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Symptom Management and Supportive Care

Quality of Life Implications of Bisphosphonate-Associated Osteonecrosis of the Jaw

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Key Words. Quality of life • Osteonecrosis • Bisphosphonates • Zoledronic acid • Pamidronate • Utility

Disclosures: Rebecca Anne Miksad: None; **Kuan-Chi Lai:** None; **Thomas Benton Dodson:** None; **Sook-Bin Woo:** None; **Nathaniel Simon Treister:** None; **Omosalewa Akinyemi:** None; **Marian Bihrle:** None; **Guy Maytal:** None; **Meredith August:** None; **G. Scott Gazelle:** None; **J. Shannon Swan:** None.

The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors or independent peer reviewers.

ABSTRACT

Purpose. **Potentially debilitating, osteonecrosis of the jaw (ONJ) is an emerging complication of bisphosphonates. However, its effect on quality of life (QoL) is unknown. We determined the ONJ-related QoL decline in a cancer patient cohort.**

Patients and Methods. **Thirty-four cancer patients with bisphosphonate-associated ONJ completed a telephone survey (October 2007 through May 2008). The Oral Health Impact Profile 14 (OHIP) retrospectively assessed participant oral health–related QoL before and after ONJ. Standardized ONJ descriptions were developed in a multidisciplinary, iterative process and were evaluated with three frequently used preference-based QoL measurement methods on a 0 (death) to 1 (perfect health) scale: Visual Analogue Scale (VAS), Time Trade-Off (TTO), and EQ-5D.**

Results. **ONJ significantly ($p < .001$) increased OHIP scores (worse QoL) for additive (3.56–16.53) and weighted (7.0–17.5) methods. Seven individual OHIP items significantly increased (Bonferroni correction $p < .0035$): pain, eating discomfort, self-consciousness, unsatisfactory diet, interrupted meals, irritability, and decreased life satisfaction. Mean preference-based QoL values significantly decreased ($p < .001$) with worsening ONJ stage (VAS, TTO, and EQ-5D): no ONJ (0.76, 0.86, 0.82), ONJ stage 1 (0.69, 0.82, 0.78), ONJ stage 2 (0.51, 0.67, 0.55), and ONJ stage 3 (0.37, 0.61, 0.32). As ONJ worsened, EQ-5D domain scores significantly increased ($p < .001$). Pain/discomfort and anxiety/depression contributed most to declining QoL.**

Conclusions. **ONJ significantly affects QoL, a detriment that increases with worsening ONJ. QoL impairments for ONJ stages 2 and 3 are similar to other treatment side effects that influence decision-making. Bisphosphonate-associated ONJ QoL is an important consideration for patients, clinicians, and policy makers.** ***The Oncologist*** 2011;16:121–132

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1083-7159/2011/$30.00/0 doi: 10.1634/theoncologist.2010-0183

Introduction

Bisphosphonate-associated osteonecrosis of the jaw (ONJ) is a growing clinical concern that affects treatment decisions because of its potential negative impact on quality of life (QoL) [1–9]. A potentially painful and debilitating condition and the subject of ongoing litigations, [10–12] ONJ is defined as exposed necrotic maxillofacial bone with complications ranging from pain to fractures [9, 12–24]. The reported risk of ONJ in cancer patients treated with intravenous bisphosphonates varies [25]: frequency estimates range from 0.7% [13] to 12% [18] and cumulative risk estimates range from a 4.8% cumulative incidence for a cohort of breast cancer patients treated for >5 years with intravenous bisphosphonates [13] to a 40% cumulative risk at 36 months for a cohort of multiple myeloma patients [25, 26]. Although less common, ONJ has been reported with oral bisphosphonates for osteoporosis [27–35] and is a priority Food and Drug Administration Targeted Post-Marketing Surveillance complication [36]. Furthermore, the cancer patients at risk for ONJ is sizeable: in 2004, >3 million individuals worldwide and one third of Americans with advanced breast cancer had received intravenous bisphosphonates such as zoledronic acid and pamidronate [37]. In 2009, sales of zoledronic acid reached nearly $1.5 billion [38]. Additionally, five recent trials may expand the role of intravenous bisphosphonates beyond advanced cancers to patients potentially cured from cancer [39–43]. Intravenous bisphosphonates improve QoL [44] by decreasing skeletal-related events (SREs) (fracture, spinal cord compression, need for radiation or surgery, and hypercalcemia) in cancer patients with bone involvement (breast or prostate cancer metastatic to the bone and multiple myeloma) [43, 45–47]. In contrast, ONJ may decrease QoL because of infected and painful necrotic jaw bone; ulcerated, painful, and swollen oral mucosa; chronic sinus tracts and facial disfigurement; impaired speech, swallowing, and eating; and/or frequent medical and dental evaluations and treatments [48–51]. Therefore, the population at risk for ONJ is large and expanding, and the public health implications may be substantial.

