

Dental health status and patient-reported outcomes at baseline in patients participating in the osteonecrosis of the jaw registry study, SWOG S0702

Catherine H. Van Poznak¹ · Amy Darke² · Carol M. Moinpour³ · Robert A. Bagramian⁴ · Mark M. Schubert⁵ · Julie R. Gralow⁶ · James L. Wade III⁷ · Joseph M. Unger²

Received: 4 August 2016 / Accepted: 21 November 2016
© Springer-Verlag Berlin Heidelberg 2016

Abstract

Purpose SWOG S0702 was a cohort study of patients with cancer with bone metastases due to any cancer. Using baseline data from S0702, this report characterizes the oral health and oral health-related quality of life (OHRQoL) of patients with advanced cancer.

Methods S0702 case report forms captured dental assessment and patient-reported outcome (PRO) data. This analysis compares PRO dental discomfort with selected clinical assessments of dental health. This analysis focuses on the 2294 patients who underwent baseline dental examination prior to

Structured Abstract: This report characterizes the oral health and OHRQoL of patients with advanced bone metastases receiving palliative therapy. These novel data serve as a foundation for future studies of interventions to maximize oral health and to positively impact OHRQoL in this patient population

Electronic supplementary material The online version of this article (doi:10.1007/s00520-016-3509-3) contains supplementary material, which is available to authorized users.

✉ Catherine H. Van Poznak
cvanpoz@umich.edu

¹ University of Michigan, Ann Arbor, MI 48109, USA

² SWOG Statistical Center, Fred Hutchinson Cancer Center, Seattle, WA, USA

³ Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA

⁴ School of Dentistry, University of Michigan, Ann Arbor, MI, USA

⁵ School of Dentistry, University of Washington, Seattle, WA, USA

⁶ University of Washington, Seattle, WA, USA

⁷ Heartland NCORP/Cancer Care Specialists of Central Illinois, Decatur, IL, USA

study registration, but also reports on the 1235 patients for whom only OHRQoL data are available. Dental characteristics including the number of teeth and the presence of gingivitis and periodontal disease were examined for correlation with PRO of oral pain, interference with eating, smiling, speech, or quality of life.

Results The median age of the study participants was 62. Greater than 60% of the 2294 patients with baseline dental assessments had none to mild plaque, calculus, gingivitis, or periodontal disease, suggesting that most of this cohort had good oral hygiene. However, in each of these same categories, approximately 6% had dental findings classified as severe conditions (poor oral hygiene). There was strong evidence that the presence of periodontal disease, gingivitis, and number of teeth was correlated with lower OHRQoL across multiple domains, including pain (mouth or jaw), interference with eating, smiling and speech, and overall quality of life.

Conclusions This report characterizes the oral health and OHRQoL of patients with advanced bone metastases receiving palliative therapy.

Trial registration [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00874211) Identifier: NCT00874211

Keywords Oral health · Cancer · Bone metastases · Patient-reported outcomes

Introduction

In the USA, it is estimated that well over one and a half million new cases of cancer will be diagnosed in 2016 [1]; of those who are not cured, many will develop distant metastases. The bone is a common site of distant spread in advanced disease, particularly in tumors originating in

the breast, prostate and lung. [2] Data generated from Medicare and MarketScan databases indicate that in 2008, there were approximately 280,000 adults in the USA with metastatic bone disease within the previous 5 years. [3] Metastases are the major cause of death from advanced cancer [4].

Palliative care is a critical component of cancer care and is structured to support the physical, emotional, spiritual and social needs of the patient [5]. Oral health-related quality of life (OHRQoL) [6, 7] is a component of overall health that is often noted when cancer therapy-induced mucositis or osteonecrosis of the jaw (ONJ) is present. Yet little is known about the general oral health and quality of life in patients with advanced cancer other than in tumors affecting the head and neck or undergoing stem cell transplantation.

