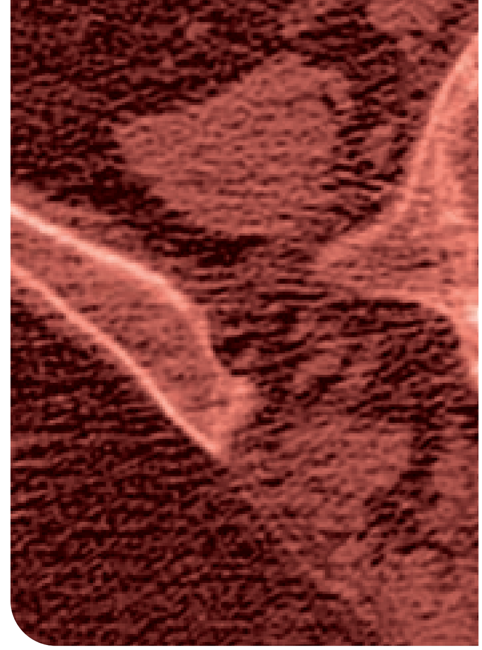

PHOTODYNAMIC THERAPY FOR BONE METASTASES

An avenue for earlier identification and treatment

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Top-line summary

With improvements in adjuvant therapies and decline in age-standardized cancer mortality, bony metastases are increasingly prevalent in the cancer population. A variety of strategies are being developed to assist in palliative care of patients with symptomatic cancer spread to bone. Researchers at the Ontario Cancer Institute at Princess Margaret Hospital and the Sunnybrook and Women's College Health Sciences Centre at Toronto Sunnybrook Regional Cancer Centre are conducting transdisciplinary research into novel applications of minimally invasive surgical (MIS) strategies to treat patients with bony metastases. One such strategy involves the use of photodynamic therapy to treat structural bone lesions in the vertebral column using MIS approaches adapted from surgical techniques used in vertebroplasty. Here, *Oncology Exchange* reviews the background of photodynamic therapy, focusing on its use in musculoskeletal applications in bone, and summarizes progress in translating preclinical work towards the goal of improving patient palliation with respect to pain, functional status and quality of life.

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The treatment of bony metastases is a multidisciplinary endeavor. In settings such as The Bone Metastases Clinic at Toronto Sunnybrook Regional Cancer Centre, integration of the efforts of palliative care specialists, radiation oncologists and orthopedic surgeons has furnished a patient-focused environment to guide decisions about applying currently available therapies to treat symptomatic bone metastases.[1,2]

Further input by medical oncologists and other allied health professionals (e.g. from nursing, occupational therapy, psychology nutrition, social work) gauges patients' functional limitations, home environment and overall health condition. This enables the team to balance the available options and choose those that will have the most impact on pain relief and quality of life, at acceptable levels of risk.

EXISTING TREATMENTS

Analgesic pain titration is critically important and often the first step. For treating symptomatic bony lesions with low risk for pathologic fracture and related complications, the use of splints, orthoses, assistive devices for walking and modifications to the home environment are important and very helpful.

Destructive bony lesions of the vertebral column and weight-bearing long bones often pose significant risk of pathologic fracture. Spine fractures entail issues of pain, instability, deformity and spinal cord compression with resultant paralysis. Pathologic fractures of weight-bearing long bones pose significant morbidity because of their impact on ambulatory capacity. Local therapies for vertebral metastases include external beam radiation therapy and a variety of surgical options — often directed towards skeletal stability and pain relief — ranging from newer minimally

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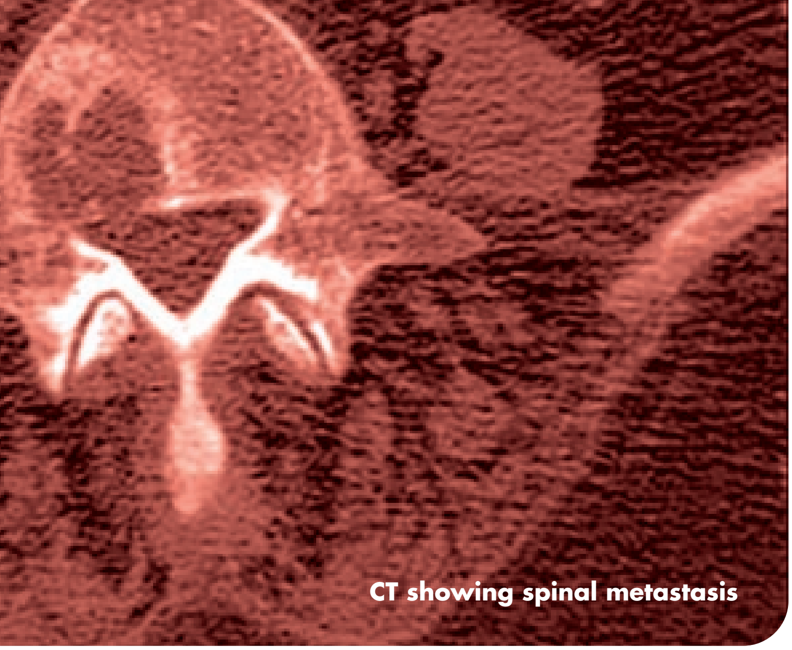

CT showing spinal metastasis

invasive surgical (MIS) strategies to more conventional decompressive and stabilization surgery.