Despite the extent of ONJ complications and evidence that oral health QoL affects overall QoL [52–59], the effect of ONJ on QoL has not been determined [43–47]. A search of PubMED and a QoL publication registry [60] identified only one oral health cancer therapy complication QoL study that used methods suitable for comprehensive economic evaluation [61]. However, this prior study evaluated short-term (7 day) stomatitis rather than a serious long-term complication such as ONJ, which is needed for full assessment of bisphosphonate benefit-risk trade-offs.

Accurate ONJ QoL data are needed to inform bisphosphonate treatment decision-making: patients and physicians must determine whether potential negative ONJ-related QoL effects outweigh the potential benefit of bisphosphonates while policy makers need to know the magnitude of ONJ-related QoL decline to evaluate the comparative value of bisphosphonates [62–65]. If the negative QoL impact of ONJ is substantially large, the favorable comparative value recently attributed to intravenous bisphosphonates may be reduced or, according to Hillner et al., may be reversed [66, 67]. In addition, ONJ QoL findings may be important for other drugs such as denosumab (a fully human monoclonal antibody against receptor activator of nuclear factor κB [RANK] ligand) that may be superior to zoledronic acid in delaying or preventing SREs but may also have a higher incidence of ONJ [68].

The primary objective of this study was to determine the QoL impact of bisphosphonate-associated ONJ in cancer patients. Our multidisciplinary team (oncology, oral medicine and surgery, QoL research, and psychiatry) developed a telephone survey to test whether oral health–specific and preference-based instruments capture the QoL effects of oral health complications of cancer therapy and whether the QoL impact of ONJ increases with ONJ disease severity.

Methods

Participant Recruitment and Eligibility

With Institutional Review Board approval, a cohort of cancer patients with ONJ was identified at two institutions by oral medicine (S.W. and N.T.) and oral/maxillofacial surgery (T.D. and M.A.) collaborators. Medical charts were reviewed to determine eligibility: (1) cancer diagnosis; (2) ONJ diagnosis [69]; (3) bisphosphonate exposure; (4) no radiation to head or neck; and (5) ability to complete English-language telephone survey.

Unless the primary oncologist declined participation on behalf of their patient, potential participants were mailed an introductory letter, information about declining participation, and a paper copy of the telephone survey questions. One week later, participants were called to request a telephone survey interview. Consent was implied by scheduling the interview.

Participants were encouraged to review the paper copy before the telephone interview. The telephone survey was administered by a single researcher (O.A.) using a standardized script and Microsoft Visual Basic cues. Health state descriptions were verbally reviewed prior to relevant survey sections. Participant responses were recorded in an Excel database by the interviewer. At survey

completion, participants were offered a $20 gift card. The survey was not changed based on pilot results and pilot participants ($n = 5$) were included in final analysis [70].

In addition to collecting demographic and clinical information, the survey consisted of four instruments: Oral Health Impact Profile and three widely used preference-based QoL methods adapted for the study [71]: Visual Analogue Scale, [71–73], Time Trade-Off [74–77], and EQ-5D [72, 78–80].

Oral Health Impact Profile

A validated psychometric instrument with face, criterion, convergent, and construct validity that assesses seven oral health–specific QoL dimensions, the Oral Health Impact Profile 14 (OHIP-14) was used to assess participant oral health QoL [81–86]. Participants were asked to recall a typical week before and after they developed ONJ (any stage) to rank on a five-point Likert scale the average number of days per week each OHIP item occurred. Pre- and post-ONJ results were summed for the OHIP-Additive Score (ADD) [81–83]. Published item weights were used to calculate the OHIP-Weighted Score (WS) [81–83].

Preference-Based QoL Assessment

To compare each ONJ stage with other health states, participants evaluated four standardized ONJ health states with three preference-based instruments that quantitatively measure QoL: VAS, TTO, and EQ-5D. These QoL values are reported on a 0 (death) to 1 (perfect health) scale and can be used as utilities to produce quality-adjusted life years (QALYs) estimates, as is commonly done in the literature [71, 73, 79, 87, 88]. Because utilities allow accurate QoL comparisons between individuals and across diseases, they are necessary to assess the comparative value of health care interventions [89, 90].

