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Prospective Evaluation

Vertebroplasty Using Transoral Approach in Painful Malignant Involvement of the Second Cervical Vertebra (C2): A Single-Institution Series of 25 Patients

Giovanni Carlo Anselmetti, MD[1], Antonio Manca, MD[1], Filippo Montemurro, MD[1], Sean Tutton, MD[2], Gabriele Chiara, MD[1], Massimo Battistella, MD[1], Maurizio Savojardo, MD[1], Stefano Marcia, MD[3], Salvatore Masala, MD[4], and Daniele Regge, MD[1]

From: [1]Institute for Cancer Research and Treatment Candiolo, Turi, Italy; [2]Medical College of Wisconsin, Milwaukee, WI; [3]University of Cagliari, Cagliari, Italy; [4]University Tor Vergata, Rome, Italy

Dr. Anselmetti, Dr. Manca, and Dr. Chiara are with the Interventional Radiology Unit, Institute for Cancer Research and Treatment, Turin, Italy. Dr. Montemurro is with the Oncology Unit, Institute for Cancer Research and Treatment, Turin, Italy. Dr. Tutton is with the Division of Vascular and Interventional Radiology, Medical College of Wisconsin, Milwaukee, WI, USA . Dr. Battistella is with the Anesthesiology Unit, Institute for Cancer Research and Treatment, Turin, Italy. Dr. Marcia is with the Radiology Unit University of Cagliari. Dr. Masala is with the Radiology Unit University Tor Vergata, Rome. Dr. Regge is with the Radiology Unit, Institute for Cancer Research and Treatment, Turin, Italy

Address correspondence:
Giovanni Carlo Anselmetti, MD
Interventional Radiology Unit,
Institute for Cancer Research and Treatment (IRCC)
Strada Provinciale n° 135 Km.3,95 - 10060 Candiolo,
Turin, Italy
E-mail:
giovanni.anselmetti@ircc.it

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Background: Vertebroplasty is a minimally invasive procedure demonstrated to be safe and effective in the treatment of painful osteoporotic and malignancy related fractures when performed in the thoracolumbar spine. Multiple randomized and nonrandomized reports have demonstrated its effectiveness. Conversely, transoral vertebroplasty (TOV) to treat the second cervical vertebra (C2) has been described in only a few case reports.

Objectives: Prospective evaluation of clinical results of TOV performed in malignant painful osteolytic lesions of C2.

Study Design: TOV was performed in 25 consecutive patients suffering from high-grade cervical pain due to malignant involvement of C2 who failed conservative therapies and did not have surgical indications. Follow-up was prospectively evaluated with clinical interviews in all patients. The Internal Review Board approved this study.

Setting: Institute for Cancer Research and Treatment

Methods: Twenty-five patients (16 women and 9 men; mean age 59.3 ± 11.5) suffering from a painful malignant involvement of C2 who did not respond to conventional therapies and did not have surgical indications, underwent TOV for pain palliation. The procedure was performed under general anesthesia with combined digital fluoroscopy and computed tomography guidance. After a beveled vertebroplasty needle was manually advanced up to the posterior odontoid wall, bone cement was injected under continuous digital fluoroscopic control. Patients were discharged from the hospital the next procedural day. The Visual Analog Scale (VAS) for pain, analgesic requirement, and use of external cervical cast support were used for evaluating efficacy. The main end point was safety and efficacy at day 15 after the procedure. Furthermore, all the patients were scheduled to be followed-up at months one, 3, and 6, and every 6 months thereafter.

Results: The median pretreatment VAS of 8 (range 5-10) significantly dropped ($P < 0.0001$) to 0 (range 0-10), with 20 patients (80%) achieving complete pain relief at day 15 after TOV. Differences in pre- and post-treatment analgesic therapy were significant ($P < 0.001$). Twenty-three patients no longer used a cervical cast after TOV (92%, $P < 0.001$). At median overall follow-up of 16 months (range 6-60 months), the projected proportion of patients free from worsening pain at 6, 12, and 24 months was 96%, 96% and 92% respectively.

Limitations: A randomized study of only 25 patients.

Conclusion: TOV is safe, effective, and long-lasting in the treatment of cervical pain resulting from malignant involvement of C2.

Key words: Vertebroplasty, pain, palliation, cervical spine, metastases.

