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Clinical Trials: Targeted Therapy

Clinical Cancer Research

Photodynamic Therapy for the Treatment of Vertebral Metastases: A Phase I Clinical Trial

Carl Fisher[1], Zakariya Ali[2], Jay Detsky[3], Arjun Sahgal[3], Elizabeth David[4], Monica Kunz[5], Margarete Akens[6,7,8], Edward Chow[3], Cari Whyne[5], Shane Burch[9], Brian C. Wilson[1,7], and Albert Yee[5]

Abstract

Purpose: Vertebroplasty (VP) and balloon kyphoplasty (KP) are minimally invasive stabilization procedures for pathologic vertebral compression fractures (VCF). Concurrent administration of photodynamic therapy (PDT) as a tumor-ablative modality has yet to be studied in humans as a potential complement to improved mechanical stability that is afforded by vertebral cement augmentation (VCA).

Patients and Methods: This first-in-human trial used a single 6 mg/m^2 dose of the clinical photosensitizer Visudyne with escalating laser light doses. Following a cohort of light-only controls ($n = 6$), the drug and light treatment groups ($n = 6$ each) were 50, 100, 150, and 200 J/cm. VCA was performed within 15 minutes following PDT. Patients were clinically reviewed at 1 and 6 weeks. The primary outcome measure was safety from a neurologic perspective.

Results: Thirty patients comprising a variety of primary tumors were treated with PDT and either KP or VP. Vertebral PDT was technically feasible and delivered in all study patients. No dose groups showed significant increases in pain as defined by the generic SF-36 as well as disease-specific EORTC-QLQ-BM22 and EORTC-QLQ-C15-PAL questionnaires. The 50 and 100 J/cm groups showed the most significant pain reduction ($P < 0.05$). Twelve (40%) patients experienced complications during the study including 3 patients with further vertebral fracture progression by 6 weeks despite VCA. No complications were directly attributed to PDT.

Conclusions: Using the parameters described, vertebral PDT as an adjunct to VCA is safe from a pharmaceutical and neurologic perspective. The results of this trial motivate scale-up study evaluating potential PDT efficacy in vertebral metastatic treatment.

Introduction

Bone is the third most common site of tumor metastases after liver and lung organs (1). Bony spread to the spine (vertebral metastases, VM) represents over half of all bone metastases. Although VM may be asymptomatic and found incidentally on radiologic imaging, skeletal-related events (SRE) such as pathologic vertebral compression fracture (VCF) and metastatic epidural spinal cord compression (MESCC) are significant causes of pain and potential limb paralysis (1). Patients are living longer with established bone metastases due to advances in systemic therapies, and, as a result, novel minimally invasive strategies achieving longer-term pain and local tumor control are in need.

Radiotherapy is a mainstay of treatment for vertebral metastases and can be delivered as conventional external-beam radiation therapy (cEBRT) or spine stereotactic body radiation therapy (SBRT; ref. 2). Although effective in tumor control, radiation treatment does not palliate pain associated with mechanical instability. Minimally invasive vertebral cement augmentation (VCA) procedures such as vertebroplasty (VP) or balloon kyphoplasty (KP) involve injecting bone cement (i.e., polymethylmethacrylate, PMMA) delivered percutaneously through bone trochar needles into diseased vertebrae under fluoroscopic guidance and/or surgical navigation. In cancer patients, VCA can treat vertebral lesions at risk for pathologic fracture or treat patients with symptomatic early fracture. It remains desirable to treat at-risk lesions prior to advanced vertebral collapse which can result in MESCC and serious neurologic complications that may require a more conventional open invasive surgical procedure.

VCA has been shown to be effective in metastatic VCF with respect to palliating mechanical pain and improving patient-reported disability scores (3, 4). Although VP or KP improves vertebral mechanical stability, they have limited biologic effects of the tumor itself which demonstrate continued growth. As a result, there has been recent interest in adjunct local treatments, administered at the same time as VCA, that can ablate the tumor and

[1]Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada. [2]Royal College of Surgeons in Ireland, Dublin, Ireland. [3]Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, Ontario, Canada. [4]Department of Medical Imaging, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada. [5]Holland Bone and Joint Program, Division of Orthopaedic Surgery, Sunnybrook Health Sciences; Orthopaedic Biomechanics Laboratory, Physical Sciences Platform, Sunnybrook Research Institute; and Department of Surgery, University of Toronto, Toronto, Ontario, Canada. [6]Techna Institute, University Health Network, Toronto, Ontario, Canada. [7]Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada. [8]Department of Surgery, University of Toronto, Toronto, Ontario, Canada. [9]Department of Orthopaedic Surgery, University of California, San Francisco, San Francisco, California.

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Corresponding Author: Albert Yee, University of Toronto, Toronto, ON M4N 3M5, Canada. Phone: 416-480-6815; Fax: 416-480-4395; E-mail: albert.yee@sunnybrook.ca

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Translational Relevance

To our knowledge, this is a first-in-human clinical trial evaluating the safety and feasibility of photodynamic therapy (PDT) in vertebral bone metastases. Novelty and translational relevance are highlighted by the application of vertebral PDT as an adjunct to vertebral cement augmentation (VCA), performed through minimally invasive vertebroplasty (VP) or kyphoplasty (KP). Coupling photoactivated tumor ablation with mechanical stabilization using percutaneous procedural techniques in a single treatment setting is clinically attractive for this patient population. Patients treated included those with symptomatic vertebral metastasis who were eligible for VCA because of an at-risk bony lesion or presenting with early pathologic fracture. Safety and feasibility were tested in clinically relevant environments that included the operating room and interventional radiology suite. Although this trial was limited to treatment at a single vertebral level, the potential to use multiple fibers for light irradiation would allow for translation to multilevel therapy.

complement the stabilizing effects of VCA. Radiofrequency ablation (5), cryoablation (6), and microwave ablation (7) are some techniques that have been explored in this context. However, these thermal techniques are limited by the proximity of lesions to the spinal canal and neurologic structures. The current clinical paradigm combines RT (including SBRT) with VCA and is effective at addressing both instability and tumor growth (8, 9). Future treatment paradigms, however, may lie in applying novel local nonionizing therapies at the time of VCA.

Photodynamic therapy (PDT) is one such potentially attractive minimally invasive adjunct technique to VCA in the metastatic spine. It uses nonthermal laser light and a photoactivated drug to produce radical oxygen species (10), leading to tumor cell destruction through several pathways (tumor cell necrosis, apoptosis or autophagy, or destruction of tumor microvasculature) depending on the photosensitizer. PDT has achieved clinical success in other tumor types, including glioblastoma (as an adjuvant or primary treatment; refs. 11–13), bladder (salvage; ref. 14), prostate (15, 16), skin (17, 18), and lung (19) cancers. These treatments have utilized different photosensitizers and photosensitizer-light dose combinations. PDT to treat bone lesions has been limited in the clinic to date, due in part to challenges in delivering light to deeper anatomic tissues such as the vertebrae (20, 21). Minimally invasive VCA procedures afford an opportunity to apply vertebral PDT immediately prior to VP or KP.

Previous preclinical rodent studies in healthy and diseased (osteolytic and mixed osteolytic/osteoblastic vertebral metastatic tumors of breast and prostate cancers; refs. 22, 23) vertebrae have established the safety and efficacy of vertebral PDT using a clinically approved photosensitizer drug Visudyne (Verteporfin for injection, Novartis Inc.). These studies demonstrated successful PDT tumor ablation when targeting single-level diseased vertebrae with no neurologic sequelae (22). Interestingly, enhanced local bone formation after treatment was also observed in treated vertebrae (24).

Motivated by these preclinical findings, the objective of the present first-in-human phase I trial was to clinically evaluate the neurologic safety, technical feasibility, and potential efficacy of Visudyne-PDT as an adjunct to VCA in patients with symptomatic vertebral metastasis (22–28). Here, we reported the findings using a single dose of Visudyne activated by locally delivered escalating light doses in metastatic vertebrae.