Zoledronic acid (a bisphosphonate) is an FDA-approved drug that reduces skeletal-related events in patients with metastatic bone disease due to multiple myeloma and solid tumor such as breast cancer. Use of bisphosphonates reduces the risk of pathological fractures, hypercalcemia of malignancy, spinal cord compression, and need for surgery or radiation therapy to bone. However, for over a decade, there have been reported cases of ONJ in cancer patients receiving intravenous bisphosphonates, resulting in painful exposed necrotic bone in the mandible, maxilla, or both. Treatment of this condition has proven to be difficult and often unsuccessful. SWOG, a cooperative group within the National Clinical Trials Network, initiated study S0702, “A Prospective Observational Multicenter Cohort Study to Assess the incidence of Osteonecrosis of the Jaw in Cancer Patients with Bone Metastases Starting Zoledronic Acid Treatment”. S0702 was a large cohort study to assess the incidence and predictors of ONJ in cancer patients receiving zoledronic acid for bone metastases due to any cancer (clinicaltrials.gov identifier NCT00874211). For this study, patients’ dentists were asked to submit data from dental evaluations using a study-specific case report form. Patients were also regularly asked about their perception of dental discomfort. Thus, S0702 provides an excellent resource to examine issues surrounding OHRQoL in patients with cancer involving the bone. OHRQoL issues can be critically important for cancer patients if dental health affects a patient’s ability and willingness to continue cancer treatment. Interventions can improve the status of oral health, which, in turn, might improve a patient’s quality of life overall and improve adherence to treatment. Using baseline data from S0702, this report characterizes the oral health and oral health-related quality of life OHRQoL of patients with advanced cancer. We believed this information on the oral health and dental discomfort of these patients with advanced cancer is both valuable and novel.

Methods

Study population

To be eligible, patients must have had cancer involving the bone from any malignancy, must have been planning to receive zoledronic acid treatment within 30 days after registration, and must not have had a pre-existing diagnosis of ONJ. Patients who received prior bisphosphonates for low bone mass up to 3 years prior to registration, or who received prior bisphosphonates for metastatic bone disease up to 180 days prior to registration, were also allowed. The accrual goal was 3500 patients. Patients enrolled in S0702 remain in follow-up and the data are still maturing. The participating sites obtained institutional review board approval. Informed, written consent was obtained from all patients prior to enrollment. The primary analysis of study results will be reported in a later manuscript.

Patients were registered beginning January 30, 2009 and ending December 13, 2013. Before November 1, 2011, patients were required to undergo a baseline dental examination prior to registration. A study-specific letter to the oral health care provider, dental evaluation case report forms, and OHRQoL questions were included. The study letter to the dental provider defined a dental exam to include dental history and exam, periodontal exam, and dental imaging. After November 1, 2011, the protocol was amended to more accurately reflect community standard (which at most only recommend regular dental care) and, among other changes, the baseline dental examination was no longer required. For those patients undergoing dental care, the study-specific dental communication and dental evaluation case report forms were used. All enrolled patients were provided the OHRQoL questions. The objective of this analysis is to compare patient-reported dental discomfort at registration with selected clinical assessments of dental health. Baseline data on the S0702 cohort are provided in this report.

Patient-reported outcomes

The brief pain inventory (BPI) is a validated patient-reported outcome measure of pain in patients with cancer [8]; we adapted questions from the BPI for use patients with oral health complications. To collect patient-reported measures of dental discomfort, study site personnel were given five specific questions to ask patients about problems experienced in the patient’s mouth or jaw over the 3-month period prior to joining the study: (1) “Please rate your pain by selecting the one number that best describes your pain on the AVERAGE” [“Average pain”], (2) “Please rate how your oral health has interfered with your eating on AVERAGE” [“Interference with eating”], (3) “Please rate how oral health has interfered with how you smile on AVERAGE” [“Interference with

smile”], (4) “Please rate how oral health has interfered with how you speak on AVERAGE” [“Interference with speech”], (5) “Please rate how your oral health has interfered with your overall quality of life on AVERAGE” [“Interference with quality of life”]. All measures of dental discomfort were collected on an 11-point rating scale (0 to 10), with 0 indicating no problems (pain or interference) and 10 indicating extreme problems (pain or interference). Based on prior literature examining 11-point pain rating scales, we considered a difference of two or more points to be clinically meaningful [9].

Clinical measures of dental health

The dental communication informed the provider of the patient’s participation on S0702 and advised the provider to treat as clinically indicated. The S0702 dental case report form captured data regarding the number of teeth, presence of dentures, and periodontal examination (dental plaque, calculus, gingivitis, pocket depth). As clinical measures of dental health, we selected periodontal disease assessment (none, mild, moderate, severe), gingivitis assessment (none, mild, moderate, severe), number of maxillary teeth, number of mandibular teeth, and total number of teeth. The reporting was done by checking boxes on the case report form. A comment box was to be used as needed. These data were collected as part of the study dental assessments. This analysis focuses on periodontal and gingival assessments. To aid in interpretation, all clinical measures were dichotomized; periodontal disease and gingivitis were categorized as none, mild, or moderate (grouped together) versus severe, in order to reflect how the worst cases of disease might correlate with patient-reported outcomes on average. The number of maxillary, mandibular, and total teeth were categorized as greater or equal to the median versus less than the median.

