Supplementary Online Content

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eFigure 1. Geographic Distribution of US Enrollments to S0702

eFigure 2. Hazard Risk of Confirmed Osteonecrosis of the Jaw (ONJ) by Baseline Factors

eFigure 3. Hazard Risk of Confirmed Plus Suspected ONJ by Baseline Predictors

eTable 1. Patient Characteristics by Baseline Dental Examination Status

eTable 2. Cumulative Incidence of ONJ

eTable 3. Description of Lesions

eTable 4. Patient-Reported Outcomes of Oral Health–Related Quality of Life

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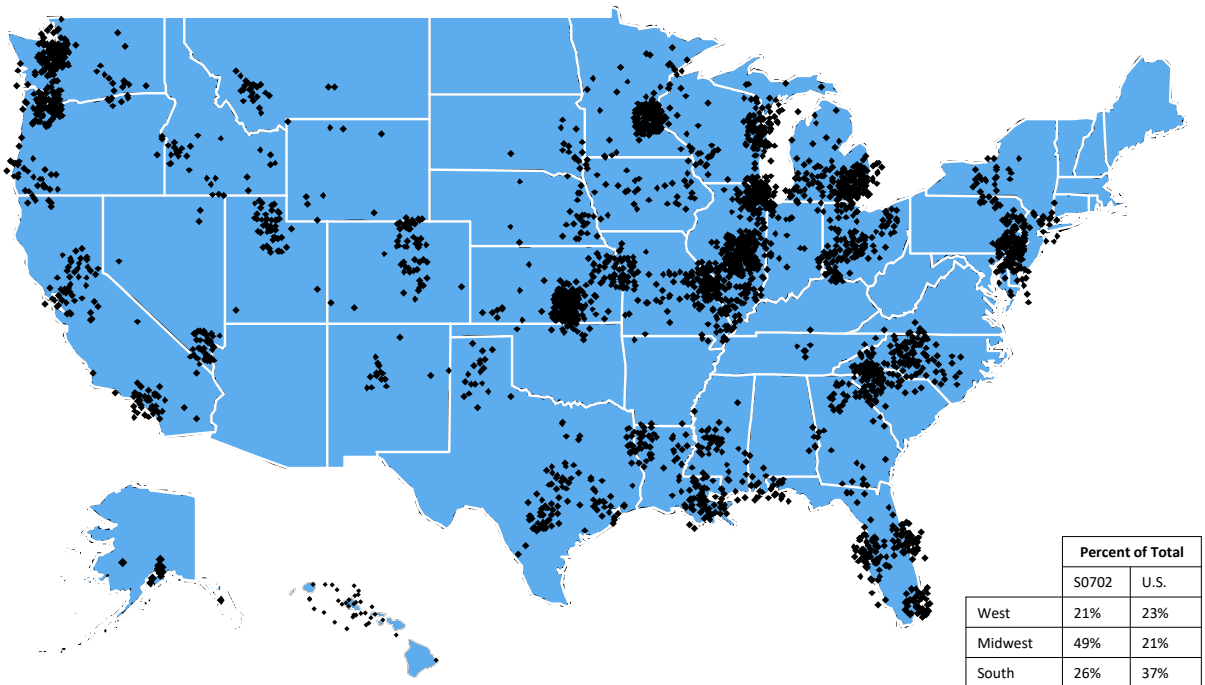
eFigure 1. Geographic Distribution of US Enrollments to S0702



	Percent of Total	
	S0702	U.S.
West	21%	23%
Midwest	49%	21%
South	26%	37%
Northeast	4%	18%