Patients and Methods

All studies were conducted following informed consent from each patient and in accordance with the Declaration of Helsinki. In addition, all procedures were approved by the institutional Research Ethics Board (REB, #403-2008) and complied with the regulations of Health Canada.

Patient selection and screening

This study was focused on patients presenting to our regional cancer center and hospital with symptomatic vertebral metastases deemed eligible for single-level minimally invasive VCA. Patients presenting with pain arising from thoracolumbar vertebral metastasis who were at significant risk for pathologic fracture or who had an early established pathologic fracture that did not cause spinal canal or neurologic compromise were included. The study involved individuals who had prior RT but was not limited to these patients and did not preclude RT following treatment.

Inclusion criteria comprised patients between the ages of 20 and 85 with established metastatic bony disease in the spine, who were eligible for single-level VCA, symptomatic with axial pain from vertebral metastatic involvement and at risk for pathologic fracture, or had symptomatic pathologic fracture and/or radiographic progression despite nonsurgical therapies. Patients were excluded if they had progressive neurological compromise, purely osteoblastic vertebral metastatic disease, vertebral body posterior wall cortical destruction, spinal canal compromise (i.e., epidural disease) and/or neurologic compression, anticipated life expectancy of less than 12 weeks, cognitive impairment and/or language barrier to study participation, severe hepatic impairment, active central nervous system metastases, hyperphotosensitivity conditions (including porphyria) and/or an inability to avoid direct sun exposure for 5 days after PDT, and hypersensitivity to verteporfin or any other ingredients of Visudyne. The Inclusion/Exclusion criteria are presented in table format in Supplementary Table S1.

Patients were screened after presenting with vertebral metastatic involvement. Eligible patients following recruitment had their medical and demographic data collected, and the lesion was assessed with preoperative CT and/or MRI. Where possible, existing preoperative images were used. Patients were categorized using established spinal metastases oncologic staging (Tomita Score) and the Spine Instability Neoplastic Score (SINS; refs. 29–31). Laboratory tests included routine hematologic, renal, and liver function. In addition, a preoperative physical examination was performed, including neurologic examination. Quality of life (QOL) assessments were evaluated using the visual analogue pain scale (VAS) and the generic SF-36 questionnaire. Disease-specific outcome measures utilized in this study included the EORTC-QLQ-BM22 and EORTC-QLQ-C15-PAL questionnaires.

Study design

The dose-escalation study was designed using a single drug dose and escalating laser light doses involving 30 patients. The

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Visudyne dose of 6 mg/m^2 and drug-light interval of 15 minutes were chosen based upon prior preclinical studies (27, 28), and were consistent with extensive clinical use of the drug in treating age-related macular degeneration (32, 33). The first cohort was light-only controls ($n = 6$), in which patients received 5% dextrose in water (D5W) but no Visudyne. The treatment groups ($n = 6$ each) started at a light dose of 50 J per cm of interstitial diffusing fiber (see procedural details below), followed by 100, 150, and 200 J/cm. VCA was performed within 15 minutes following PDT delivery. PDT was delivered in either the interventional radiology (IR) suite or the operating room where VCA was being performed.

Patients were seen preoperatively for a medical history and physical evaluation, and completion of study surveys. An anesthetic consult within 2 weeks of the procedural date was performed as clinically indicated. Following treatment, patients were clinically reviewed in the postprocedure recovery room, and at 1 and 6 weeks. They were observed for any neurologic symptoms or signs using postprocedure history and physical examination. Routine clinical follow-up, as per institutional protocol, typically included radiographic scans (CT and/or MRI) along with clinical follow-up every 3 months. Local vertebral tumor control was evaluated at all timepoints using radiographic and clinical assessments as per the SPINO criteria (34).

Adverse events were graded using the NIH Common Terminology Criteria for Adverse Events (CTCAE) system that grades each event according to severity from 1 to 5, with 1 being a mild event and 5 being a fatal event (35). All adverse events were also assessed for causality/relatedness to PDT and expectedness. Safety data were collected for all patients prior to dose escalation, including the 1-week assessment for all patients and the 6-week assessment for 4 of the 6 patients as per the study protocol regarding stopping rules and dose escalation. All data were reviewed by a Data Safety Meeting Board (DSMB, consisting of spinal surgical, clinical trial, and pharmacologic expertise) before escalation to the next light dose group.

Minimally invasive vertebral PDT

All procedures were performed at a single institution in either the IR or surgical operative suite as clinically indicated. Patients treated under neurolept and local anesthesia were monitored by neurologic physical examination during the procedure, and patients who required general anesthesia received intraoperative neuromonitoring [e.g., motor-evoked potentials (MEP), somatosensory-evoked potentials (SSEP), and electromyography (EMG)]. Following anesthesia, the targeted vertebra was cannulated to accommodate a 10G bone trochar access needle (Stryker or Medtronic) of 5-inch length to enable placement of the PDT fiber sheath and optical fiber. A unilateral or bilateral pedicular cannulation to the targeted vertebra was performed as directed clinically by structural considerations for subsequent VP or KP. Multiplanar fluoroscopy or 3D surgical navigation validation (Medtronic, O-Arm) was performed to confirm trochar placement. PDT optical fibers were guided into place using 13G flexi-needles (Best Medical) as fiber sheaths through the bone access trochars. The cylinder diffuser of the optical fiber tip produces an ellipsoid of light surrounding two radiomarkers at each end, producing a volume of approximately 1 to 2 cm across. Light power delivery calibration was performed prior to fiber insertion.

Following vertebral trochar placement, Visudyne was given intravenously at a dose of 6 mg/m^2 over 10 minutes. There is extensive safety data for this Visudyne dose, which is on the lower range of those used for treating age-related macular degeneration. It was administered in 5% dextrose in water through a 0.22 μm filter and protected from light. A drug-light interval of 15 minutes was utilized, based on extrapolation from prior preclinical studies, to maximize the drug concentration within the tumor while minimizing concentration in the neural tissues (29).

PDT was performed using a semiconductor diode laser light source (Opal Photoactivator, Lumenis Inc.) at a wavelength of 690 nm and a fluence rate of 150 mW/cm, which is well within the nonthermal range. Light delivery was achieved using a 10 mm long, 800 μm diameter radiomarked cylindrically diffusing fiber (Medlight SA) placed within a 13G sheath (Flexi-Needle; Best Medical), a device commonly used to deliver brachytherapy seeds. The light power was calibrated with the Flexi-Needle attached using an integrating sphere power meter. Irradiation times varied between 333 seconds (50 J/cm) and 1,333 seconds (200 J/cm), and the light was delivered continuously.

In cases where bilateral vertebral cannulation to a targeted vertebra was performed, a second detector fiber was placed down the contralateral sheath to measure light penetration through the lesion. This fiber had a spherically diffusing tip (Medlight SA) and was coupled to a dosimetry platform previously developed for PDT in prostate cancer (36). The placement of both fibers was confirmed using 3D O-arm radiographic imaging, and relative positions were calculated from converted DICOM images. An image of the operating setup and trochar placement is shown in Supplementary Fig. S1.

VCA (VP or KP) was completed immediately following PDT by injecting 1.5 to 3 cc of PMMA bone cement through bone access needle(s). Patients were advised to avoid direct sunlight for a period of 5 days following the procedure to prevent photosensitivity reactions and were advised to wear sunglasses to prevent retinal damage.

Clinical endpoints

This trial was designed to establish the technical feasibility and safety of PDT as an adjunct to VCA (Tables 1–3). If any neurologic deficit was noted following treatment, a plan was in place for immediate performance of MRI or CT imaging. Local control of tumor growth was measured using all available radiographic images obtained after procedure, either as part of the study follow-up or as was required clinically. The criteria for local control or failure were evaluated in accordance with the study of Thibault and colleagues (34), using the SPINO Criteria. Overall patient survival was determined through to November 2018.