Statistical methods

The primary analysis for this report was conducted in all eligible patients with available baseline dental status and patient-reported outcomes. We also considered that patients likely to have dentures (as indicated by self-report of full dentures or zero total teeth) might have a qualitatively different oral symptom experience. For instance, such patients might no longer have gingivitis or periodontal disease but might experience discomfort due to their denture. As such, a secondary sensitivity analysis excluded these patients in the examination of the correlations between gingivitis and periodontal disease with patient-reported outcomes. Differences between groups were assessed with chi-squared tests (when categorical) or *t* tests (when linear). Analyses were performed with SAS statistical software version 9.4 (SAS Institute, Cary, NC) and *p*-values are two sided. This analysis is considered

descriptive and hypothesis generating. As such, we did not control for multiple comparisons; $p < 0.05$ was considered statistically significant.

Results

In total, S0702 registered 3571 patients, of whom 42 were known to be ineligible or were missing the pre-study form, leaving 3529 patients eligible for this analysis. Patients were recruited from over 100 institutions in the USA. There were 2294 patients who underwent a baseline dental examination prior to registration, and who also completed a patient-reported pre-study form. This cohort represents the evaluable patients set for this analysis and the focus of this report.

Patient demographic, behavioral, and clinical characteristics

Table 1 shows characteristics of patients registered to S0702. The characteristics of all eligible patients are shown in column A. Forty-two percent of patients were >65 years with a median age of 62 years and slightly more than half were female. Black patients comprised nearly 11% of the cohort and Hispanic patients nearly 6%. The most common cancer types were breast (32%) and prostate (20%). Most patients were not current smokers (87%), rarely drank (80% drank ≤ 3 /month), and had good performance status (0–1; 88%). Results to assess whether evaluable patients differed from non-evaluable patients are shown in columns B and C, respectively. The evaluable patients were less likely to be black and current smokers, but were more likely to have ≥ 1 drink per week and to have better performance status. However, distributions by age, sex, ethnicity, and presence of ≥ 1 comorbid condition were approximately similar between the groups.

Patient dental characteristics

Table 2 shows clinical assessments of dental health for those patients in the analysis set. Of note, half of patients reported having 26 or more natural teeth (with 297 patients (13%) reporting either 0 maxillary or 0 mandibular teeth), and 22% reported partial or complete dentures.

Patient-reported outcomes

Table 3 shows patient-reported outcomes for all eligible patients and contrasts those in the evaluable analysis set with those not evaluable. Overall, most patients reported no problems, with over 75% of those reporting 0 (no problem) on all