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The spine is the most common site of metastasis, with 50% to 80% of patients presenting with spinal lesions during the course of their disease (1-4). Due to a relatively large blood flow, the thoracic spine is a frequent site of metastasis. The cervical spine, by contrast, is less commonly involved, accounting for only 8%- 20% of all spinal metastases (1,2,5-8). In particular, metastases to the cervical junction (C1 and C2) are uncommon and represent less than 1% of all spinal metastases (1,3).

Nonsurgical options for spinal metastases depend on tumor histology, the presence of neurologic symptoms, and spinal stability (1,9). Recent progress in anticancer therapy (6,10) and newer radiotherapy techniques such as cyberknife radiosurgery (6,10-12) or intensity modulated stereotactic radiotherapy (13,14) have improved the management of patients with spinal metastases. Unfortunately, a significant proportion of patients with spinal metastases will develop symptoms of bone progression during the course of the disease despite these therapies (15). In particular, patients with cervical metastases, because of the difficult anatomical localization, represent a subgroup where there are unmet medical needs. An osteolytic lesion at C2 with clinical signs of mechanical instability and uncontrolled pain is, in most cases, suggestive of an impending fracture with high risk of severe consequences; in these patients, surgery (16-18) is a preferred option. However, surgical stabilization poses the risk of severe complications (17) since these patients present frequently with poor clinical conditions and an advanced, multi-metastatic disease.

A less invasive procedure is represented by percutaneous vertebroplasty (PV), a technique first introduced by Galibert and Deramond in 1987 for the treatment of symptomatic vertebral angioma of C2 (19). Presently, PV is extensively applied for the palliative treatment of spine metastases in the thoracic and lumbar region (20-23). Despite being less invasive than surgery, cervical spine PV remains a challenging procedure. Only one relatively large series of PV for cervical metastases (24) and case reports of PV for malignant lesions of C2 have been reported in the medical literature (5,25-29).

In the current paper, we present a series of 25 patients who received minimally invasive transoral PV of C2 for painful malignant involvement, prospectively evaluated during long-term follow-up of 21.8 ± 16.3 months (range 6-60 months).

Methods

Study design and patient population

This study was designed as a single cohort with consecutive prospectively acquired data. The data examined after transoral vertebroplasty were cement leakages, clinical complications, analgesic drugs requirements, external cervical cast support, and early and long-term pain management in patients with a malignant osteolytic lesion of C2 that was poorly responsive to conventional therapies.

From July 2003 to January 2010, 25 patients (16 women and 9 men; mean age 59.3 ± 11.5 from 39 to 77 years) were referred to our institution suffering from a painful malignant involvement of C2 with impending fracture. In all patients computed tomography (CT) scans with 2 dimensional reconstruction and magnetic resonance (MR) (Fig. 1) confirmed an osteolytic lesion at C2 and did not reveal any lesion or compression to the spinal cord. Patients' demographics are summarized in Table 1.

A multidisciplinary team consisting of medical oncology, radiation therapy, interventional radiology, and spine surgery evaluated all patients. Patients were referred due to persistent pain as well as an absence of bone consolidation having failed previous noninvasive therapies such as chemotherapy, bisphosphonates, radiotherapy, and analgesic drugs. All patients had been judged ineligible for spinal surgery because of high surgical risk and comorbidity. To treat pain and impending fracture, transoral vertebroplasty was offered to the patients.

Patients were fully informed of potential treatment-related complications and provided signed informed consent before each procedure. Vertebroplasty has been offered as a standard palliative treatment at our institution since 2002. Outcomes data were collected in a prospectively maintained database and the Internal Review Board approved this study.