Statistical analysis

Testing of significance differences such as age, procedure, and type of cancer between groups (Table 1) was performed with either a two-tailed Student t test using the Welch correction for unequal variance and sample size or a χ^2 test for categorical data. Differences in reported constant pain and back pain scores between groups were tested using a two-way ANOVA with Tukey correction for multiple comparisons. ANOVAs were performed after testing data for normality using the Shapiro–Wilk method. For all tests, if unequal variance was found, the Welch Test was performed. Findings were considered significant at a level of $P < 0.05$.

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Table 1. Patient demographics

Group	Patient	Age[a]	Gender[b]	Primary tumor[a]	Treatment history	Radiotherapy prior to surgery	Radiotherapy after surgery	Lesion location	Lesion type	KPS[a]
Control group	1	62	M	Lung	None	0	1	Posterior	Lytic	90
	2	41	F	Breast	Sx, chemo, RT	1	0	Anterior	Mixed	80
	3	54	F	Lung	Sx, RT	2	1	Anterior	Lytic	70
	4	36	F	Colon	Sx, chemo, RT	1	0	Anterior	Mixed	70
	5	55	F	Breast	Sx, chemo, RT, HT	0	1	Anterior	Lytic	80
	6	68	M	Prostate	Sx, RT, HT	0	1	Anterior	Mixed	70
50 J group	7	54	F	Breast	Sx, RT	2	0	Missing	Mixed	80
	9	59	F	Breast	Sx, RT, HT	2	0	Anterior	Mixed	80
	10	52	F	Lung	chemo, RT	0	2	Anterior	Lytic	80
	11	69	F	Bladder	Sx	0	0	Anterior	Lytic	80
	12	68	F	Breast	Sx, Chemo, RT, HT	2	0	Anterior, lateral	Lytic	70
100 J group	13	79	M	Prostate	Sx, RT, HT	1	0	Lateral	Lytic	80
50 J group	14	58	F	Rectal	Sx, chemo	2	0	Lateral	Lytic	8080
100 J group	16	65	F	Breast	Sx, chemo	2	0	Anterior	Mixed	90
	17	33	F	Lung	Sx, chemo, RT	1	0	Anterior	Lytic	70
	18	73	M	Kidney	Sx	2	0	Anterior	Lytic	80
	19	56	F	Breast	Sx, chemo, RT, HT	1	1	Anterior	Lytic	70
	20	61	F	Breast	Sx, chemo, RT, HT	1	2	Lateral	Lytic	80
150 J group	22	70	M	Lungs	Sx, chemo	0	2	Anterior	Lytic	80
	23	61	F	Uterus	Sx, chemo, RT	2	2	Anterior	Mixed	70
	24	73	M	Prostate	RT	2	2	Anterior	Mixed	80
	25	67	F	Endometrial	Sx, chemo, RT	0	2	Anterior	Mixed	80
	26	79	M	Kidney	Sx	0	2	Anterior	Lytic	70
	27	65	F	Breast	Sx chemo, RT, HT	3	0	Anterior	Lytic	80
200 J group	28	64	F	Breast	Sx, chemo, RT, HT	0	2	Anterior, lateral	Mixed	80
	30	73	M	Lungs	Sx, RT, HT	2	2	Anterior	Lytic	80
	31	55	M	Kidney	Sx	2	0	Anterior	Lytic	90
	32	53	M	Rectal	Sx, chemo, RT	2	0	Anterior	Mixed	90
	33	75	F	Lung	chemo, RT, TT	2	0	Anterior	Mixed	90
	34	47	F	Breast	Sx, chemo, RT	2	0	Anterior	Mixed	90

NOTE: Radiation type scoring: 0, none, 1, conventional, 2, SBRT, 3, both; Lytic, osteolytic; mixed, mixed osteolytic/osteoblastic; KPS, Karnofsky's performance status; Sx, surgery.

[a]No significant differences were found between age, gender, primary tumor, and KPS between groups.

[b]Female participants in the trial were significantly younger than male participants (mean age of 57 vs. 70 years, $P < 0.05$); however, this did not bias any group.

Results

Thirty-four patients were deemed eligible for the trial, 4 of whom did not participate because of declining enrollment or becoming ineligible prior to vertebral PDT treatment.

The PDT procedure added up to 45 minutes to the VCA procedure, which depended in part on the light energy dose used, the delivery of which required between 5 and 22 minutes. Technical setup and efficiency for PDT delivery improved over the course of the trial. The VP/KP procedure itself ranged from 1.5 to 2 hours and was successfully performed after PDT in all patients without technical or procedural challenges. Visudyne and light were successfully delivered to all experimental patients. Procedures took place in the operating room (OR) with patient under general anesthesia ($n = 14$) or in the IR suite for patients under local/neurolept anesthesia ($n = 16$). There were no technical differences in delivery of PDT in either setting. In those patients under neurolept anesthesia, there were no significant increases in reported pain during the PDT delivery phase of the procedure.

Baseline patient characteristics are shown in Table 1, with any significant differences between groups reported. The primary tumor type varied in each of the light dose-escalation groups, the most common being breast (37%), lung (23%), prostate (10%), and kidney (10%). Other primary tumors included colon, bladder, uterine, and endometrial. The average age of the enrolled patients was 61 years, with a female-to-male ratio of 2:1. Of the 30 patients who underwent the trial, 17 received VP and 13 received KP. The majority of the VP cases were treated in the IR suite, whereas most KP cases were conducted in the OR.

All patients had interventions prior to study enrollment, including nonspinal surgery, chemotherapy, and/or RT (Table 1). Two thirds of the patients had RT prior to PDT (5 with cEBRT alone, 15 with SBRT alone, and 1 with one course of cEBRT as well as one course of SBRT who was sent for salvage KP for fracture). Conventional EBRT was prescribed to 8 Gy in 1 fraction ($n = 1$), 20 Gy in 5 fractions ($n = 3$), or 30 Gy in 10 fractions ($n = 1$), whereas SBRT was delivered as 24 to 28 Gy in 2 fractions ($n = 12$) or 18 to 24 Gy in 1 fraction ($n = 3$). Ten of the 20 patients had RT within 1 month after PDT (3 with cEBRT and 7 with SBRT), these patients being referred for prophylactic VCA due to mechanical instability.

Procedural details for all patients are presented in Table 2. Following PDT, no patients experienced any acute side effects ascribed to the PDT treatment. A DSMB comprised of independent experts in VP/KP, clinical trials, as well as drug pharmacology relating to PDT reviewed all patients during each light energy dose, prior to subsequent dose escalation. Confirmation of pharmaceutical and neurologic safety was key endpoint to dose escalation. An example of the pre-, intra-, and postprocedural imaging is presented in Fig. 1. Light transmission studies were performed in 7 patients through the 50 J to 150 J groups. These studies, although not statistically