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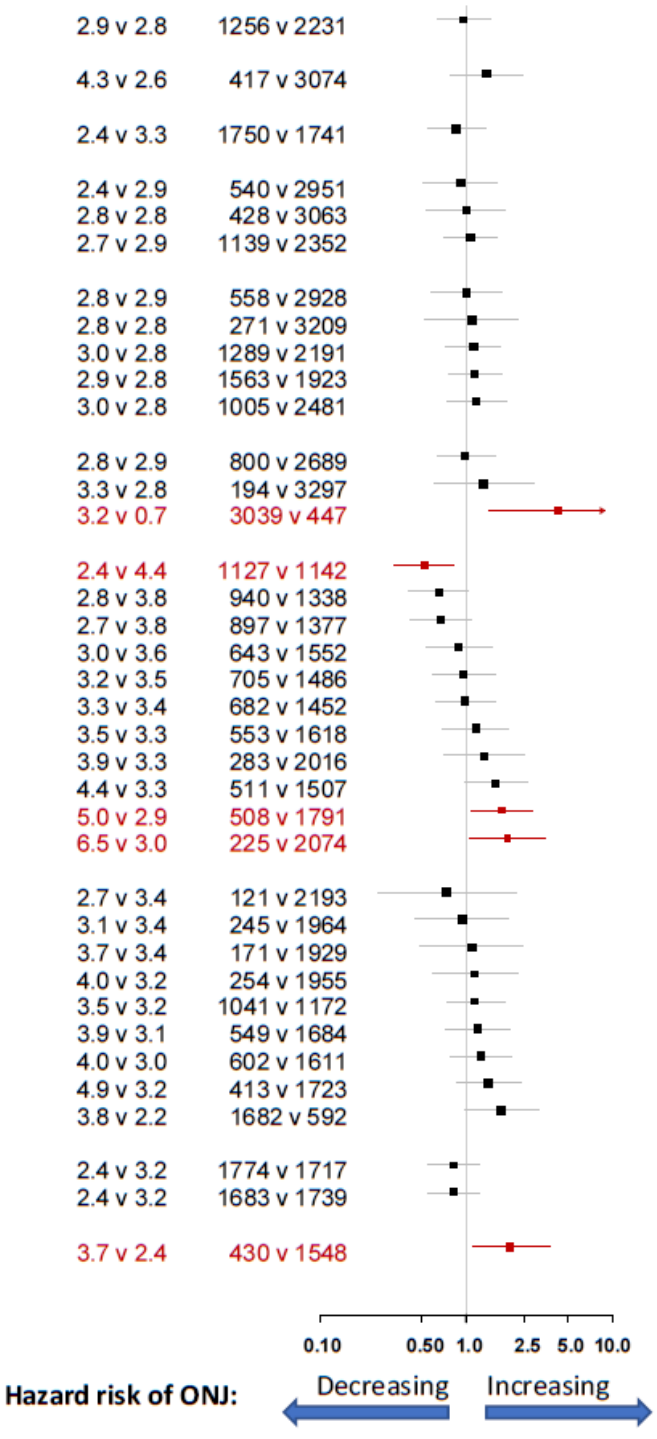
eFigure 2. Hazard Risk of Confirmed Osteonecrosis of the Jaw (ONJ) by Baseline Factors