Procedure

After monitoring vital parameters (ECG, blood pressure, O2 saturation) the patients were placed in the supine position on the digital angiography table (Allura X-per CT, Philips, The Netherlands) of the interventional radiology suite. The patients were all premedicated with IV antibiotics (one gm of vancomycin hydrochloride and 100 mg of gentamycin immediately before the procedure). General anesthesia (propofol 200 mg and

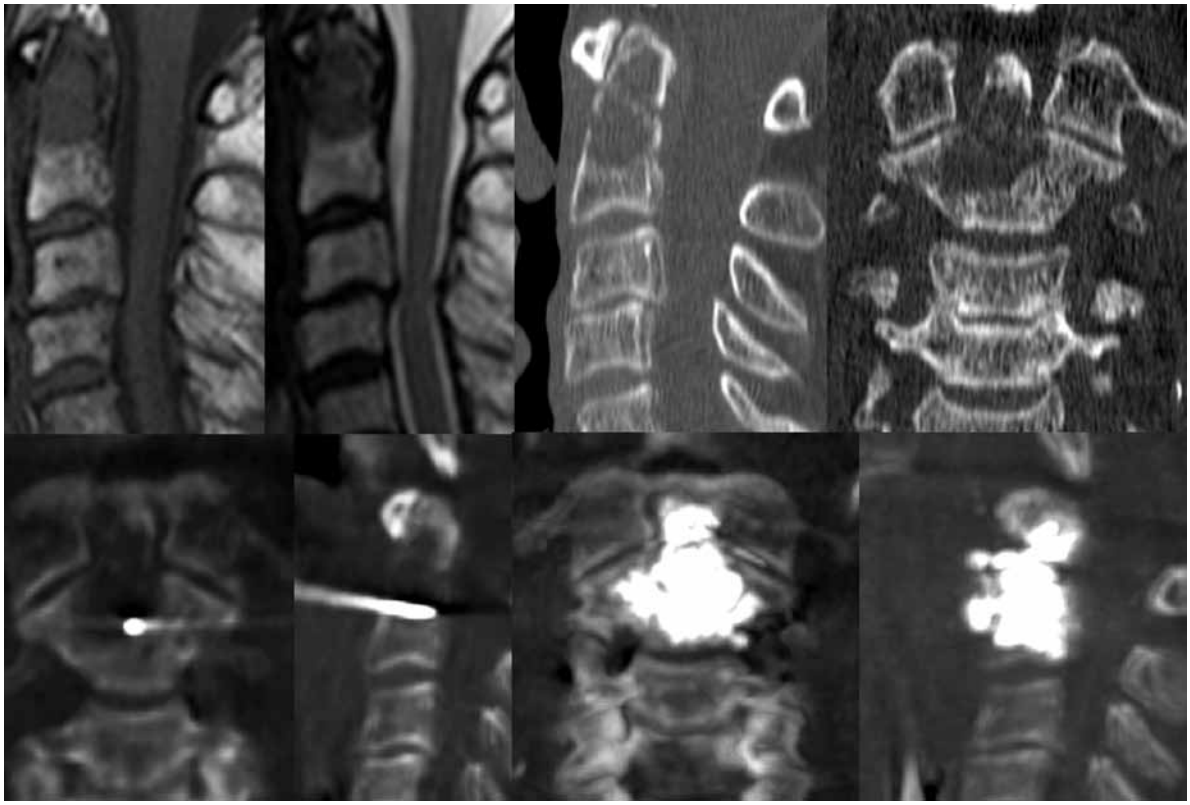

Fig. 1. *(left to right) Magnetic resonance and computed tomography with 2 dimensional reconstruction pre-procedural evaluation confirmed osteolytic lesion at C2 and did not reveal any lesion or compression to the spinal cord. Procedural CT confirmed needle placement within the lesion allowing satisfactory bone cement injection (lower left to right).*

fentanyl 0.1 mg) was administered with placement of a flexible reinforced endotracheal tube. The oral cavity and posterior oropharynx were then cleansed with povidone-iodine; a self-retaining pharyngeal retractor (an otolaryngologic device commonly used for tonsil resection) was then placed for tongue depression and visualization.

The caudocranial fluoroscopic projection allowed good visualization of the C2 odontoid process. Either a 15-gauge (4 patients) or 13-gauge (21 patients) beveled vertebroplasty needle (OptiMed, Ettlingen, Germany) were employed for the procedure. The posterior oropharynx wall was puncture under direct fluoroscopic guidance in the caudocranial projection. After a thru-cut bone biopsy was obtained coaxially using the Bard Magnum(Bard Inc., Tempe, AZ) for subsequent histopathological analysis, the vertebroplasty needle was manually advanced up to the posterior odontoid wall during lateral fluoroscopic view. Prior to polymethylmethacrylate (PMMA) injection, rotational acquisition with 2 dimensional multiplanar reconstructions (2DMPR) was obtained in 21 patients to confirm correct needle position within the lesion. PMMA was then injected under continuous digital fluoroscopic control for early detection of possible PMMA leakages up to satisfactory bone lesion filling. The injection was performed with a low-pressure gun, the Cemento-RE, (OptiMed, Ettlingen, Germany) for a better-graduated control of the injection. After the stylet was reinserted, the needle was manually withdrawn. The patients were then awakened from anesthesia and underwent extubation. Patients were discharged from the hospital the next procedural day. A post-procedural 7-day course of oral clindamycin 150 mg every 6 hours was prescribed for all patients.