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Table 2. Procedural data

Group	Patient	Location of surgery	Procedure	Vertebral lesion level	Pathologic status	Light dose (J/cm)	Laser time (seconds/min)	Drug dose (mg/m^2)	Neuromonitoring	Local disease control
Control group	1	OR	VP	T3	Fracture	50	333/5.5	NA	MEP, SSEP	0
	2	OR	KP	T7	Fracture	50	333/5.5	NA	MEP, SSEP	0
	3	IR	VP	L2	Fracture	150	999/16.65	NA	Physical exam	0
	4	OR	KP	L4	At risk	150	999/16.65	NA	EMG	1
	5	OR	KP	L5	Fracture	200	1,333/22.22	NA	EMG	0
	6	IR	VP	L3	Fracture	200	1,333/22.22	NA	Physical exam	0
50 J group	7	OR	KP	L4	Fracture	50	333/5.5	6	EMG	0
	9	OR	KP	T8	Fracture	50	333/5.5	6	MEP, SSEP	0
	10	OR	KP	L2	Fracture	50	333/5.5	6	SSEP, EMGs	0
	11	OR	KP	L4	Fracture	50	333/5.5	6	EMGs	1
	12	OR	KP	L4	At risk	50	333/5.5	6	EMGs	0
100 J group	13	OR	KP	L2	Fracture	100	666/11.1	6	EMGs	0
50 J group	14	OR	KP	L5	Fracture	50	333/5.5	6	EMGs	1
100 J group	16	OR	KP	T12	Fracture	100	666/11.1	6	MEP, SSEP	0
	17	IR	VP	L3	At risk	100	666/11.1	6	Physical exam	0
	18	IR	VP	T12	Fracture	100	666/11.1	6	Physical exam	0
	19	OR	KP	T11	Fracture	100	666/11.1	6	SSEP	0
	20	IR	VP	L2	Fracture	100	666/11.1	6	Physical exam	1
150 J group	22	IR	VP	T11	At risk	150	999/16.65	6	Physical exam	0
	23	IR	VP	T11	Fracture	150	999/16.65	6	Physical exam	0
	24	OR	KP	L1	Fracture	150	999/16.65	6	MEP, SSEP, EMG, physical exam	0
	25	IR	VP	L3	At risk	150	999/16.65	6	Physical exam	1
	26	IR	VP	L5	At risk	150	999/16.65	6	Physical exam	0
	27	IR	VP	T5	At risk	150	999/16.65	6	Physical exam	0
200 J group	28	IR	VP	L3	Fracture	200	1,333/22.22	6	Physical exam	0
	30	IR	VP	L3	Fracture	200	1,333/22.22	6	Physical exam	1
	31	IR	VP	L4	Fracture	200	1,333/22.22	6	Physical exam	0
	32	IR	VP	L4	Fracture	200	1,333/22.22	6	Physical exam	0
	33	IR	VP	T9	Fracture	200	1,333/22.22	6	Physical exam	1
	34	IR	VP	T9	At risk	200	1,333/22.22	6	Physical exam	0

NOTE: Local Disease Control Scoring: 0, stable, no progression of disease; 1, progression of disease; at risk, lesion at risk for vertebral fracture.

significant given the sample size, were performed in order to measure light transmission in the diseased bone. PDT light dosimetry values ranged from 0.72 to 33.90 mW/cm^2 in the 8 patients studied and were independent of primary tumor type. Mixed lytic/blastic tumors represented a higher overall average light power measured across the tumor.

Preoperative and postoperative pain scores were measured using the SF-36, VAS, EORTC-QLQ-BM22, and EORTC-QLQ-C15-PAL systems. No patient showed an increase in pain following VP or KP when combined with PDT as compared with their baseline score. The 50 J/cm and 100 J/cm PDT groups demonstrated significant decreases in both back pain and constant pain after treatment, as per the EORTC-QLQ-BM22 questionnaire (Fig. 2, $P < 0.05$). Over time, PDT did not lead to any increase in pain at either the 1- or 6-week follow-up timepoints, with lower pain scores reported in the 50 and 100 J/cm groups as compared with the control group.

All adverse events as per the CTCAE reporting system from the time of Visudyne administration to the final study visit were assessed over the 6-week follow-up period (Table 3). Three patients (2 patients treated with KP in the 50 J/cm group and 1 patient treated with VP in the 200 J/cm group) experienced fracture progression at the 6-week visit, with evidence of disease progression and VCA failure (loss of stability; Table 3). These 3 patients were neurologically intact 1 week following the PDT/VCA procedure. Two (50 J/cm group) developed lumbar radiculopathy associated with the VCA failure at 6 weeks, with the third patient remaining neurologically asymptomatic. Representative pre-, intra-, and postoperative imaging of the 50 J/cm group patient is presented in Fig. 3. DSMB review concluded that further pathologic fracture collapse was attributed to disease progression with associated loss of VCA mechanical stabilization. Greater initial bone cement fill was also considered potentially desirable in 2 patients (50 J/cm group) and was considered, in part, a contributing factor by the DSMB. Postprocedural development of lumbar radiculopathy at 6 weeks after procedure was opined unlikely related to an immediate drug-light effect with drug concentrated in neural tissues as the half-life of Visudyne is 5 to 6 hours and is rapidly cleared from the body (37). There was insufficient evidence to exclude whether radicular effects could be delayed due to potential PDT effects on tumor and related worsening of spinal stability.

The median follow-up time after vertebral PDT was 12 months (range, 1–44). Local tumor progression was noted in 9 of the 30 patients. The median time from PDT to tumor progression was 2.5 months (range, 1–12). Two of the patients with local progression (50 J/cm group) had never received RT at the site of intervention and, therefore, were classified as having local mechanical failure due to VCA but not to RT. The third patient (200 J/cm group) received SBRT prior to VCA (Table 1). Of the 9 patients who were noted to have tumor progression on serial MRI imaging (classified as RT failure, Table 2), 3 patients declined further local RT therapy, 2 received further cEBRT, 3

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Table 3. Summary of adverse events as per CTCAE criteria

Group	Patient	Complications—day 7	Related to PDT	Complications—day 42	Related to PDT
Control group	1	DVT	Unrelated	DVT	Unrelated
	2	None		None	
	3	None		None	
	4	None			
	5	None		None	
	6	None			
50 J group	7	None		None	
	9	None		None	
	10	None		None	
	11	Shingles	Unrelated	Progression of disease with further fracture and kyphoplasty failure	Unlikely related
	12	None		None	
100 J group	13	None		None	
50 J group	14	None		Progression of disease with failure of kyphoplasty	Unlikely related
100 J group	16	None		None	
	17	None		None	
	18	None		None	
	19	None		None	
	20	None		None	
150 J group	22	None		None	
	23	None		None	
	24	None		None	
	25	None		None	
	26	None		Ankle fracture	Unrelated
	27	Cold extremities after VP	Unrelated	None	
200 J group	28	Incisional back pain for 8 days starting day of surgery; decreased oxygen saturation day of surgery only for 1 hour	Unrelated	None	
	30	Constipation; another lung lesion	Unrelated	Bilateral hip pain; progression of disease with further superior L3 endplate depression	Unrelated
	31	None		None	
	32	None		Right thigh pain	Unrelated
	33	None		None	
	34	None		None	

received further SBRT, and 1 patient received both cEBRT and SBRT.

Overall survival data were examined to determine any potential preliminary efficacy. As of November 2018, the control group (light with no activatable drug) had a median survival time of 428 days following the procedure, compared with 489 days for the 50 J/cm group, 514 days for the 100 J/cm treatment group, and 410 days for the 150 J/cm group. These differences were not statistically significant. At the time of this writing, there were not enough events in the 200 J group to compare overall survival.

Discussion

The application of vertebral PDT in conjunction with VCA for patients presenting with symptomatic bone metastases has been demonstrated here to be feasible and safe. The potential of PDT to selectively ablate tumor tissue through nonthermal mechanisms when combined with VP or KP to mechanically stabilized diseased vertebra has potential as a minimally invasive approach to treating symptomatic local disease in the spine. This study evaluated vertebral PDT in the VCA clinical settings of either VP or KP, in both the operating room and the IR suite environments.

There was no significant increase in reported pain during PDT delivery in those patients treated under neurolept anesthesia. Using PDT added between 30 and 45 minutes to the VCA procedure. Scale-up clinical trials will be required to determine and validate the therapeutic efficacy of PDT and to optimize the treatment parameters. The most significant potential concern is the anatomic proximity of normal neurologic structures, including the spinal cord. However, there was no evidence of neurologic deficit as a result of PDT applied to the thoracic and lumbar spine under the conditions investigated. Nerve sparing with PDT has been reported in other anatomic sites such as in the head and neck which is a significant advantage over thermal ablation (38).