Standardized health states were developed to minimize bias from variations in participant experience (not all patients have all ONJ stages) and to ensure validity of comparisons. Iteratively developed following published recommendations [89], health state descriptions were drawn from ONJ diagnostic criteria [69], literature review/case analysis [91], and multidisciplinary expertise. On the basis of testing with clinical and nonclinical colleagues, written descriptions were used instead of pictures. Each health state depicted the same hypothetical, gender-neutral patient with an unnamed cancer with bone involvement ("cancer in the bone") and one ONJ health state: no ONJ, ONJ stage 1, ONJ stage 2, or ONJ stage 3 (Table 1 and supplemental online Appendix pages 5–8).

Visual Analogue Scale (VAS)

The VAS familiarizes participants with the task of scoring and ordering standardized health states according to perceived QoL [72]. On the paper copy of the telephone survey, the VAS was represented by a vertical line marked "100 (Perfect Health)" at the top and "0 (Death)" at the bottom (adapted from the EQ-5D [72], supplemental online Appendix page 9). Color-coded health state summaries and removable, self-adhesive arrows were provided to assist ranking during the telephone interview. Final VAS scores for each standardized health state were recorded during the interview and rescaled to the 0 to 1 QoL scale by dividing by 100.

Time Trade-Off (TTO)

Generally accepted as an alternative to the standard gamble, the TTO method identifies the indifference point (X) at which the respondent believes that a longer amount of time in a less desirable health state is equivalent to a shorter amount of time in a more desirable health state such as perfect health [74, 76]. A two-stage approach was used to isolate the QoL impact of ONJ (supplemental online Fig. 1 and Appendix pages 10 and 11) [75, 77].

Participants initially compared a set life span (48 months) in the standardized cancer in the bone *without* ONJ health state to varying amounts of time in perfect health (QoL = 1). For example, if 48 months of perfect health was preferred over 48 months with cancer, the scenario was varied to the opposite extreme: 1 month in perfect health versus 48 months with cancer. If both choices were equivalent, the indifference point (X) was 1 month. Otherwise, the time in perfect health was varied until the participant considered X time in perfect health equivalent to 48 months with the standardized cancer *without* ONJ health state. This indifference point value (X) was divided by 48 months to obtain the QoL of cancer *without* ONJ on a zero-to-one scale.

With use of a similar pattern of questions, participants then compared a set life span (48 months) with cancer in the bone *with* ONJ to varying amounts of time with cancer in the bone *without* ONJ. The participant's indifference point was divided by 48 months and converted from a death-to-cancer scale to a 0 (death) to 1 (perfect heath) QoL scale by re-scaling proportionally with the QoL value of cancer *without* ONJ reported in the first TTO exercise. The resulting value is the QoL of the standardized patient with cancer *and* ONJ.

To identify the key clinical components affecting the QoL impact of ONJ, each ONJ stage was evaluated separately. A hypothetical life span of 48 months was chosen as the average survival for most cancers expected in the cohort [92, 93].

Table 1. Health states summary description and ONJ stage definition

Health State	Health State Summary[a]	ONJ[b] Staging	Stage Definition[c]
Cancer only	Cancer in the bone	At risk	No apparent exposed or necrotic bone
	Chemotherapy once a week, resulting in tiredness and nausea	Stage 0	Nonspecific clinical findings and symptoms without clinical evidence of necrotic bone
Cancer and ONJ stage 1	Cancer in the bone	Stage 1	Exposed or necrotic bone without evidence of infection
	Exposed jawbone without pain		
	Antiseptic mouth rinse twice per day that may alter taste		
	Oral exam every 3 months		
Cancer and ONJ Stage 2	Cancer in the bone	Stage 2	Exposed or necrotic bone with infection, pain, and erythema
	Pain and infection in the jaw and mouth		
	Can only eat soft foods		
	Difficulty in speech		
	Scraping of necrotic bones every week and antibiotic pill twice a day for 3 months		
	Antiseptic mouth rinse twice per day that may alter taste		
	Oral exam every month		
Cancer and ONJ stage 3	Cancer in the bone	Stage 3	Exposed or necrotic bone with infection, pain, and one or more of: pathologic fracture, extra oral fistula, or osteolysis
	Pain and infection in the jaw and mouth		
	Can only eat soft foods		
	Difficulty in speech		
	Embarrassed about pus draining from the chin		
	Antiseptic mouth rinse twice per day that may alter taste		
	Scraping of necrotic bones twice a week and antibiotic pill twice a day for 4 weeks		
	Surgical removal of necrotic bone requiring general anesthesia and 3 days in hospital		
	Intravenous antibiotics and jaw bandage changes at home daily and doctor's appointment twice a week for 6 weeks		
	Oral exam every month and scraping of necrotic bones every few months		
	Persistent pain and scar on chin		

[a]See supplemental online data (eSurvey) for a complete description.
[b]ONJ is defined as >8 weeks of exposed necrotic maxillofacial bone in a patient with bisphosphonate exposure and without radiation to the jaw.
[c]In 2009 (after initiation of this study), the American Association of Oral and Maxillofacial Surgeons [65] subdivided patients without ONJ into two categories: at risk and stage 0.