Table 1. *Patients demographics before Vertebroplasty (VP) and at the end-point*

Pt	Sex	Age	Pathology	Brace before VP	Brace after VP	Analgesic before VP	Analgesic after VP	VAS before VP	VAS after VP	Follow-up (months)
SA	F	69	HCC Mts	Halo vest	None	I.V. opiates	None	9	0	13
MG	M	59	Thyroid Ca Mts	Halo vest	Minerva	I.V. opiates	NSAD	9	2	6
BL	F	39	Breast Ca Mts	Minerva	None	Oral opiates	None	7	0	62
RL	F	73	Gastric Ca Mts	Minerva	None	Oral opiates	NSAD	5	0	9
VI	M	77	Renal Ca Mts	Minerva	None	Oral opiates	NSAD	10	3	60
MV	F	59	Uterine Ca Mts	Minerva	None	Oral opiates	NSAD	8	3	25
AM	F	52	Breast Ca Mts	Minerva	None	Oral opiates	None	6	0	45
EM	M	43	Oropharyngeal Mts	Minerva	None	Oral opiates	None	7	0	9
PG	M	60	Myeloma	Halo vest	None	I.V. opiates	NSAD	10	3	38
MA	F	48	Breast Ca Mts	Minerva	None	Oral opiates	None	8	0	20
LB	F	55	Breast Ca Mts	Minerva	None	Transdermic opiates	None	5	0	31
MR	F	77	Hystiocytosis X Mts	Halo vest	None	I.V. opiates	NSAD	10	3	14
DP	M	45	Nasopharyngeal Ca Mts	Minerva	None	Oral opiates	None	6	0	13
VC	M	48	Myeloma	Minerva	None	Oral opiates	None	6	0	25
CFM	F	52	Breast Ca Mts	Minerva	Minerva	Transdermic opiates	Oral opiates	10	10	24
VR	F	66	Breast Ca Mts	Minerva	None	Oral opiates	None	5	0	23
FS	M	47	Myeloma	Minerva	None	Oral opiates	None	9	0	16
LC	F	47	Sarcoma Mts	Minerva	None	Oral opiates	NSAD	10	1	7
SE	M	72	Colon Ca Mts	Minerva	None	Oral opiates	None	8	0	20
BR	F	60	Breast Ca Mts	Minerva	None	Oral opiates	None	9	0	8
LL	F	72	Myeloma	Minerva	None	Oral opiates	None	10	0	9
AAM	F	56	Myeloma	Minerva	None	Oral opiates	None	10	0	14
PS	F	66	Breast Ca Mts	Minerva	None	Oral opiates	None	8	0	6
DG	M	76	Renal Ca Mts	Minerva	None	Oral opiates	None	10	0	6
CMS	F	64	Breast Ca Mts	Minerva	None	Oral opiates	None	8	0	43

I.V.= Intravenous; NSAD= Non Steroidal Analgesic Drug; VAS= Visual Analog Scale

Assessment of Complications and Cement Leakage

Postprocedural 2DMPR were obtained in all the patients to precisely visualize the filling of the defect by the bone cement and to detect possible complications.

Follow-up and Clinical Outcome Evaluation

A dedicated software database was developed to prospectively collect clinical data and technical information on treated patients.

Follow-up was completed by clinical interviews at 2 and 15 days after vertebroplasty, and by clinical or phone interview thereafter (months one, 3, 6, 12, 18, and every 6 months).

Pain was evaluated by the 11-point pain intensity numerical rating Visual Analog Scale (VAS) where 0 represents no pain and 10 the worst experienced pain. The raw change in the VAS was computed by subtracting the baseline value from the endpoint for each patient. Analgesic drugs prescribed at baseline and at follow-up interviews were classified as none, nonsteroidal anti-inflammatory drugs (NSAIDs), oral narcotic, and transdermal or intravenous opioid therapy with implanted pump.