PDT was delivered under fluoroscopic and/or 3D cone beam CT image guidance. Stereotaxy facilitated precise bone trochar placement, informed by preprocedural treatment planning which has been utilized for other solid-tumor sites (16, 36, 39). Such technology platforms including accurate PDT dosimetry are becoming available to optimize treatment delivery. Dosimetry data were collected in only a few patients (those scheduled for bilateral cement injection) in the current study. PDT light dosimetry values ranged from 0.72 to 33.90 mW/cm^2 in the 8 patients studied, that was independent of primary tumor type. Mixed lytic/

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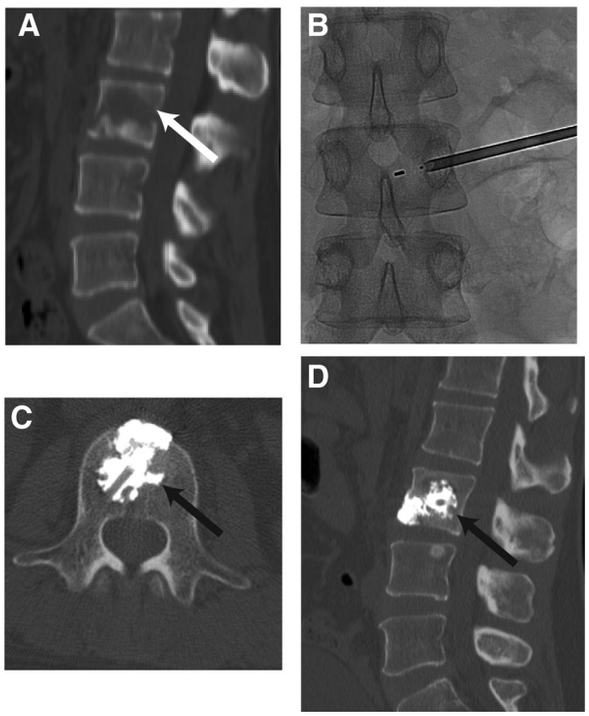

Figure 1.
Example of imaging in a patient treated at 50 J/cm. **A,** Preoperative sagittal CT image demonstrating a single-level lumbar lesion. **B,** Intraoperative fluoroscopy image of the PDT optical fiber: the cylindrical diffuser output is between the two radiomarkers. **C** and **D,** Postoperative CT sagittal and axial planes demonstrating VCA.

blastic tumors represented a higher overall average light power measured across the tumor, albeit in a small sample size. Results confirmed that there was adequate light penetration in human tumor-involved vertebral bone.

To our knowledge, this study is the first to describe light transmission through diseased human bone. Utilizing existing rodent and swine literature on light transmission and attenuation in bone, dosimetry can be extrapolated to map out the anticipated PDT dose administered to targeted vertebrae (40). However, optical properties of bone have similar characteristics to other soft tissues in the body, being highly scattering with little absorption (40). This suggests PDT treatment volumes which could be achieved would potentially be similar to other PDT targeted lesions (such as those found in lung, prostate, and brain). Treatment volumes would then be directly informed by light dose, number of cannulas/fibers, and availability of oxygen and drug. More extensive dosimetry measurements in future trials can be used to directly inform treatment progression (36, 41, 42). As 200 J/cm represented a light dose that was 2.5 times less than that used safely in our preclinical canine vertebral studies in a healthy bone model (43), further increases in the dose may be feasible within diseased bone in order to maximize potential efficacy.

Considering the short (5–6 hours) clearance half-life of Visudyne (37) and its prior extensive ophthalmologic use, any short-term drug-based complication would be anticipated to occur within 3 days after treatment (44). Given the rapid photocytotoxicity of PDT (45, 46), one would expect any short adverse events to manifest by 1 week following treatment. No neurologic symptoms or deficits on examination were reported, either immediately or in the 1-week follow-up in all patients. In addition, no patients suffered any reported photosensitivity reaction.

Three VCA failures (one VP, two KP) were documented at 6 weeks follow-up. All 3 patients were neurologically intact immediately after procedure and at the 1-week follow-up. Two patients reported lumbar radiculopathy symptoms and signs, with subsequent DSMB review determining that these changes were due to disease progression leading to VCA failure and further vertebral collapse. Suboptimal bone cement fill was also considered, in part, a factor in 2 of 3 patients. All 3 patients presented at 6 weeks with increased systemic tumor burden as well, despite having received ongoing systemic and local treatments. We note that the VCA failure rate experienced in our study (3/30) is broadly in line with that reported from meta-analyses of VP and KP outcomes of 19% (47). It is important to note, however, that there is insufficient evidence to conclude that the progression of mechanical instability experienced by some patients in this study is unrelated to PDT. Just because the drug is cleared from the body does not mean that longer term PDT effects are not present. For example, the tumor itself may provide some degree of stability, and gradual loss of the tumor secondary to PDT may in fact contribute to instability. Alternately PDT could adversely affect normal bone in the treatment region with instability manifesting over the longer term. Preclinical studies using this drug in rodent vertebral PDT models were noted to demonstrate improved structural integrity; however, this may not necessary translate to the human situation (25, 26). At this point, it is uncertain whether PDT may in fact contribute to progression of instability, and further studies are required.

The goal of VCA is to improve QOL and reduce pain through prevention of fracture or further vertebral collapse. Hence, PDT combined with VP/KP was successful from a patient-reported outcomes perspective. No treatment group, including the control, demonstrated significant increase in pain in the follow-up period and indeed there was a significant reduction in pain in the 50 and 100 J/cm groups. However, the groups were highly heterogeneous with respect to the metastatic location and the primary tumor type. The patients were not stratified according to RT spinal status which could also be a confounding factor. Because PDT may operate through either vascular and/or direct cytotoxicity pathways, the impact of tumor type (vascularity and other characteristics) on pain reduction and efficacy warrants further study.

Local vertebral progression of disease was found in 9 of the 30 patients, with a median time to progression of 2.5 months. However, this is not unexpected in this patient population, many of whom have had multiple systemic and local treatments prior (including radiation) to study enrollment (Table 1). The present trial has demonstrated that PDT is safe and feasible. Further studies are required to optimize PDT and evaluate its potential efficacy in achieving local tumor control. For example, in high-risk patients with resistant tumor or prior SBRT (e.g., colon carcinoma; ref. 48), and mechanical instability, the use of VCA, PDT, and SBRT as trimodality therapy may be an optimal strategy to achieve the goals of local control and stability. In addition, PDT may be an attractive strategy in patients who have achieved maximum RT tolerance limits and have few other alternatives, or as a bridge in those patients