EQ-5D

A well-validated preference-based QoL instrument, the EQ-5D evaluates five QoL domains: mobility, self-care, activities, pain/discomfort, and anxiety/depression [72]. Participants rated the level of domain dysfunction (no problems, some problems, or extreme problems) for each standardized ONJ description (supplemental online Appendix page 12). Responses were converted to a 0 to 1 QoL scale using published U.S. societal weights [79, 80].

QoL Decrement

The amount of QoL lost because of ONJ was calculated using the mean across respondents. For each ONJ stage and method, the mean QoL value was divided by the mean QoL

value of cancer *without* ONJ and the result subtracted from 1 [94].

Emotional Discomfort

Participant emotional discomfort was formally evaluated by the interviewer using a post-survey emotional assessment approach inspired by prior studies [95]. Participants indicating discomfort were immediately offered psychiatry referral (G.M.). Emotional discomfort results were reviewed (R.M.) after the pilot study ($n = 5$) and then after every 10 interviews to assess whether an early stopping rule was met: ≥50% of participants indicating greater than or equal to moderate emotional upset.

Statistical Analysis

The participants' own pre- and post-ONJ (any stage) scores for each OHIP item and the composite total score were compared across respondents using the nonparametric Wilcoxon signed rank test for paired data. To account for multiple comparisons, the *p*-value threshold was modified with Bonferroni adjustment ($\alpha = 0.05/14 = 0.0035$). For overall QoL measurements, the significance of differences between ONJ stages and between instruments was tested with repeated measure analysis of variance.

All statistical analyses were performed using SAS [96]. Strengthening the Reporting of Observational Studies in Epidemiology guidelines were followed [97].

Results

The medical records of 117 patients were reviewed from October 15, 2007, to May 2, 2008, and 64 were eligible. No patients were excluded by the primary oncologist. Telephone contact was established with 84.4% (54 of 64) of potential participants, and 35 (64.8%) completed the survey (overall response rate, 54.7%). Contact was not achieved for 10, largely because of no answer to the telephone call (8). The primary reasons for nonparticipation were not interested (47%) and deceased (32%). One respondent was ineligible because of undisclosed radiation. Data for 34 participants were included in the final analysis (Fig. 1).

Mean participant age was 61.3 years and cancer diagnoses were multiple myeloma [24], breast cancer (8), prostate cancer (1), and lung cancer (1) (Table 2). There were slightly more men (59%) and the majority of subjects were white (91%). The most common bisphosphonate received immediately prior to ONJ diagnosis was zoledronic acid (71%) (mean exposure, 2.3 years). With overall mean bisphosphonate exposure of 4.3 years, participants had received both intravenous (zoledronic acid [79%] and pamidronate [59%]) and oral (alendronate [6%] and risedronate [6%]) bisphosphonates. At the time of study, participants had been diagnosed with ONJ for a mean of 1.9 years (0.3–3.9 years), and most had stage 1 (50%) or stage 2 (32%) ONJ. The most common self-reported ONJ symptoms were exposed bone (76%), pain (62%), and infection (41%).

OHIP

In retrospective assessment of participant oral health, the mean frequency of all OHIP items increased after ONJ diagnosis, indicating worse QoL. This change was statistically significant after Bonferroni adjustment ($p < .0035$) for seven items: painful aching (+1.82), discomfort eating (+1.53), self-consciousness (+0.91), unsatisfactory diet (+1.32), interrupted meals (+1.15), irritability (+0.79), and decreased life satisfaction (+0.97) (Table 3). Composite OHIP scores significantly increased ($p < .001$) after ONJ (from 3.56 to 16.53, OHIP-ADD; from 7.00 to 17.50, OHIP-WS).