Statistical analysis

The outcome of interest was the change, with respect to pretreatment values, of the following variables

measured at 15 days from the procedure:

- The VAS, which was studied as both a continuous and a categorical ordinal variable
- The pattern of analgesic use, which was coded into four categories: 1 = None, 2 = NSAIDs, 3 = oral opiates, 4 = transdermal/intravenous opiates and studied as both a categorical nominal and categorical ordinal variable
- The use of an external orthopedic cast, which was dichotomized into "yes" or "no."

Pain control failure occurring during follow-up was defined as a worsening of 2 or more VAS points with respect to the 15-day value. Time to pain relapse was studied by the Kaplan Meier method. Patients without pain recurrence were amended at the date of the most recent follow-up contact. For the variables of interest, pre- and post-PV values were compared by the Wilcoxon test (continuous variables), the McNemar test (dichotomous variables), and by the marginal homogeneity test (nominal variables with more than 2 levels). Significance was set at a $P < 0.05$.

Statistical analyses were performed by the SPSS Version 17 statistical package (SPSS Inc., Chicago, IL).

Results

Transoral vertebroplasty of C2 was feasible in all 25 patients (Table 1 for demographics) without any early major complications such as death, symptomatic vascular leakages and spinal or extraspinal tissue injuries.

No delayed complications occurred during follow-up. Specifically, no infections occurred in this group.

In 6 patients (24%), minimal PMMA leakage occurred in the soft tissues surrounding the bone along the needle tract. All these leakages were asymptomatic and did not require any further treatment. One patient, with extensive osteolytic metastasis from thyroid cancer who obtained significant pain relief from PV, underwent posterior surgical fixation after 6 months to increase bone consolidation.

Pain and Quality of Life Evaluation

Data regarding the variables of interest were available for the entire dataset of 25 patients.

All the patients had pretreatment VAS scores of 5 or higher. All patients achieved a reduction in the VAS score of at least 2 points as a result of treatment (Table 2). The median VAS reduction was 7 points (range 2 to 10 points). The median pre- and post-treatment VAS values were 8 (5-10) and 0 (0-10), respectively, and the difference was statistically significant by both the Wilcoxon test (considering VAS as a continuous variable, $P < 0.001$) and by the signed test (considering VAS as a categorical ordinal variable, $P < 0.001$). Notably, 24 patients (96%) achieved a clinically relevant VAS reduction (2 or more points) within 48 hours of the procedure. Twenty patients (80%) achieved complete pain relief (VAS = 0) within 15 days after the procedure. At a minimum follow-up of 6 months, (median 16 months, range 6 to 60 months), a total of 4 patients experienced worsening pain of 2 or more VAS points (range 2-3 VAS points). The Kaplan Maier estimate of time to worsening pain is depicted in Fig. 2. The projected proportion of patients

Table 2. *Joined distribution of VAS score before and after PV. The pre-treatment median VAS of 8 (range 5-10) significantly dropped to 0 (0-10) at the 15-day time point.*

		VAS score after PV										
VAS score before PV		0	1	2	3	4	5	6	7	8	9	10
	0	-	-	-	-	-	-	-	-	-	-	-
	1	-	-	-	-	-	-	-	-	-	-	-
	2											-
	3											-
	4											-
	5	3										-
	6	3										-
	7	2										-
	8	4			1							-
	9	3		1								-
	10	3	1		3							1