Table 1 Baseline patient characteristics

Characteristic	A. All patients(<i>n</i> = 3529)		B. Analysis set (<i>n</i> = 2294)		C. Not in analysis set (<i>n</i> = 1235)		B vs C χ^2 <i>p</i> value
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Age							0.048
≤55	876	24.8	536	23.4	340	27.5	0.006
56–65	1167	33.1	771	33.6	396	32.1	0.35
66–75	978	27.7	644	28.1	334	27.0	0.51
>75	508	14.4	343	15.0	165	13.4	0.20
Sex							0.15
Female	1821	51.6	1204	52.5	617	50.0	
Male	1708	48.4	1090	47.5	618	50.0	
Race							<.0001
White	2970	84.2	1956	85.3	1014	82.1	0.014
Black	381	10.8	194	8.5	187	15.1	<.0001
Asian	57	1.6	46	2.0	11	0.9	0.012
Other	121	3.4	98	4.3	23	1.9	0.0002
Ethnicity							0.46
Not Hispanic/Latino	3218	94.3	2083	94.1	1135	94.7	
Hispanic/Latino	193	5.7	130	5.9	63	5.3	
Unknown	118		81		37		
Current smoker							<.0001
Yes	435	12.3	214	9.3	221	17.9	
No	3091	87.7	2077	90.7	1014	82.1	
Not answered	3		3		0		
Cancer type							<.0001
Breast	1134	32.1	765	33.3	369	29.9	0.035
Multiple myeloma	587	16.6	385	16.8	202	16.4	0.75
Prostate	714	20.2	508	22.1	206	16.7	0.0001
Lung	673	19.1	386	16.8	287	23.2	<.0001
Other	421	11.9	250	10.9	171	13.8	0.010
Performance status							<.0001
0–1	3092	87.6	2072	90.3	1020	82.6	
≥2	437	12.4	222	9.7	215	17.4	
Alcoholic drinks in past 3 months							<.0001
Never or <1/month	2258	64.1	1401	61.2	857	69.4	<.0001
1–3 per month	549	15.6	373	16.3	176	14.3	0.11
≥1 per week	718	20.4	516	22.5	202	16.4	<.0001
Not answered	4		4		0		
Comorbidities reported							
Reports any condition below	1169	33.1	767	33.4	402	32.6	0.59
Auto-immune disease	81	2.3	51	2.2	30	2.4	0.70
Chronic infection (including HIV/AIDS)	33	0.9	20	0.9	13	1.1	0.59
Coagulopathy or blood clotting problems	156	4.4	103	4.5	53	4.3	0.78
Diabetes	546	15.5	345	15.0%	201	16.3	0.33
Malnutrition	20	0.6	8	0.3%	12	1.0	0.019
Osteoporosis or osteopenia	430	12.2	320	13.9%	110	8.9	<.0001
Paget's disease of bone or metabolic bone disease	15	0.4	11	0.5%	4	0.3	0.50
Renal failure or renal insufficiency	122	3.5	76	3.3%	46	3.7	0.52

questions in all subgroups. Those included in the analysis set had slightly lower average discomfort ratings on all questions than those not included in the analysis set (for example, 0.90 Average pain not in Analysis Set vs 0.78 Average pain Analysis Set, $p = 0.06$); however, none of these differences were clinically significant (all were less than two points on an 11-point scale) and none of these differences were statistically significant.

Correlations between baseline dental characteristics and patient-reported outcomes

We examined the clinical correlations between dental status and patient-reported outcomes. Given that more than 75% of patients reported no problems for all of the patient-reported outcomes (Table 3), to aid in the interpretation, we dichotomized the measures of patient-reported

Table 2 Baseline dental characteristics

Characteristic	Analysis set (<i>n</i> = 2294)	
	<i>n</i>	%
Dental visit within the last 6 months		
No	114	5.0
Yes	2180	95.0
Number of dental cleanings within the past 2 years		
0	555	25.3
1	325	14.8
2	276	12.6
3	272	12.4
4	550	25.0
>4	220	10.0
Unknown	96	
Prior oral surgery		
No	548	24.8
Yes	1663	75.2
Number of extractions		
1–3	602	38.1
>3	980	61.9
Unknown number of extractions	81	
Unknown	83	
Prior periodontal treatments		
No	1599	75.0
Yes	534	25.0
Unknown	161	
Dental implants		
No	2115	94.4
Yes	126	5.6
Number of implants		
1–3	86	69.9
>3	37	30.1
Unknown number of implants	3	
Unknown	53	
Tori present		
No	1655	80.8
Yes	393	19.2
Unknown	246	
Plaque		
None	210	9.8
Mild	1241	58.0
Moderate	558	26.1
Severe	132	6.2
Unknown	153	
Calculus		
None	324	15.1
Mild	1187	55.4
Moderate	511	23.9
Severe	120	5.6
Unknown	152	
Gingivitis		
None	541	25.3
Mild	1048	49.1
Moderate	421	19.7
Severe	126	5.9
Unknown	158	
Periodontal disease		
None	623	32.6
Mild	801	41.9
Moderate	355	18.6
Severe	131	6.9
Unknown	384	
Number of teeth		
0–20	594	26.6
21–25	526	23.6

Table 2 (continued)