Preference-Based QoL

The mean QoL across respondents significantly decreased as ONJ severity increased ($p < .001$, for each evaluation method) (Fig. 2A). On the 0 (death) to 1 (perfect heath) QoL scale, mean QoL was highest (VAS, TTO, and EQ-5D, respectively) for cancer *without* ONJ (0.76, 0.86, 0.82) and lowest for ONJ stage 3 (0.37, 0.61, 0.32). The largest QoL change (VAS, EQ-5D, and TTO, respectively) occurred between ONJ stage 1 (0.69, 0.82, 0.78) and ONJ stage 2 (0.51, 0.67, 0.55).

On the 0 to 1 scale, mean QoL lost because of ONJ stage 3 was 0.51, 0.29, and 0.61 (VAS, TTO, and EQ-5D, respectively). The mean of these values (0.47) was similar to the QoL decrement from hip and vertebral fractures in women with osteoporosis (0.53) [98] (Fig. 2B). The mean QoL lost because of ONJ stage 2 was 0.33, 0.22, 0.33 (VAS, TTO, and EQ-5D, respectively). The mean of these values (0.29) was similar to the QoL decrement from urinary incontinence and bowel problems in prostate cancer patients (0.30) [99].

Each EQ-5D domain score significantly increased (lower QoL) as ONJ severity increased ($p < .001$, Fig. 2C). Domains that contributed most to declining QoL were pain/discomfort and anxiety/depression.

Consistent with published literature [78], VAS values were generally lower than TTO values, and differences among the three instruments was significant by health state ($p < .005$). However, contrast (pairwise) comparisons showed that TTO and EQ-5D QoL values were not significantly different for cancer *without* ONJ and *with* ONJ stage 1, whereas VAS and EQ-5D were not significantly different for cancer *with* ONJ stages 2 and 3.

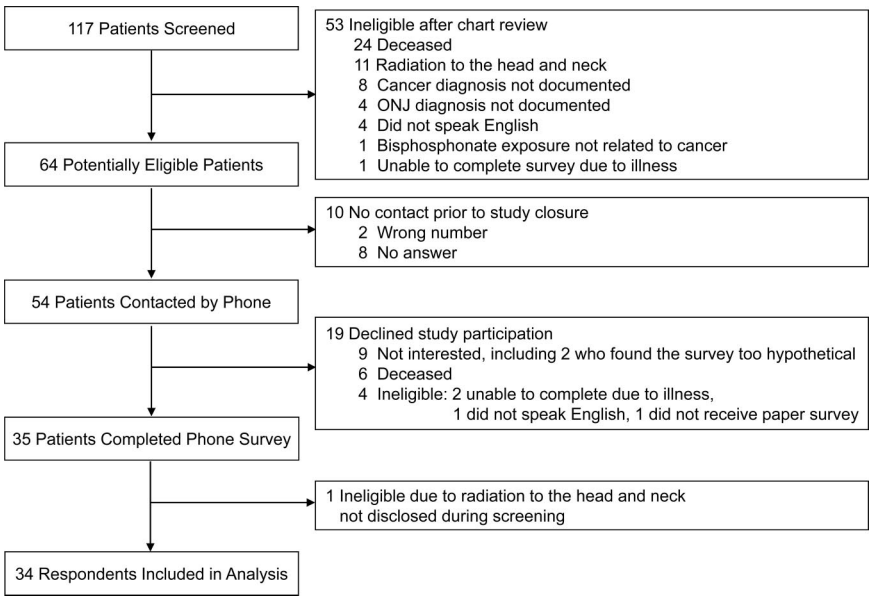

Figure 1. Enrollment of patients.

Emotional Discomfort

One patient (3%) found the survey "moderately" upsetting and 9 (26%) were "a little" upset. However, after survey completion only 6 (18%) still felt "a little" emotionally upset. All declined psychiatry referral. Early stopping rules were not met.

Discussion

This study provides the first empirical evidence that bisphosphonate-associated ONJ significantly impairs QoL, the effect increasing with ONJ stage severity. ONJ adversely affects a wide range of oral health–specific and overall QoL domains, as supported by the concordance of results for three preference-based QoL methods and psychometric oral health–specific data. The magnitude of the negative QoL effects of ONJ stages 2 and 3 are equivalent to other cancer treatment side effects that influence treatment decisions [99–101]. Similarly, ONJ QoL may be an important factor for patients and their physicians considering bisphosphonate therapy.

To our knowledge, this is the first evaluation of the QoL effects of long-term oral health complications of cancer treatments using methods suitable for comprehensive economic evaluation. All QoL instruments were sensitive to QoL differences by ONJ stage, and the ordinal relationship between QoL values elicited by each instrument followed published patterns [71, 76, 78]. The QoL values also corresponded with psychometric (OHIP) and EQ-5D domain results. Finally, the response rate was consistent with prior studies and respondent fatigue was minimal. These findings of sensitivity, practicality, face, construct, and convergent validity [102] support the use of preference-based QoL instruments to assess oral health complications.