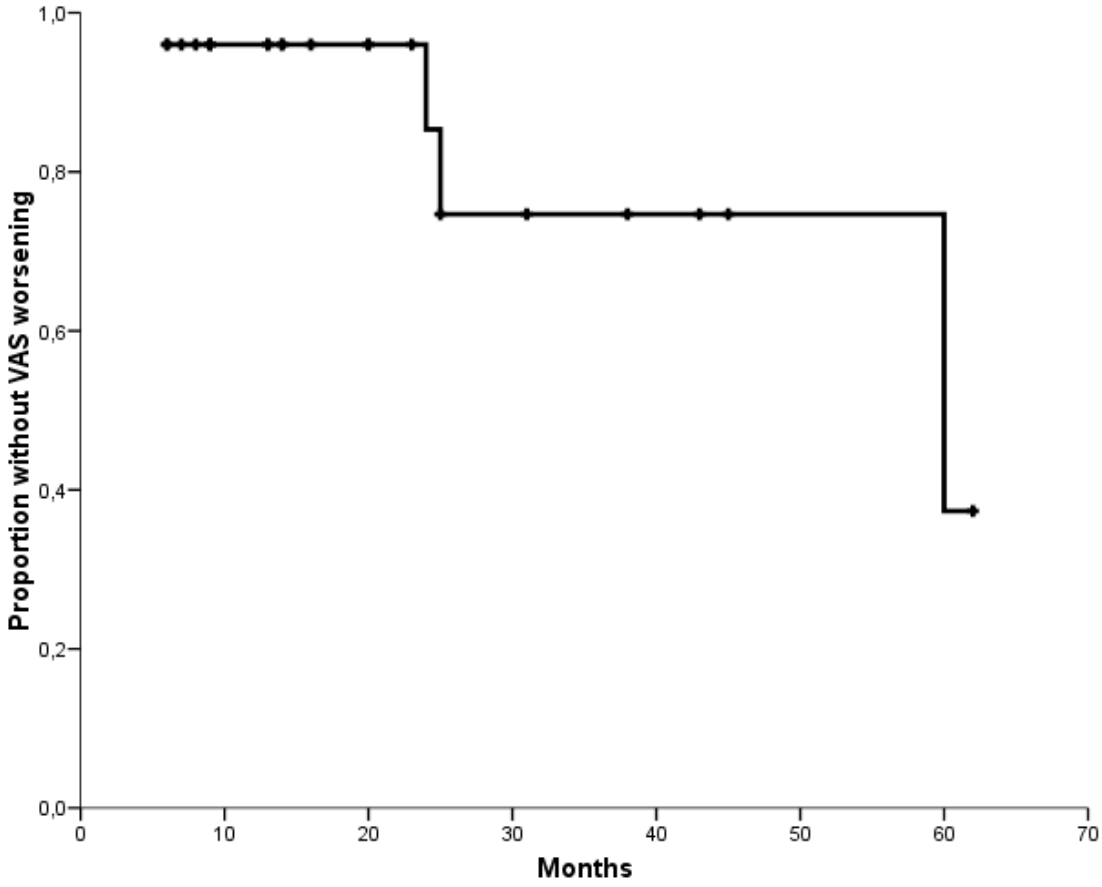

Fig. 2. *Kaplan Maier estimation of time to worsening pain.*

Table 3. *Analgesic drugs use before and after transoral vertebroplasty. Patient's number and percentages before and after PV. Marginal homogeneity test: P <0.001*
Sign test: P <0.001

Analgesic Medication	Before PV Number (%)	After PV Number (%)
None	0	17 (68%)
NSAIDs	0	7 (28%)
Oral Opiates	21 (84%)	1 (4%)
Transdermic/I.V. opiates	4 (16%)	0 (0%)

(NSAIDs non-steroidal anti-inflammatory drugs; I.V., intravenous.)

free from worsening pain at 6, 12 and 24 months was 96%, 96% and 92%, respectively.

Use of Analgesic Drugs

All the patients were on opiate analgesic drugs before the procedure, with 19 patients (76%) receiving oral opiates, 2 patients (8%) receiving transdermic opiates, and 4 patients (16%) receiving intravenous opiates (Table 1).

Table 3 summarizes the type and frequency of analgesic treatments before, and 15 days after the procedure. Differences in pre- and post-treatment frequencies in each analgesic drug category were statistically significant by the marginal homogeneity test (P < 0.001) and the sign test (P < 0.001). All but one patient achieved a downshift in the category of analgesic drugs, with 17 patients (68%) discontinuing any analgesics use.

External Brace Support Evaluation

Before vertebroplasty, all the patients wore an orthopedic cervical cast (Halo vest in 4 and Minerva in 21). As a result of the procedure, 23 out of 25 of these patients (92%) no longer use it (Table 4 – $P < 0.001$).