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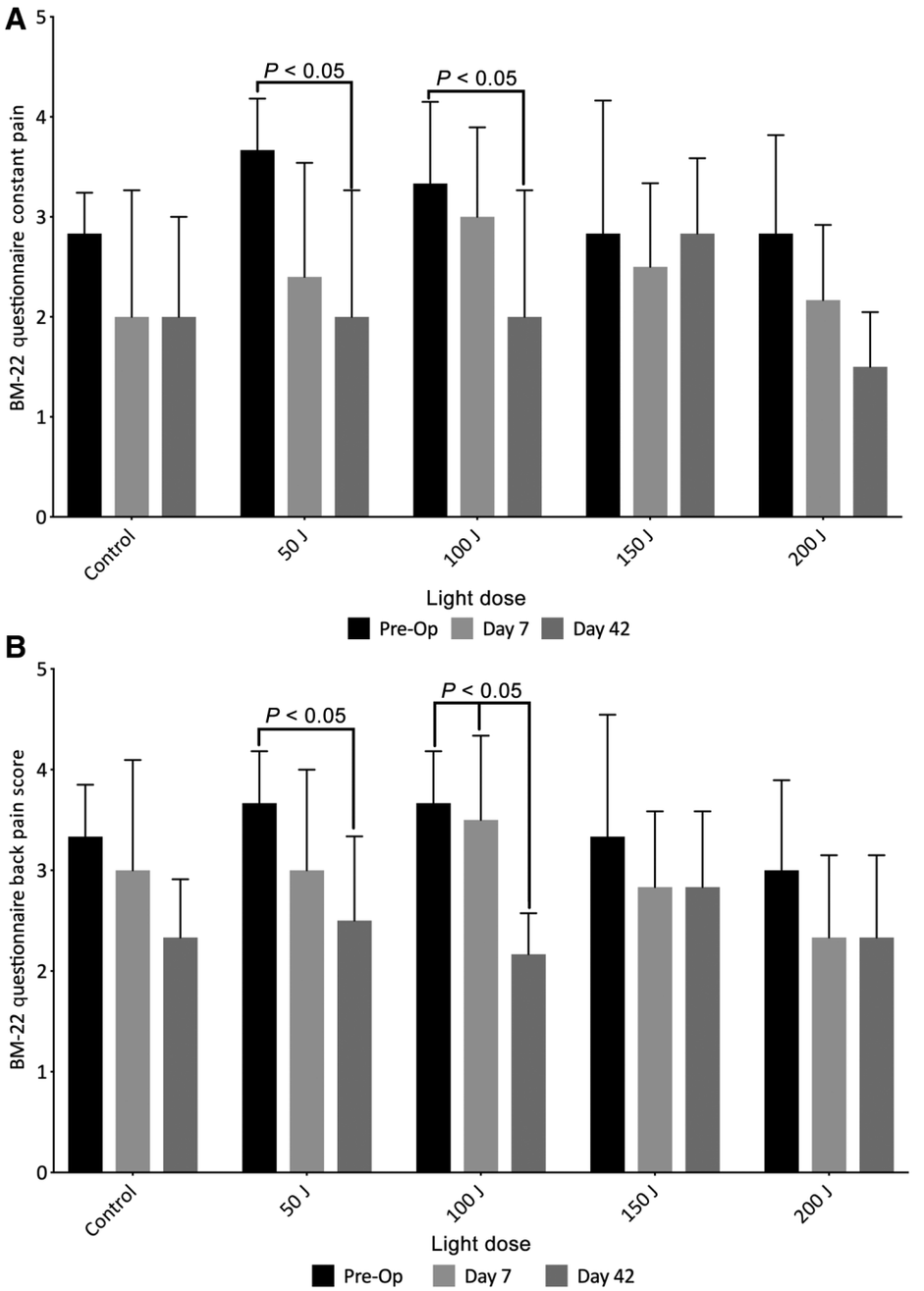

Figure 2.
Overview of BM22 scores for pain characteristic (constant; **A**) and painful site (back; **B**).

where a break in systemic therapy is suboptimal to allow for radiation delivery.

This trial was confined to patients with pain symptoms and at risk for vertebral fracture or with established early fracture for which single-level VCA would be clinically indicated (i.e., SINS score between 7 and 12). As such, we did not study patients who have significant symptomatic multilevel disease or patients in whom advanced vertebral collapse has already occurred, with or without neurologic symptomatology. Hence, our findings are not directly relevant to patients with substantive mechanical instability (i.e., a SINS score of greater than 12) who would require a more conventional open surgical procedure such as neurologic decompression with associated multilevel instrumented vertebral reconstruction. PDT potentially could also be a useful adjuvant in this open surgical setting as it has been demonstrated in other surgical sites; however, this would require further study (49–51).

This study was also limited by the fact that the immediate injection of bone cement confounds radiographic interpretation of potential PDT effects which could otherwise be readily visualized by MRI imaging (43). Hence, in considering a scale-up efficacy study, mechanical stabilization may be achieved through other minimally invasive procedures such as percutaneous spinal instrumentation (i.e., percutaneous screws/rods for segmental stabilization) that spans the vertebral body at risk for fracture or

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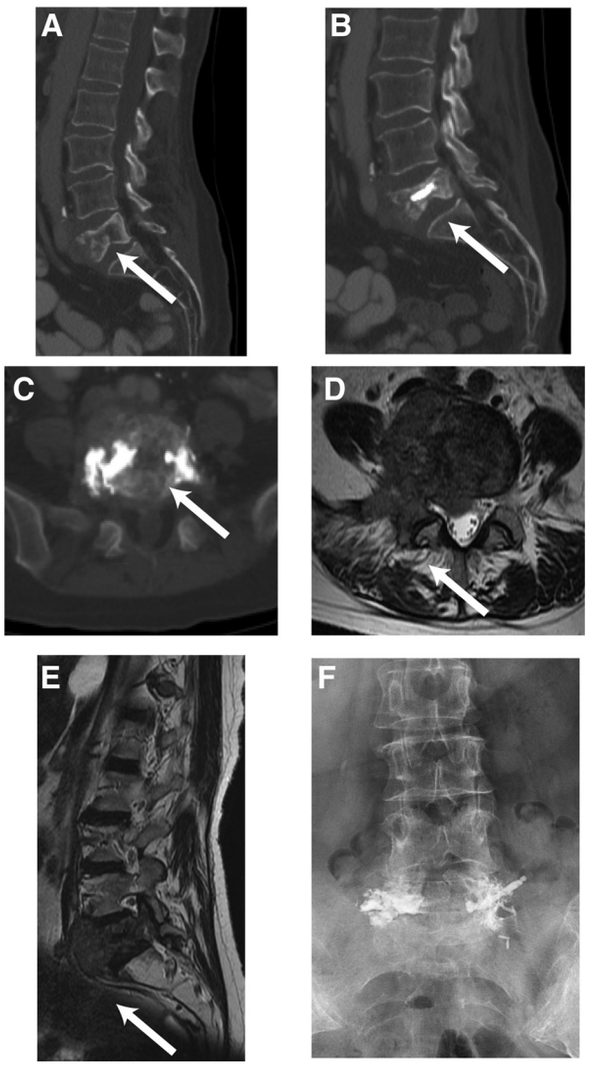

Figure 3.
A patient 6 weeks after procedure (PDT applied at 50 J/cm). **A,** Preoperative sagittal CT image demonstrating single-vertebra lesion. **B** and **C,** Seven-day postoperative sagittal and axial CT images demonstrating placement of PMMA cement following kyphoplasty + PDT. **D** and **E,** Six-week axial and sagittal T_2w MRI images demonstrating tumor progression and spread with mechanical failure of the VCA with further vertebral collapse. **F,** AP radiograph demonstrating further fracture at the KP site.

with established early fracture. PDT could be simultaneously applied to the targeted vertebra, with follow-up radiologic imaging quantifying tumor response to PDT (52).

Future studies may also examine the drug-light interval of Visudyne to best modulate the biological effect. In the current study, a 15-minute interval was chosen based on prior preclinical study to maximize the concentration of Visudyne in the tumor relative to adjacent neurologic tissues (29). This timing specifically targets tumor vasculature. Alternatively, longer drug-light intervals, demonstrated effectively in the preclinical setting (53, 54), could be considered in order to more selectively target the tumor cells. We do note that a clinical study using Visudyne for PDT in pancreatic cancer used 60- to 90-minute drug-light time intervals (55). Cell death following PDT is also not immediate. Later staging of VCA to optimize PDT necrosis may additionally reduce tumor volume and/or alter tumor consistency that may enhance subsequent bone cement fill. However, it would be preferable to combine PDT and VCA in a single procedural setting if the clinical result is acceptable.

From a practical workflow perspective in the procedural room, the ability to initiate the drug infusion as soon as the bone trochar cannulation is confirmed radiologically followed by infusion of the drug over a 15-minute period aligns well with the time required for the insertion of the optical fibers/sheaths through bone trochars (including the time required for laser fiber light calibration prior to fiber insertion). Although alternate photosensitizer drugs could also be considered of photosensitizers we studied in the preclinical setting, Visudyne demonstrated the greatest vertebral bone to neural tissue selectivity with the added advantage of its pharmacologic experience clinically in the ocular field (56).