The QoL implications of ONJ may be increasingly important if oral bisphosphonates also cause ONJ and recent studies expand the indication for intravenous bisphosphonates to patients with early breast cancer and other conditions [40–42, 103, 104]. Because ONJ is difficult to cure, otherwise healthy osteoporosis patients and cancer survivors may suffer long-term reduced QoL from ONJ. QoL information may, therefore, improve bisphosphonate treatment decision-making.

The potential mechanisms by which bisphosphonates induce ONJ remain unclear, hampering treatment and prevention [105–107]. In addition, the bone half-life of bisphosphonates may be as long as 10 years [108], the ONJ incidence is unpredictable [9, 12–24, 109, 110], and bisphosphonate "drug holidays" may not be medically appropriate for some cancer patients [9, 12–24, 109, 110]. Preventative dentistry may decrease ONJ incidence, but it unfortunately does not eliminate the risk [111, 112]. Our findings support early detection and treatment approaches that reduce ONJ severity to improve QoL and potentially allow continued bisphosphonate therapy.

The results of our study must be considered in the context of the limitations. For resource allocation decisions, some economists prefer societal preferences. However, feedback during survey development demonstrated that visual depictions necessary to educate nonpatients were considered graphic and biasing. For "at risk" patients, ethical concerns were raised about disclosing potential complications outside of a patient-clinician relationship. Moreover,

Table 2. Demographic and clinical presentation of participants

	No. (%) (n = 34)
Age (years)	
mean (SD)	61.3 (12.0)
Gender	
male	20 (59)
female	14 (41)
Race	
white	31 (91)
black	1 (3)
unknown	2 (6)
ONJ stage	
1	17 (50)
2	11 (32)
3	6 (18)
ONJ symptoms[a]	
pain	21 (62)
swelling	13 (38)
infection	14 (41)
loose teeth	9 (26)
exposed bone	26 (76)
broken bone	3 (9)
other[b]	4 (12)
Duration of ONJ (years)	
mean (SD)	1.9 (1.0)
Cancer and stage at diagnosis[c]	
multiple myeloma	24 (71)
stage I	4 (17)
stage II	6 (25)
stage III	13 (54)
unknown	1 (4)
breast	8 (24)
stage I	1 (13)
stage II	1 (13)
stage III	2 (25)
stage IV	2 (25)
unknown	2 (25)
prostate, stage II	1 (3)
lung, stage IV	1 (3)
Duration of cancer (years)	
mean (SD)	6.9 (2.9)
Duration of most recent bisphosphonate (years)	
24 zoledronic acid, mean (SD)	2.3 (1.3)
10 pamidronate, mean (SD)	3.8 (3.0)
Duration of total bisphosphonate exposure[d] (years)	
27 zoledronic acid, mean (SD)	2.2 (1.4)
20 pamidronate, mean (SD)	3.3 (2.7)
2 alendronate, mean (SD)	9.3 (8.1)
2 risedronate, mean (SD)	1.5 (0.7)
overall exposure, mean (SD)	4.3 (3.6)

[a]Total percentages do not equal 100 because some participants had multiple symptoms.
[b]One rough patch in mouth, one sliver of bone in mouth, one hole in mouth, and one tongue torn by bone.
[c]Total percentages do not equal 100 because of rounding.
[d]Some participants received multiple bisphosphonates.

patients experienced with at least one ONJ stage may be better able to distinguish QoL differences between standardized descriptions of all ONJ stages. Finally, prior work suggests cancer patients and volunteers give similar QoL values and any discrepancies favor conservative allocation decisions [113]. Therefore, we believe the patient cohort knowledge increases accuracy of stage-specific QoL values, minimizes ethical concerns, and avoids biases from visual depictions. This choice is supported by consistency between our EQ-5D societal preference results and other study findings.

Logistical considerations (short life expectancy of target population and relative patient scarcity) constrained the sample size, prevented testing/retesting, and may limit generalizability. However, our cohort was drawn from two institutions, the overall response rate (54.7%) was consistent with other telephone surveys [114], and time to ONJ development was similar to other studies [115]. Finally, study findings are statistically significant after correction for multiple comparisons and are clinically compelling.