Characteristic	Analysis set (<i>n</i> = 2294)	
	<i>n</i>	%
26–28	871	39.1
>28	238	10.7
Unknown	65	
Dentures, partial, or complete		
No	1745	78.1
Yes	489	21.9
Unknown	60	

discomfort, contrasting 0 scores (no problem) with any report of problems (>0). For each patient-reported outcome, patients with severe periodontal disease or gingivitis were much more likely ($p < 0.01$ in all cases) to have worse patient-reported outcomes (Fig. 1a, b). While power to analyze correlations within the five major groups of cancers on S0702 (breast, prostate, lung, multiple myeloma, and other) was limited, a sensitivity analysis showed similar patterns of association in all five cancer subgroups (data not shown). When patients likely to have full dentures were excluded, the results were very similar (Fig. 1c, d). Similarly, patients with fewer maxillary or mandibular teeth were much more likely ($p < .01$ in all cases) to have worse patient-reported outcomes (Fig. 2a, b). Finally, we examined the correlations between patient-reported outcomes and the total number of teeth (Fig. 2c); again, there was a strong correlation between fewer teeth and worse patient-reported outcomes. Thus, the finding of a very strong correlation between baseline dental health and patient-reported outcomes was consistently strong across all correlative analyses.

Discussion

This report defines the OHRQoL and associated clinical dental assessments in patients with metastatic bone disease. The study population was drawn from community and academic oncology clinics across the USA with the median age of 62 and with 15% of participants being non-white. In the 2294 patients who had dental evaluations, the majority (>60%) had none to mild plaque, calculus, gingivitis, or periodontal disease, suggesting that most of this cohort had good oral hygiene. However, in each of these same categories, approximately 6% had dental findings classified as severe conditions (poor oral hygiene). There was strong evidence that the presence of periodontal disease, gingivitis, and fewer teeth was correlated with lower OHRQoL across multiple domains, including pain

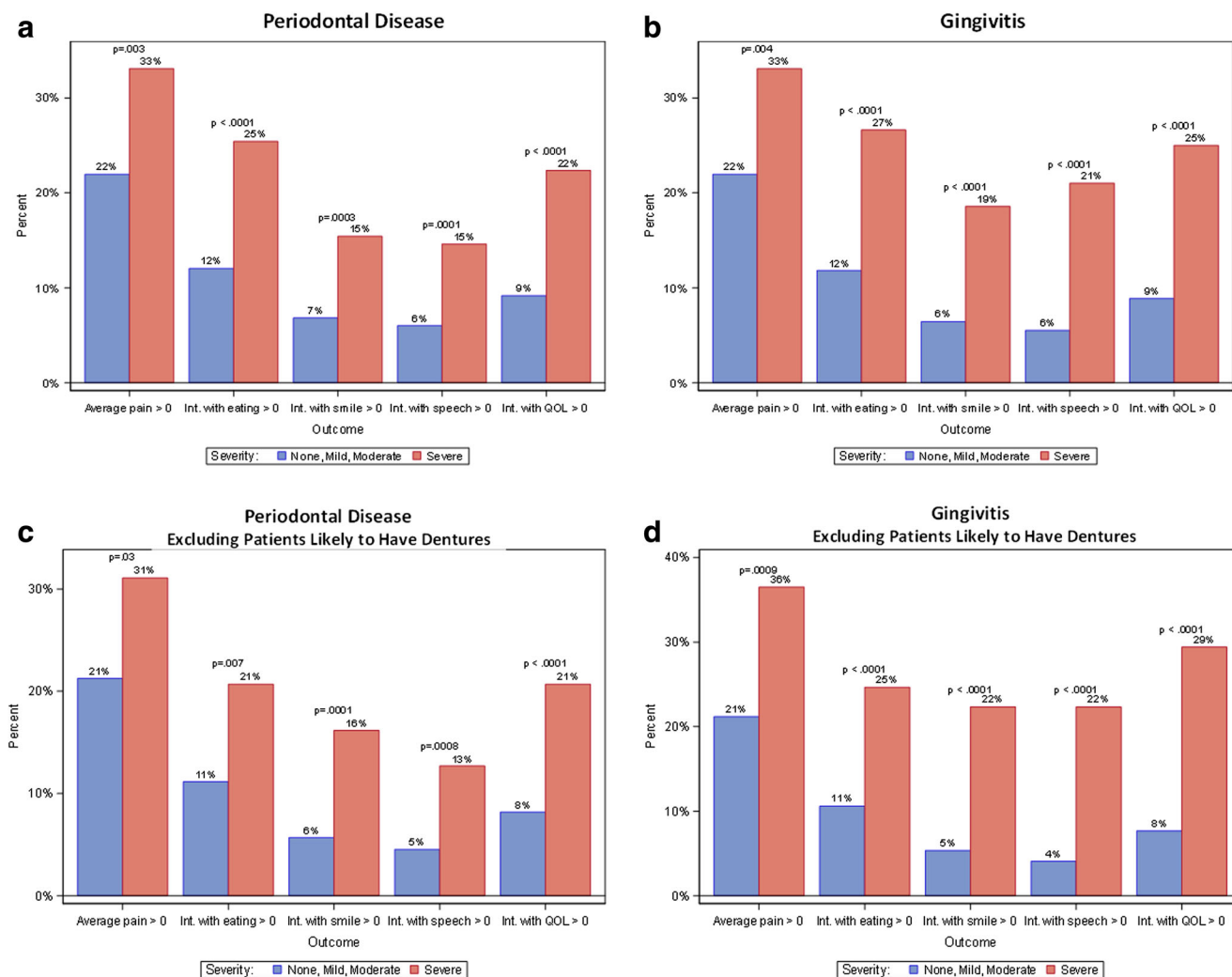
Table 3: Baseline patient-related outcomes