Conclusions

We have confirmed the feasibility and initial neurologic and pharmaceutical safety of delivering PDT to vertebrae using a minimally invasive therapeutic approach when delivered in conjunction with VP or KP in patients with symptomatic metastases who are eligible for single-level VCA. The ability to deliver combined tumoricidal treatment and mechanical stabilization in a single setting in either the IR or OR environment is attractive in what is typically an out-patient or overnight hospital short stay procedure. The results of this trial motivate scale-up study evaluating potential PDT efficacy in vertebral metastatic treatment.

Disclosure of Potential Conflicts of Interest

A. Sahgal reports receiving commercial research grants from Elekta AB, is a consultant/advisory board member for Abbvie, Merck, Roche, Varian, Elekta, BrainLAB, and VieCure, and other remuneration from International Stereotactic Radiosurgery Society, Elekta AB, Accuray Inc., Varian, BrainLAB, Medtronic Kyphon, Elekta, and Varian. S. Burch is a consultant/advisory board member for Medtronic. A. Yee is an executive committee member of Canadian Spine Society. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: A. Sahgal, C. Whyne, B.C. Wilson, A. Yee
Development of methodology: A. Sahgal, M. Akens, C. Whyne, B.C. Wilson, A. Yee
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Fisher, Z. Ali, A. Sahgal, E. David, M. Kunz, E. Chow, A. Yee
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Fisher, J. Detsky, A. Sahgal, E. Chow, B.C. Wilson, A. Yee
Writing, review, and/or revision of the manuscript: C. Fisher, J. Detsky, A. Sahgal, E. David, M. Kunz, M. Akens, E. Chow, C. Whyne, S. Burch, B.C. Wilson, A. Yee
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Z. Ali, J. Detsky, A. Sahgal, M. Kunz, B.C. Wilson, A. Yee
Study supervision: A. Sahgal, A. Yee

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References

1. Spratt DE, Beeler WH, de Moraes FY, Rhines LD, Gemmete JJ, Chaudhary N, et al. An integrated multidisciplinary algorithm for the management of spinal metastases: an International Spine Oncology Consortium report. Lancet Oncol 2017;18:e720–e30.
2. Ejima Y, Matsuo Y, Sasaki R. The current status and future of radiotherapy for spinal bone metastases. J Orthop Sci 2015;20:585–92.
3. Health Quality Ontario, Pron G, Holubowich C, Kaulback K. Vertebral augmentation involving vertebroplasty or kyphoplasty for cancer-related vertebral compression fractures: a systematic review. Ont Health Technol Assess Ser 2016;16:1–202.
4. Lutz S, Balboni T, Jones J, Lo S, Petit J, Rich SE, et al. Palliative radiation therapy for bone metastases: update of an ASTRO evidence-based guideline. Pract Radiat Oncol 2017;7:4–12.
5. Wallace AN, Tomasian A, Vaswani D, Vyhmeister R, Chang RO, Jennings JW. Radiographic local control of spinal metastases with percutaneous radiofrequency ablation and vertebral augmentation. AJNR Am J Neuroradiol 2016;37:759–65.
6. Tomasian A, Wallace A, Northrup B, Hillen TJ, Jennings JW. Spine cryoablation: pain palliation and local tumor control for vertebral metastases. AJNR Am J Neuroradiol 2016;37:189–95.
7. Simon CJ, Dupuy DE.Image-guided ablative techniques in pelvic malignancies: radiofrequency ablation, cryoablation, microwave ablation. Surg Oncol Clin N Am 2005;14:419–31.
8. Versteeg AL, van der Velden JM, Hes J, Eppinga W, Kasperts N, Verkooijen HM, et al. Stereotactic radiotherapy followed by surgical stabilization within 24 h for unstable spinal metastases; a stage I/IIa study according to the IDEAL framework. Front Oncol 2018;8:626.
9. Steverink JG, Willems SM, Philippens MEP, Kasperts N, Eppinga WSC, Versteeg AL, et al. Early tissue effects of stereotactic body radiation therapy for spinal metastases. Int J Radiat Oncol Biol Phys 2018;100:1254–8.
10. Agostinis P, Berg K, Cengel KA, Foster TH, Girotti AW, Gollnick SO, et al. Photodynamic therapy of cancer: an update. CA Cancer J Clin 2011;61:250–81.
11. Akimoto J. Photodynamic therapy for malignant brain tumors. Neurol Med Chir (Tokyo) 2016;56:151–7.
12. Muragaki Y, Akimoto J, Maruyama T, Iseki H, Ikuta S, Nitta M, et al. Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors. J Neurosurg 2013;119:845–52.
13. Eljamel S. Photodynamic applications in brain tumors: a comprehensive review of the literature. Photodiagn Photodyn Ther 2010;7:76–85.
14. Han WR, Hill JS, Stylli SS, Kaye AH. Photodynamic therapy in the treatment of subcutaneously implanted human bladder tumour. Aust N Z J Surg 1992;62:643–9.
15. Barrett T, Davidson SR, Wilson BC, Weersink RA, Trachtenberg J, Haider MA. Dynamic contrast enhanced MRI as a predictor of vascular-targeted photodynamic focal ablation therapy outcome in prostate cancer post-failed external beam radiation therapy. Can Urol Assoc J 2014;8:E708–14.
16. Shafirstein G, Bellnier D, Oakley E, Hamilton S, Potasek M, Beeson K, et al. Interstitial photodynamic therapy-a focused review. Cancers 2017;9.
17. Fabian ID, Stacey AW, Harby LA, Arora AK, Sagoo MS, Cohen VML. Primary photodynamic therapy with verteporfin for pigmented posterior pole cT1a choroidal melanoma: a 3-year retrospective analysis. Br J Ophthalmol 2018;102:1705–10.
18. Morton CA, Dominicus R, Radny P, Dirschka T, Hauschild A, Reinhold U, et al. A randomized, multi-national, non-inferiority, phase III trial to evaluate the safety and efficacy of BF-200 ALA gel versus MAL cream in the treatment of non-aggressive basal cell carcinoma with photodynamic therapy (PDT). Br J Dermatol 2018.
19. Lowdell CP, Ash DV, Driver I, Brown SB. Interstitial photodynamic therapy. Clinical experience with diffusing fibres in the treatment of cutaneous and subcutaneous tumours. Br J Cancer 1993;67:1398–403.
20. Tennert C, Feldmann K, Haamann E, Al-Ahmad A, Follo M, Wrbas KT, et al. Effect of photodynamic therapy (PDT) on Enterococcus faecalis biofilm in experimental primary and secondary endodontic infections. BMC Oral Health 2014;14:132.
21. Borekci T, Meseli SE, Noyan U, Kuru BE, Kuru L. Efficacy of adjunctive photodynamic therapy in the treatment of generalized aggressive periodontitis: A randomized controlled clinical trial. Lasers Surg Med 2018;51:167–75.
22. Lo VC, Akens MK, Wise-Milestone L, Yee AJ, Wilson BC, Whyne CM. The benefits of photodynamic therapy on vertebral bone are maintained and enhanced by combination treatment with bisphosphonates and radiation therapy. J Orthop Res 2013;31:1398–405.
23. Lo VC, Akens MK, Moore S, Yee AJ, Wilson BC, Whyne CM. Beyond radiation therapy: photodynamic therapy maintains structural integrity of irradiated healthy and metastatically involved vertebrae in a pre-clinical in vivo model. Breast Cancer Res Treat 2012;135:391–401.
24. Wise-Milestone L, Akens MK, Lo VC, Yee AJ, Wilson BC, Whyne CM. Local treatment of mixed osteolytic/osteoblastic spinal metastases: is photodynamic therapy effective? Breast Cancer Res Treat 2012;133:899–908.
25. Won E, Akens MK, Hardisty MR, Burch S, Bisland SK, Yee AJ, et al. Effects of photodynamic therapy on the structural integrity of vertebral bone. Spine (Phila Pa 1976) 2010;35:272–7.
26. Won E, Wise-Milestone L, Akens MK, Burch S, Yee AJ, Wilson BC, et al. Beyond bisphosphonates: photodynamic therapy structurally augments metastatically involved vertebrae and destroys tumor tissue. Breast Cancer Res Treat 2010;124:111–9.
27. Akens MK, Hardisty MR, Wilson BC, Schwock J, Whyne CM, Burch S, et al. Defining the therapeutic window of vertebral photodynamic therapy in a murine pre-clinical model of breast cancer metastasis using the photosensitizer BPD-MA (Verteporfin). Breast Cancer Res Treat 2010;119:325–33.
28. Burch S, Bisland SK, Bogaards A, Yee AJ, Whyne CM, Finkelstein JA, et al. Photodynamic therapy for the treatment of vertebral metastases in a rat model of human breast carcinoma. J Orthop Res 2005;23:995–1003.
29. Versteeg AL, Verlaan JJ, Sahgal A, Mendel E, Quraishi NA, Fourney DR, et al. The Spinal Instability Neoplastic Score: impact on oncologic decision-making. Spine (Phila Pa 1976) 2016;41Suppl 20:S231–s7.
30. Campos M, Urrutia J, Zamora T, Roman J, Canessa V, Borghero Y, et al. The Spine Instability Neoplastic Score: an independent reliability and reproducibility analysis. Spine J 2014;14:1466–9.
31. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. Spine (Phila Pa 1976) 2001;26:298–306.
32. Azab M, Boyer DS, Bressler NM, Bressler SB, Cihelkova I, Hao Y, et al. Verteporfin therapy of subfoveal minimally classic choroidal neovascularization in age-related macular degeneration: 2-year results of a randomized clinical trial. Arch Ophthalmol (Chicago, Ill: 1960) 2005;123:448–57.
33. Miller JW, Schmidt-Erfurth U, Sickenberg M, Pournaras CJ, Laqua H, Barbazetto I, et al. Photodynamic therapy with verteporfin for choroidal neovascularization caused by age-related macular degeneration: results of a single treatment in a phase 1 and 2 study. Arch Ophthalmol (Chicago, Ill: 1960) 1999;117:1161–73.
34. Thibault I, Chang EL, Sheehan J, Ahluwalia MS, Guckenberger M, Sohn MJ, et al. Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. Lancet Oncol 2015;16:e595–603.
35. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for