The survey was designed to minimize cognitive burden: personal experience was assessed first, and standardized health states were presented with the most familiar state (cancer in the bone *without* ONJ) first. To familiarize participants with rank ordering, health states were first evaluated with VAS. The most complex task (TTO) was placed mid-survey to minimize fatigue. Although ordering effects were not directly tested, ordering did not appear to affect results because (1) baseline state (cancer in the bone *without* ONJ) results were similar to the literature [116–118], (2) data were well distributed (no floor/ceiling effect), and (3) VAS, TTO, and EQ-5D results were similar.

In summary, our findings suggest ONJ significantly affects the QoL of patients with cancer and may be an impor-

Table 3. Oral health status before and after ONJ as assessed by OHIP-14

		Pre-ONJ			Post-ONJ			Change			
Dimension	**Question**	**Mean**	**Range[a]**	**SD**	**Mean**	**Range[a]**	**SD**	**Mean**	**Range**	**SD**	***p*-Value**
Functional limitation	Did you have trouble *pronouncing any words* because of problems with your teeth or mouth?	0.21	[0, 3]	0.69	0.59	[0, 4]	1.13	0.38	[−2, 3]	0.95	0.04
	Did you feel that your *sense of taste* was worsened because of problems with your teeth or mouth?	0.06	[0, 1]	0.24	0.65	[0, 4]	1.32	0.59	[0, 4]	1.28	0.02
Physical pain	Did you have *painful aching* in your mouth?	0.53	[0, 4]	1.26	2.35	[0, 4]	1.65	1.82	[−3, 4]	2.05	<0.001[c]
	Did you find it *uncomfortable to eat any foods* because of problems with your teeth or mouth?	0.50	[0, 4]	1.02	2.03	[0, 4]	1.70	1.53	[−3, 4]	1.88	<0.001[c]
Psychological discomfort	Did you feel *self-conscious* because of problems with your teeth or mouth?	0.24	[0, 4]	0.96	1.15	[0, 4]	1.52	0.91	[0, 4]	1.36	<0.001[c]
	Did you *feel tense* because of problems with your teeth or mouth?	0.50	[0, 4]	1.24	1.50	[0, 4]	1.64	1.00	[−4, 4]	1.95	0.008
Physical disability	Was your *diet unsatisfactory* because of problems with your teeth or mouth?	0.15	[0, 3]	0.61	1.47	[0, 4]	1.69	1.32	[0, 4]	1.57	<0.001[c]
	Did you have to *interrupt meals* because of problems with your teeth or mouth?	0.06	[0, 2]	0.34	1.21	[0, 4]	1.72	1.15	[0, 4]	1.65	<0.001[c]
Psychological disability	Did you find it *difficult to relax* because of problems with your teeth or mouth?	0.44	[0, 4]	1.24	1.35	[0, 4]	1.63	0.91	[−4, 4]	1.93	0.01
	Were you a bit *embarrassed* because of problems with your teeth or mouth?	0.29	[0, 4]	1.00	0.88	[0, 4]	1.39	0.59	[0, 4]	1.13	0.004
Social disability	Were you a bit *irritable with other people* because of problems with teeth or mouth?	0.21	[0, 3]	0.69	1.00	[0, 4]	1.39	0.79	[0, 4]	1.27	0.0005[c]
	Did you have *difficulty doing your usual jobs* because of problems with your teeth or mouth?	0.06	[0, 2]	0.34	0.68	[0, 4]	1.20	0.62	[−1, 4]	1.23	0.006
Handicap	Did you feel that life in general was *less satisfying* because of problems with your teeth or mouth?	0.32	[0, 4]	1.01	1.29	[0, 4]	1.57	0.97	[−4, 4]	1.66	0.002[c]
	Were you totally *unable to function* because of problems with your teeth or mouth?	0.00	[0, 0]	0.00	0.38	[0, 4]	0.92	0.38	[0, 4]	0.92	0.02
	OHIP-ADD score	3.56	[0, 32]	7.20	16.53	[0, 48]	15.73	12.97	[−14, 48]	15.86	<0.001
	OHIP-WS[b] score	7.00	[4.37, 26.28]	5.46	17.50	[4.37, 44.61]	13.44	10.50	[−9.53, 40.24]	13.36	<0.001

[a]The frequency of each item per week was ranked on a five-point scale (4 = "6–7 per week", 3 = "4–5 per week", 2 = "2–3 per week", 1 = "once per week", and 0 = "never"), corresponding to the original OHIP-14 Likert-type scale (4 = "very often", 3 = "fairly often", 2 = "occasionally", 1 = "hardly ever", and 0 = "never") [80].
[b]After the Dimension-WSs were calculated by summing weighted raw item scores, each pre-ONJ Dimension-WS was standardized to a common mean and SD (1 ± 1) and each post-ONJ Dimension-WS was standardized to the mean and SD of the corresponding pre-ONJ Dimension-WS. Finally, standardized Dimension-WSs were summed to produce pre- and post-ONJ OHIP-WSs [80–82].
[c]Significant *p*-value is <0.0035 after Bonferroni adjustment.
Abbreviations: SD, standard deviation; WS, weighted score.