Patient-reported outcome	A. All patients with pre-study Form(<i>n</i> = 3529)		B. Analysis set(<i>n</i> = 2294)		C. Not in analysis set(no dental exam)(<i>n</i> = 1235)		<i>t</i> test/ <i>p</i> value
	Mean (SD)	% 0 scores(no problem)	Mean (SD)	% 0 scores(no problem)	Mean (SD)	% 0 scores(no problem)	
Average pain	0.82 (1.85)	76.3%	0.78 (1.78)	76.8%	0.90 (1.98)	75.5%	0.06
Interference with eating	0.50 (1.54)	86.4%	0.49 (1.52)	86.8%	0.53 (1.58)	85.8%	0.48
Interference with smile	0.32 (1.37)	92.0%	0.30 (1.33)	92.7%	0.36 (1.43)	90.7%	0.24
Interference with speech	0.23 (1.07)	93.2%	0.23 (1.07)	93.3%	0.24 (1.06)	93.0%	0.96
Interference with quality of life	0.35 (1.29)	89.4%	0.34 (1.27)	89.8%	0.38 (1.34)	88.6%	0.37

For all questions and groups of patients shown, the median value was 0 (no problem) and the range 0 to 10

(mouth or jaw), interference with eating, smiling and speech, and overall quality of life. The data generated from S0702 are consistent with what would be empirically expected, yet are novel data for this patient population.

A recent publication estimated the prevalence of severe periodontitis in the USA to be slightly less than 9% in adults aged 30 to 79 years; [10] approximately 7% of S0702 participants had severe periodontitis. The results