Bone Cement Leakage

Post-procedural CT detected a minimal bone cement extravasation in 6 (24%) patients. Cross sectional imaging with CT scans provides the most sensitive method of evaluating these leaks. These PMMA leakages were located in the submucosal tissue along the needle track in 5 and into the left pedicular joint in one. All these leakages were asymptomatic during the procedure, post-procedural clinical observation, and at final follow-up.

Discussion

Although PV is a widely performed procedure in vertebral osteoporotic compression fractures or for painful neoplastic vertebral involvement at the thoracic and lumbar level, this procedure is not well established as a treatment in the cervical spine (24) and is rarely performed in the upper C2 level (5,25-29). The anterolateral approach, commonly used for cervical percutaneous vertebroplasty, places many neurovascular structures at risk if performed to treat the second cervical vertebra: the spinal accessory, lingual, hypoglossal, vagus, marginal, and laryngeal nerves as well as carotid and vertebral arteries. For this reason a transoral approach is more frequently used in reported cases.

Considering the high infection rate of cervicovertebral spine surgery (17,30), minimally invasive transoral vertebroplasty has the potential advantage of lowering the infection rate for minimal disruption of the posterior oropharyngeal tissues. Surgical stabilization in cancer patients carries a risk of infection and the failure of bone healing due to poor clinical conditions and comorbidities (17,31). As a result, many patients do not undergo surgical treatment and are relegated to narcotics and chronic use of an external brace impacting quality of life and the ability to perform ADLs need full term for this abbreviation. The encouraging results of percutaneous vertebroplasty in the treatment of malignant vertebral body involvement and concomitant surgical high risk in these cancer patients led us to adopt this minimally invasive procedure. While not the established standard treatment, this is more appropriate for palliation and improvement of the quality of life of the patients with limited life expectancies and multi-metastatic disease.

As previously described in case reports, the advantages of transoral vertebroplasty include precise needle placement, decreased risk to adjacent neurovascular structures, and potential reduction of infection rate. To minimize the complication rate and to obtain precise needle positioning, digital flat panel fluoroscopic guidance with rotational CT imaging was always employed. We believe that this also increased the possibility of achieving an adequate cementation of C2.

In the majority of patients (20 out of 25 – 80%), pain relief was complete within 15 days from the procedure and this favorable clinical outcome was durable during an average follow-up of 16 months (from 6 to 60 months) with 4 patients only showing worsening pain (VAS 2 to 3 points) during long-term evaluation. Considering quality of life, 92% of patients no longer required the external cervical brace after the procedure, and 17 out of 25 (68%) discontinued any analgesic use. These results are meaningful in cancer patients presenting with poor clinical conditions.

Based on our experience, transoral vertebroplasty could be unsuccessful if the lesion extends to involve the posterior vertebral elements. In this situation, a satisfactory stabilization is difficult to achieve. In these select cases, by avoiding the risks of the anterior surgical approach, vertebroplasty and surgical posterior fixation may represent a safer option for patients presenting with this type of involvement as occurred in one patient of this series.

In this series treating osteolytic malignant C2 involvement, we believe that minimal bone cement leakage occurred because of the use of high quality intraprocedure image guidance employing digital flat-panel fluoroscopy and rotational CT. The observed leakages were limited (6 out of 25 – 24%) and asymptomatic both immediately after the procedure and during follow-up, demonstrating that transoral vertebroplasty is a safe procedure.

Table 4. *Joined distribution of use of brace before and after vertebroplasty. Numbers in rows contain represent pre-treatment frequencies and numbers in columns represent post-treatment frequencies. McNemar test: $P < 0.001$*

		Halo/Minerva after PV		
		No	Yes	
Halo/Minerva before PV	No	0	0	0
	Yes	23	2	25
		23	2	25

Study limitations include the relatively small number of patients as well as the lack of a control group treated by conservative medical therapy (radiotherapy and chemotherapy) only, but randomization was considered unethical when an impending fracture was present.

Conclusion

Though surgery can achieve complete disease control if vertebrectomy and stabilization is performed, there is a relatively high risk in cancer patients with poor clinical condition and advanced multi-metastatic disease. This relatively large nonrandomized prospective series demonstrates that transoral vertebroplasty is an effective and safe palliative treatment for painful malignant involvement of the second cervical vertebra in nonsurgical patients. In our opinion, this option should always be considered in this patient setting.

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