Published OnlineFirst July 2, 2019; DOI: 10.1158/1078-0432.CCR-19-0673

Adverse Events (CTCAE) Version 5.0. In: Services USDoHaH, editor. Rockville, MD: National Institute of Health; 2017. p. 155.
36. Weersink RA, Bogaards A, Gertner M, Davidson SR, Zhang K, Netchev G, et al. Techniques for delivery and monitoring of TOOKAD (WST09)-mediated photodynamic therapy of the prostate: clinical experience and practicalities. J Photochem Photobiol B 2005;79:211–22.
37. Houle JM, Strong A. Clinical pharmacokinetics of verteporfin. J Clin Pharmacol 2002;42:547–57.
38. Lou PJ, Jäger HR, Jones L, Theodossy T, Bown SG, Hopper C. Interstitial photodynamic therapy as salvage treatment for recurrent head and neck cancer. Br J Cancer 2004;91:441–6.
39. Samkoe KS, Bryant A, Gunn JR, Pereira SP, Hasan T, Pogue BW. Contrast enhanced-magnetic resonance imaging as a surrogate to map verteporfin delivery in photodynamic therapy. J Biomed Opt 2013;18:120504.
40. Rossi VM, Gustafson SB, Jacques SL. Characterizing light propagation in bone for photodynamic therapy of osteosarcoma. Proc of SPIE 2009;7166: 12.
41. Wang KK, Finlay JC, Busch TM, Hahn SM, Zhu TC. Explicit dosimetry for photodynamic therapy: macroscopic singlet oxygen modeling. J Biophotonics 2010;3:304–18.
42. Wilson BC, Patterson MS, Lilge L. Implicit and explicit dosimetry in photodynamic therapy: a new paradigm. Lasers Med Sci 1997;12:182–99.
43. Bisland SK, Burch S. Photodynamic therapy of diseased bone. Photodiagn Photodyn Ther 2006;3:147–55.
44. Photodynamic therapy with verteporfin (Visudyne) for macular degeneration. Med Lett Drugs Ther 2000;42:81–2.
45. Ochsner M. Photophysical and photobiological processes in the photodynamic therapy of tumours. J Photochem Photobiol B 1997; 39:1–18.
46. Brown SB, Brown EA, Walker I. The present and future role of photodynamic therapy in cancer treatment. Lancet Oncol 2004;5:497–508.
47. Fribourg D, Tang C, Sra P, Delamarter R, Bae H. Incidence of subsequent vertebral fracture after kyphoplasty. Spine (Phila Pa 1976) 2004;29: 2270–6.
48. Ito K, Ogawa H, Shimizuguchi T, Nihei K, Furuya T, Tanaka H, et al. Stereotactic body radiotherapy for spinal metastases: clinical experience in 134 cases from a single Japanese institution. Technol Cancer Res Treat 2018;17:1533033818806472.
49. Stepp H, Beck T, Pongratz T, Meinel T, Kreth FW, Tonn J, et al. ALA and malignant glioma: fluorescence-guided resection and photodynamic treatment. J Environ Pathol Toxicol Oncol 2007; 26:157–64.
50. Nanashima A, Yamaguchi H, Shibasaki S, Ide N, Sawai T, Tsuji T, et al. Adjuvant photodynamic therapy for bile duct carcinoma after surgery: a preliminary study. J Gastroenterol 2004;39:1095–101.
51. van Doeveren TEM, Karakullukcu MB, van Veen RLP, Lopez-Yurda M, Schreuder WH, Tan IB. Adjuvant photodynamic therapy in head and neck cancer after tumor-positive resection margins. Laryngoscope 2018;128: 657–63.
52. Dahdaleh NS, Smith ZA, Hitchon PW. Percutaneous pedicle screw fixation for thoracolumbar fractures. Neurosurg Clin N Am 2014;25: 337–46.
53. Tong ZS, Miao PT, Liu TT, Jia YS, Liu XD. Enhanced antitumor effects of BPD-MA-mediated photodynamic therapy combined with adriamycin on breast cancer in mice. Acta Pharmacol Sin 2012;33: 1319–24.
54. Pogue BW, O'Hara JA, Goodwin IA, Wilmot CJ, Fournier GP, Akay AR, et al. Tumor PO(2) changes during photodynamic therapy depend upon photosensitizer type and time after injection. Comp Biochem Physiol A Mol Integr Physiol 2002;132:177–84.
55. Huggett MT, Jermyn M, Gillams A, Illing R, Mosse S, Novelli M, et al. Phase I/II study of verteporfin photodynamic therapy in locally advanced pancreatic cancer. Br J Cancer 2014;110:1698–704.
56. Akens MK, Yee AJ, Wilson BC, Burch S, Johnson CL, Lilge L, et al. Photodynamic therapy of vertebral metastases: evaluating tumor-to-neural tissue uptake of BPD-MA and ALA-PpIX in a murine model of metastatic human breast carcinoma. Photochem Photobiol 2007;83: 1034–9.

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Clinical Cancer Research

Photodynamic Therapy for the Treatment of Vertebral Metastases: A Phase I Clinical Trial

Carl Fisher, Zakariya Ali, Jay Detsky, et al.

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