**Fig. 1.** Periodontal disease and patient-reported outcomes

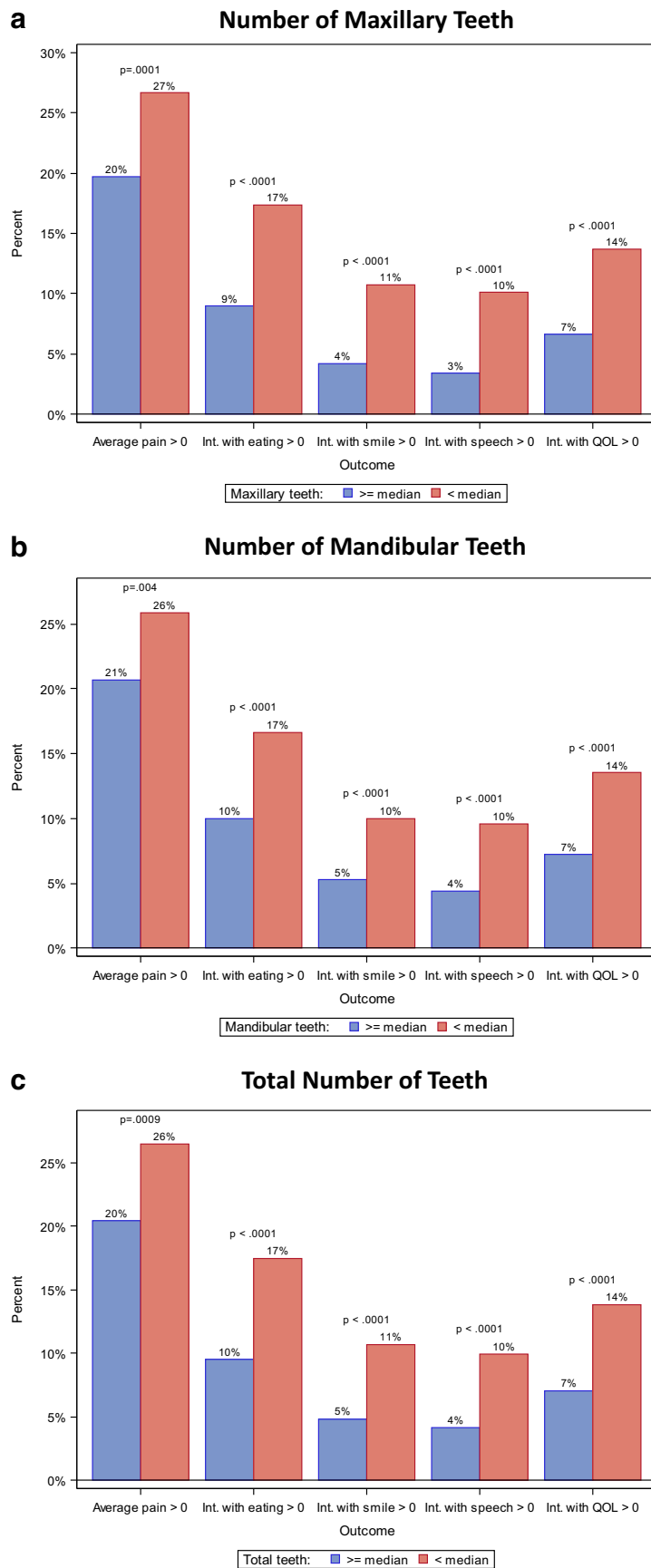


Fig. 2. Teeth and patient-reported outcomes

of this analysis illustrate an area where additional attention may be given to aid palliative interventions for patients with metastatic bone disease.

It is estimated that over a quarter million patients in the USA have metastatic bone disease [3], and the S0702 study population sheds insight into the oral health of this patient population. If the overall population with metastatic bone disease has a similar frequency of poor oral hygiene (6%), then approximately 15,000 patients would be affected. The Surgeon General's Report on Oral Health in America highlights the importance of oral health for its ability to impact the ability to eat, food choices, appearance, and communication [11]. Indeed, the Surgeon General's Report identifies the mouth as the center of vital functions that are critical to total health and well-being. With this in mind, patients with advanced cancer may benefit from optimizing oral health as a palliative intervention.

Conditions affecting the oral cavity can be wide ranging. In the general population, there is a correlation between oral health and overall health as noted in patients with cardiovascular disease and diabetes [11]. Tooth loss has been shown to affect food choice and overall nutritional status [11]. Gingivitis and periodontal disease can lead to tooth loss, but the direct impact of gingivitis and periodontal disease on food choice has not been documented. Sensitive teeth hurt when exposed to hot, cold, and/or acidic foods and beverages; those with sensitive teeth may avoid foods that cause pain. [11] In addition the condition of the oral cavity may influence speech, socialization, and self-confidence [11].

Data on the general US population suggest that in 2013, approximately 40% of the adult population did not have a dental visit within the past year. [12] In S0702, approximately one third of enrolled patients did not have a dental exam within 6 months of study entry (1227/3529), which is roughly consistent with the typical US experience. Moreover, S0702 was designed to capture a broad spectrum of patients receiving zoledronic acid that was representative of the cancer treatment population. To that end, eligibility criteria were broadly written. Within the study, however, there were differences between those patients who did ($N = 2294$) and did not ($N = 1277$) have a baseline dental assessment, suggesting that the analyzed cohort was a somewhat selected patient group. Most notably, S0702 participants not in the analysis set were more likely to be black, current smokers, and to have a higher performance status. S0702 does not permit analysis by insurance type but it is notable that S0702 provided funds for the baseline dental assessment on an as needed basis. The reason why 34% of overall S0702 enrolled patients did not undergo baseline assessments is not evaluable from the study data.