Currently available local treatments have limitations. Certain neoplasms are relatively radioresistant. Further, complications such as radiation enteritis and myelopathy limit the amount of radiation that can be locally directed. Rates of major wound complications are higher in people who have had prior local radiation therapy: in spinal surgery they are 3- to 4-fold greater.[3,4] Minimally invasive surgical approaches such as vertebroplasty can provide significant pain relief in acute pathologic vertebral body fracture. While helping improve stability, however, such an approach does not address any biologic aspects of tumour growth — it adds nothing to tip the balance between tumour growth and host bony repair in favour of repair and skeletal stability. An important general orthopedic principle is that any surgical fixation device used for fracture will eventually fail from repetitive cyclic loading unless bony healing occurs.

Toward improved treatments

With growing numbers of patients affected by bony metastases, research aiming to develop efficacious local therapies with minimal side effects and low associated patient morbidity is needed. New therapies should be directed both at ablating the local tumour and enhancing bony stability, likely favouring a multimodality therapeutic approach. The most promising strategy is early identification of clinically significant, precritical bone metastatic lesions followed by early institution of treatment.

PHOTODYNAMIC THERAPY BASICS

Photodynamic therapy (PDT) is a promising cancer treatment that induces localized tumour destruction by the photochemical generation of cytotoxic singlet oxygen.[5] PDT employs wavelength-specific light combined with a photosensitizing agent. Photosensitizing agents are delivered to the tissues orally, intravenously or by slow-release injection (depot). The drug accumulates in neoplastic cells and is activated by light at low power without causing thermal effects. Subsequent generation of toxic oxygen-free radicals leads to oxidative stress, damaging plasma and intracellular membranes and eliciting direct local tumour cell death. The effective treatment size is governed by characteristics of the light (energy) delivered to the tissue, level of tissue oxygenation and the tissue's optical properties. Longer light typically penetrates deeper into tissues than does light of shorter wavelength. Two main parameters govern selective targeting of tumour while preserving normal adjacent tissue:

- certain photosensitizers preferentially accumulate within tumour cells as compared to normal, nonmalignant cells[6,7]
- photodynamic reactions occur only in tissues that contain adequate photosensitizer drug and that are exposed to light of the correct wavelength

In vitro studies in human breast cancer cell lines have provided evidence supporting PDT efficacy in eliciting tumour cell death.[8,9] Clinically, PDT has achieved encouraging early results in treating breast cancer recurrences and other primary malignancies.[10,11,12]

