid dose, or need to get back on steroids at any time before, during, or after RT. Secondary endpoints of interest are: response to steroids, incidence of steroid side effects (comparison with literature and our retrospective review), and predictors of deviation from steroid protocol if sufficient number of patients deviate. This study plans to accrue at least 50 patients over one year. The patients will be assessed at their initial consultation visit, when the new steroid dose will be recommended (with careful telephone assessment to ensure no deterioration has occurred), on day three (just prior to RT), last day of RT, at two weeks, four weeks and two months post-RT for symptomatic patients (one week, three weeks and two months for asymptomatic patients) – by telephone interviews and clinic assessment. The successful completion of this study will provide an answer to whether lower doses of DXM could be as effective as 16 mg/day in controlling neurological symptoms and avoiding severe steroid side effects in patients diagnosed with BM.

For comments about the study, you can contact us as follows: alina.sturdza@rmp.uhn.on.ca andrea.bezjak@rmp.uhn.on.ca

References
Drs. Alina Sturdza, PGY 2, Radiation Oncology, University of Toronto, and Andrea Bezjak, MD, MSc, FRCP, Department of Radiation Oncology, Princess Margaret Hospital, University of Toronto.
Palliation in patients with metastatic cancer to the brain

Relevant issues in assessing patients with brain metastases

1. Patient’s symptoms (neurologic, systemic, treatment-related)
2. Patient’s performance status
3. Extracranial disease activity (stable, progressive, unknown)
4. Previous and current therapies
5. Co-morbidities

Diagnostic work-up

1. Pathologic confirmation of cancer [from primary or metastatic site(s)]
2. Radiographic imaging of brain:
   - CT scan with contrast or MRI with gadolinium
   - Multiple brain metastases
   - Single brain metastasis
3. Rule out non-malignant brain lesion(s) [eg. abscess, stroke]
4. Rule out other malignant brain lesion(s) [eg. malignant glioma]

Prognosis

RTOG RPA class:

- Class I – age < 60 years, Karnofsky Performance Status (KPS) $\geq$ 70, controlled primary tumour with brain as the only site of metastasis (median survival 7.1 months)
- Class II – all others (median survival 4.2 months)
- Class III – KPS < 70 (median survival 2.3 months)
Management of brain metastases

Multiple brain metastases

**Aims of treatment**
To improve neurologic function, delay intracranial disease progression.

**Medical therapy**
Dexamethasone is used to reduce brain edema and improve neurologic symptoms. The dose of dexamethasone depends on patient’s symptoms and degree of intracranial edema. Typically, patients are weaned off dexamethasone after completion of whole brain radiotherapy. Recurrence or progression of neurologic symptoms due to recurrent intracranial edema may be alleviated with an increase in dexamethasone dose.

**Radiation therapy**
Many patients with multiple brain metastases will receive five or 10 fractions of whole brain radiotherapy.

**Possible side effects of whole brain radiotherapy**
Hair loss; irritation of scalp; fatigue; risk of increased intracranial pressure with radiation therapy resulting in increased neurologic symptoms such as headaches, nausea/vomiting requiring increased dexamethasone dose; neurocognitive change.

**Radiosurgery**
Patients may be considered for radiosurgery based on the following characteristics:
1. Good performance status
2. Stable or minimal extracranial disease
3. Small number of brain metastases (optimal number not known; typically one to three brain metastases)
4. Small size of brain metastases (typically less than 3 or 4 cm)

For selected patients, radiosurgery may be considered: at the time of relapse after whole brain radiotherapy; as boost therapy with whole brain radiotherapy, or (less commonly) as primary treatment, with whole brain radiotherapy held in reserve. The intent of treatment is to improve intracranial control with the possible benefit of decreased steroid requirements. Survival may not be improved. The optimal sequence of radiosurgery in relation to whole brain radiotherapy in selected patients is not known.

**Repeat whole brain radiotherapy**
Patients who have had previous brain radiotherapy may be considered for repeat whole brain radiotherapy. These patients tend to have good performance status, stable or slowly progressive extracranial disease burden, and have demonstrated a durable response to previous whole brain radiotherapy.

**Supportive care alone (e.g., dexamethasone without radiotherapy)**
May be considered in patients with poor performance status and/or widely disseminated cancer.

**Multiple brain metastases and surgery**
Since treatment in this disease is considered palliative, local invasive treatment should be individualized. Selected patients with multiple brain metastases and severe intracranial hypertension despite high dose dexamethasone may be considered for emergency decompression.

Single brain metastasis

**Surgical resection for a single brain metastasis should be considered in patients with the following characteristics:**
1. Patients with good performance status
2. Controlled or minimal extracranial disease
3. Surgically accessible single brain metastasis amenable to complete excision

The aim of surgery (in selected patients) is to improve survival as compared to the use of whole brain radiotherapy alone.

Post-operative whole brain radiotherapy is given to improve brain control.

**When to refer patients with a diagnosis of brain metastases**
1. When brain metastases are diagnosed, for consideration of further management.
2. At the time of intracranial relapse after previous treatment for brain metastases, for consideration of further management.
3. For extracranial cancer symptoms in which palliative radiotherapy may help alleviate symptoms such as bone pain, spinal cord compression, superior vena cava obstruction, hemoptysis, airway obstruction, nerve compression, etc.
4. For assistance with managing possible radiation side effects.