This study has limitations. The patient-reported outcomes may not have been collected synchronously with the dental assessments because S0702 allowed a 6-month time window for the dental assessments, which is within the American

Dental Association standard time frame for dental care [13]. The significance of this 6-month time window on OHRQoL is unknown. S0702 did not collect data on dental insurance, income, or education. Patients who participate in SWOG clinical trials may reflect higher education and income levels than the general population. [14, 15] These factors in the general population correlate with oral health. [12, 13] How these factors impact the study population cannot not be analyzed from the present S0702 data. But the study also has notable strengths. Unique findings in the S0702 baseline dental assessments paired with the patient-reported outcomes add to the OHRQoL and health care literature. The sample was large, including over 2000 evaluable patients. The data were collected prospectively. Also, the sample represented a demographically and clinically diverse range of patients. Although the study did not formally adjust for multiple comparisons, nearly all of the observed correlations between dental status and patient-reported outcomes would have been statistically significant even under a conservative Bonferroni multiple comparisons approach. We plan to extend our examinations of these data to include clinical outcomes, including survival, after follow-up for the study has been completed.

Baseline assessments of the 2294 patients enrolled in S0702 who had dental care within 6 months of study entry confirms the importance of OHRQoL in patients with advanced cancer involving the bone. Across all patient-reported outcomes, the more severe the dental periodontal or gingivitis condition, the greater negative effect on pain, eating, smiling, speech, and overall OHRQoL. There are established, standard interventions to improve oral health [12], [16, 17]; however, insurance coverage, personal preference, and access to care, as well as other factors may serve as barriers for seeking dental care [11]. This report serves as a foundation for future studies to further assess how oral health and interventions to maximize oral health can impact QoL, OHRQoL, and financial expenditures (personal and other), as well as whether factors associated with oral health interfere with care of the underlying cancer.

Acknowledgements Danika L. Lew, MD, provided statistical assistance; Lisa Hansen, RN, MS, provided clinical input; and Kimberly Kaberle and Diane Liggett, BS, were responsible for protocol coordination and data management.

No compensation was received beyond their salary for this work.

Compliance with ethical standards The participating sites obtained institutional review board approval. Informed, written consent was obtained from all patients prior to enrollment.

Conflict of interest The authors declare that they have no conflicts of interest. SWOG and the authors have full control of the primary data. We agree to allow the journal to review aggregate level data, if requested.

Funding Funding for this work was provided National Institutes of Health, National Cancer Institute, NCI Community Oncology Research Program (NCORP) Research Base grant, 5UG1CA189974.

References

1. Siegel RL, Miller KD, Jemal A (2016) Cancer statistics, 2016. *CA Cancer J Clin* 66(1):7–30
2. Coleman RE (2001) Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 27(3):165–176
3. Li S, Peng U, Weinhandl ED, et. al. Estimated number of prevalent cases of metastatic bone disease in the US adult population. *Clinical Epidemiology* 2012;4:87–93
4. World Health Organization <http://www.who.int/mediacentre/factsheets/fs297/en/> Accessed 31 May 2016
5. Smith TJ, Temin S, Alesi ER et al (2012) American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care. *J Clin Oncol* 30(8):880–887
6. Sischo L, Broder HL (2011) Oral health-related quality of life: what, why, how, and future implications. *Critical Reviews in Oral Biology & Medicine* 90(11):1264–1270
7. Bennadi D, Reddy CVK (2013) Oral health related quality of life. *Journal of International Society of Preventive & Community Dentistry* 3(1):1–6
8. Cleeland CS, Ryan KM (1994) Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singap* 23(2):129–138
9. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 94(2):149–158
10. Eke PI, Zhang X, Lu H et al (2016) Predicting periodontitis at state and local levels in the United States. *J Dent Res* 95(5):515–522
11. U.S. Department of Health and Human Services. Oral health in America: a report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, National Institute of Dental and Craniofacial Research, National Institutes of Health, 2000.
12. Center for Disease Control and Prevention; oral and dental health. <http://www.cdc.gov/nchs/fastats/dental.htm>
13. American Dental Association guidelines; update and recommendations. American Dental Association Council on Scientific Affairs (2006) *J Am Dent Assoc* 137:1304–1312
14. Unger JM, Hershman DL, Albain KS, Moinpour CM, Petersen JA, Burg K, Crowley JJ (2013) Patient income level and cancer clinical trial participation. *J Clin Oncol* 31(5):536–542. doi:10.1200/JCO.2012.45.4553
15. Unger JM, Gralow JR, Albain KS, Ramsey SD, Hershman DL (2016) Patient income level and cancer clinical trial participation: a prospective survey study. *JAMA Oncol* 2(1):137–139
16. American Dental Association <http://www.ada.org>
17. Center for Disease Control and Prevention; oral health for adults https://www.cdc.gov/oralhealth/publications/factsheets/adult_oral_health/adults.htm accessed 5-31-2016