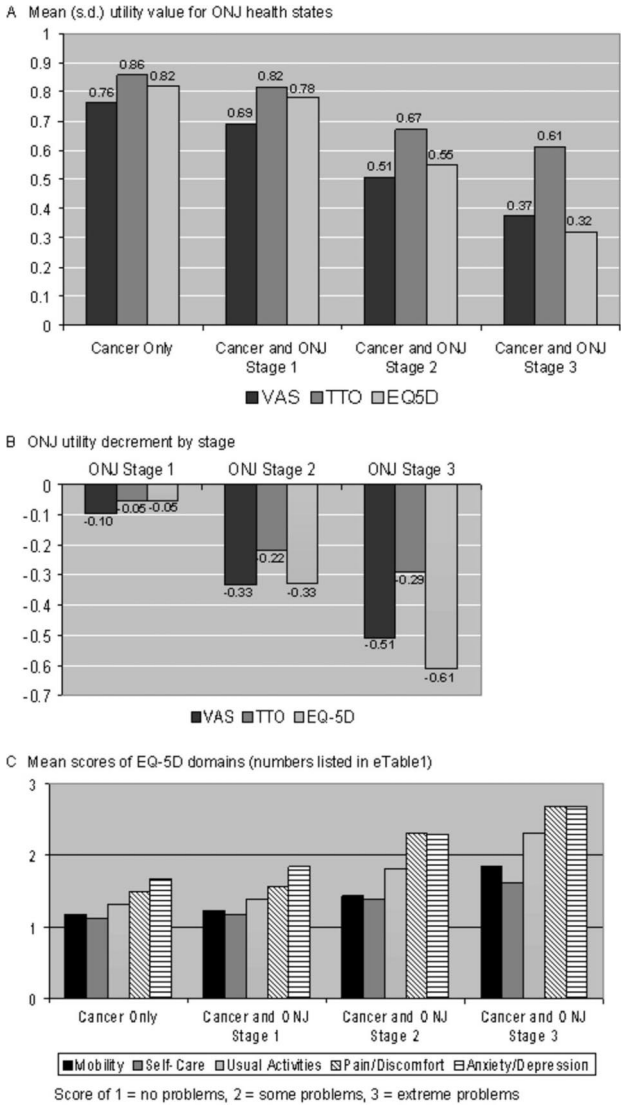

Figure 2. Preference-based QoL assessment. **(A):** Mean (SD) utility value for ONJ health states. **(B):** ONJ utility decrement by stage. **(C):** Mean scores of EQ-5D domains (numbers listed in supplemental online Table 1). Abbreviations: ONJ, osteonecrosis of the jaw; QoL, quality of life; TTO, Time Trade-off; VAS, Visual Analogue Scale.

tant consideration for intravenous and oral bisphosphonate treatment decisions by patients, clinicians, and policy makers. With the pending introduction of denosumab into routine clinical practice and the increasing longevity of cancer survivors, ONJ and its impact on QoL may become more frequently encountered issues. As the first assessment of long-term oral health complications of cancer therapy with findings validated by three QoL instruments and oral health–specific psychometric data, this work also serves as a benchmark. Additional studies are needed to further elucidate the relationship of ONJ pathophysiology and QoL and to establish the comparative value of bisphosphonates and other drugs, such as denosumab, used to prevent SREs.

Acknowledgments

R. Miksad was supported by the following grants during the conduct of this research: American Society of Clinical Oncology Young Investigator Award, Dana-Farber Harvard Cancer Center Timely Opportunity Award, the Program in Cancer Outcomes Research Training (5R25CA 092203-04) and the Department of Medicine, Beth Israel Deaconess Medical Center, and the Clinical Investigator Training Program: Beth Israel Deaconess Medical Center–Harvard/MIT Health Sciences and Technology, in collaboration with Pfizer Inc. and Merck & Co. Funding sources had no role in study design, data collection, data analysis, data interpretation, writing of this manuscript, or the decision to submit for publication.

Pilot study results were presented at the Annual International Meeting of the International Society for Pharmacoeconomics, Toronto, May 2008, and the American Society of Clinical Oncology Annual Meeting, Chicago, June 2008.

R. Miksad, K.C. Lai, and J.S. Swan had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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