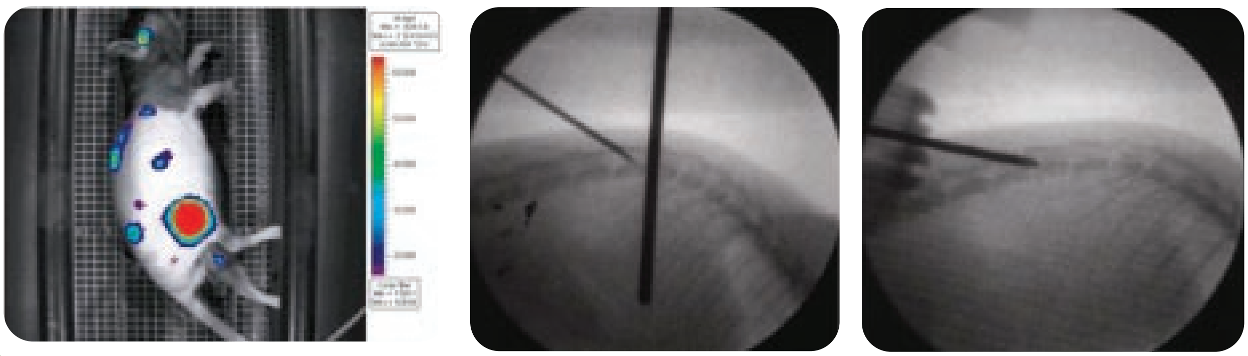
ACCESSING BONE BY MIS

Minimally invasive surgical strategies are at the forefront of current research and clinical use in treating a variety of medical conditions, including orthopedic disorders, and are associated with reduced surgical morbidity. Endoscopic-guided spinal surgery is used to treat adult deformity and degenerative spinal conditions, and recent reports describe MIS in routine surgical lumbar decompression and instrumentation (rod insertion).[13,14,15] Vertebroplasty, used clinically to treat painful osteoporotic spinal compression fractures and spinal metastases, is gaining increasing acceptance and use.[16,17] This minimally invasive local technique employs percutaneous fluoroscopic placement of a spinal needle or trocar into the vertebral body to allow direct injection of polymethylmethacrylate (PMMA, i.e. bone cement) to mechanically stabilize the vertebra. It can afford significant pain relief in patients with pathologic and osteoporotic vertebral fractures,[18] and has become an important adjunct in the treatment of painful vertebral metastases. More recently, a few centres have used a similar technique — cementoplasty — to treat periacetabular bony metastases.[19,20,21] Adapting MIS techniques to access bone allows placement of optical fibres adjacent to osteolytic lesions. Preclinical research is underway on the feasibility and potential of photodynamic therapy to treat bone metastases, as well as on other local adjuvant treatments including laser and radioablation.[22,23]

PDT VIA VERTEBROPLASTY

Knowledge regarding the use of PDT to treat structural bone lesions is currently limited.[24,25] A key challenge is delivering light to the target location. To address this issue in vertebral metastases, our research group has adapted the MIS technique of vertebroplasty to apply PDT: percutaneous fluoroscopy guides placement of small-diameter optical fibres adjacent to affected vertebrae. A variety of murine and rodent models of bone metastases are available to evaluate novel local therapies. Initial feasibility and efficacy studies on the use of PDT to treat vertebral metastases were supported by a Canadian Breast Cancer Research Alliance (formerly Canadian Breast Cancer Research Initiative) IDEA grant, which is a type of grant supporting small-scale pilot studies or investigations of concepts. In vivo bioluminescent reporter imaging (a molecular imaging technique that labels tumour cells with an optical

FIGURE 1. Bioluminescence imaging and a custom stereotactic frame being used to localize a targeted vertebra for subsequent fluoroscopically guided vertebral PDT.



marker, then noninvasively monitors cell proliferation using photon detection) in an animal model using human breast carcinoma cells demonstrated the efficacy of a single percutaneous treatment of PDT to elicit significant reduction in local tumour growth in vertebral metastasis.[26]

Remaining issues

While initial feasibility studies have solved technical concerns regarding implantation of optical fibres to target specific vertebrae, critical issues remain, chiefly involving light and drug dosimetry to closely define the therapeutic window of safety and efficacy. Ongoing funding by the Canadian Breast Cancer Foundation's Ontario Chapter has been integral to this work.

The choice of ideal initial photosensitizing drugs requires further study. Several agents with minimal systemic side effect profiles are available. BPD-MA (benzoporphyrin-derivative monoacid A) is a photosensitizer that can be used to target either the neovasculature (which provides essential nutrients to the cells) or the cells directly, depending on the drug–light interval. Its absorption spectrum is stimulated by a longer wavelength of light, possibly desirable to achieve greater depth penetration. BPD-MA used clinically for ocular macular degeneration has demonstrated minimal systemic side effects.[27,28] ALA (5-aminolevulinic acid, a prodrug that leads to endogenous synthesis of the photosensitizer protoporphyrin IX, [PpIX]) has the potential for high tumour-to-neural tissue selectivity — an important consideration for applications in areas near the spinal cord.

Understanding of the optical properties of light transmission and attenuation in human bone is limited, so requires ongoing in vivo study.[29,30] Preliminary safety of PDT in non-tumorous porcine lumbar spine has been demonstrated and planning is underway for multicentre preclinical studies to evaluate PDT efficacy in structurally larger bone lesions.[31]

PROMISING OUTLOOK

PDT poses an interesting potential adjunct for local treatment of bone metastases. There are no known contraindications to the use of PDT pre- or post-radiation or surgery. Unlike radiotherapy — where there are limits to the amount of spinal irradiation that can be administered, and where wound complications following subsequent conventional spinal surgery are a significant problem — no limits are anticipated on the number of PDT treatments that can be administered, once the correct light and drug dosimetry is determined. Further, PDT can potentially be applied to radioresistant tumours. Given its potential biologic benefits on tumour growth kinetics, PDT could be used as a neo-adjuvant treatment just prior to PMMA injections given in vertebroplasty to mechanically stabilize metastatically involved vertebrae. The selectivity of PDT in being able to locally target cancer cells is particularly appealing in the spine, where conservation of healthy neural tissue of the spinal cord is critical.

More study is needed on the potential need for fractionated treatments. A practical solution may be percutaneous implantation of an optical fibre that can be left in situ, as in brachytherapy. Such a transdisciplinary approach encompassing tumour biology and minimally invasive surgical strategies will likely provide important future adjuncts to patient palliation. Œ

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