CATEGORY and FACTOR	Hazard Ratio (95% CI)	p-value	3-Year CI (Yes vs. No, %)	Sample Sizes (Yes vs. No, N)
ALCOHOL USE				
Alcoholic drinks/yr > median	0.97 (0.63 - 1.50)	0.898	2.9 v 2.8	1256 v 2231
ANTI-ANGIOGENIC EXPOSURE				
Past Exposure to anti-angiogenic therapy	1.42 (0.78 - 2.58)	0.251	4.3 v 2.6	417 v 3074
CANCER HISTORY				
Time from dx to bone disease > median	0.86 (0.54 - 1.39)	0.548	2.4 v 3.3	1750 v 1741
COMORBID DISEASES				
Diabetes	0.92 (0.50 - 1.69)	0.786	2.4 v 2.9	540 v 2951
Osteoporosis or osteopenia	1.01 (0.53 - 1.90)	0.981	2.8 v 2.8	428 v 3063
Any comorbidity	1.10 (0.70 - 1.71)	0.687	2.7 v 2.9	1139 v 2352
CORTICOSTEROID THERAPY				
Past steroids	1.02 (0.57 - 1.81)	0.951	2.8 v 2.9	558 v 2928
Steroids, >= 6 months	1.11 (0.51 - 2.40)	0.796	2.8 v 2.8	271 v 3209
Steroids, < 6 months	1.14 (0.72 - 1.80)	0.579	3.0 v 2.8	1289 v 2191
Any steroids	1.17 (0.75 - 1.83)	0.497	2.9 v 2.8	1563 v 1923
Current steroids	1.20 (0.73 - 1.98)	0.474	3.0 v 2.8	1005 v 2481
OSTEOCLAST INHIBITOR EXPOSURE				
Planned ZA duration <= 2 yrs	1.00 (0.62 - 1.64)	0.984	2.8 v 2.9	800 v 2689
Prior osteoclast inhibitor	1.36 (0.59 - 3.12)	0.474	3.3 v 2.8	194 v 3297
Planned ZA dosing interval=Q 3-4 wks	4.65 (1.46 - 14.81)	0.009	3.2 v 0.7	3039 v 447
PRE-EXISTING DENTAL DISEASE				
Number of teeth (total) > median	0.51 (0.31 - 0.83)	0.006	2.4 v 4.4	1127 v 1142
Number of mandibular teeth > median	0.64 (0.39 - 1.06)	0.082	2.8 v 3.8	940 v 1338
Number of maxillary teeth > median	0.67 (0.40 - 1.10)	0.115	2.7 v 3.8	897 v 1377
Calculus moderate or severe	0.89 (0.52 - 1.54)	0.687	3.0 v 3.6	643 v 1552
Dental plaque moderate or severe	0.97 (0.58 - 1.63)	0.909	3.2 v 3.5	705 v 1486
Number of caries > median	1.00 (0.60 - 1.68)	0.995	3.3 v 3.4	682 v 1452
Gingivitis moderate or severe	1.19 (0.69 - 2.06)	0.53	3.5 v 3.3	553 v 1618
Complete dentures	1.37 (0.70 - 2.70)	0.354	3.9 v 3.3	283 v 2016
Periodontal disease moderate or severe	1.65 (0.98 - 2.79)	0.061	4.4 v 3.3	511 v 1507
Any dentures	1.83 (1.10 - 3.03)	0.02	5.0 v 2.9	508 v 1791
Removable dentures	2.02 (1.08 - 3.78)	0.028	6.5 v 3.0	225 v 2074
PRIOR DENTAL PROCEDURES				
Any implants	0.73 (0.23 - 2.32)	0.59	2.7 v 3.4	121 v 2193
Minor periodontal treatments	0.94 (0.43 - 2.05)	0.874	3.1 v 3.4	245 v 1964
Prior orthodontics	1.11 (0.47 - 2.62)	0.813	3.7 v 3.4	171 v 1929
Intermediate periodontal treatments	1.17 (0.58 - 2.37)	0.655	4.0 v 3.2	254 v 1955
>3 extractions	1.18 (0.73 - 1.90)	0.506	3.5 v 3.2	1041 v 1172
Any periodontal treatments	1.23 (0.72 - 2.09)	0.444	3.9 v 3.1	549 v 1684
1-3 extractions	1.29 (0.77 - 2.15)	0.331	4.0 v 3.0	602 v 1611
Tori	1.46 (0.86 - 2.51)	0.165	4.9 v 3.2	413 v 1723
Any oral surgery	1.81 (0.97 - 3.38)	0.061	3.8 v 2.2	1682 v 592
RADIOTHERAPY				
Any RT	0.83 (0.54 - 1.27)	0.388	2.4 v 3.2	1774 v 1717
Total cGy > median	0.83 (0.54 - 1.28)	0.404	2.4 v 3.2	1683 v 1739
SMOKING HISTORY				
Current smoker	2.12 (1.12 - 4.02)	0.022	3.7 v 2.4	430 v 1548



The boxes show the hazard ratio (HR) and the horizontal lines represents the 95% CIs. The vertical line is the line of equal hazard. ZA indicates zoledronic acid.

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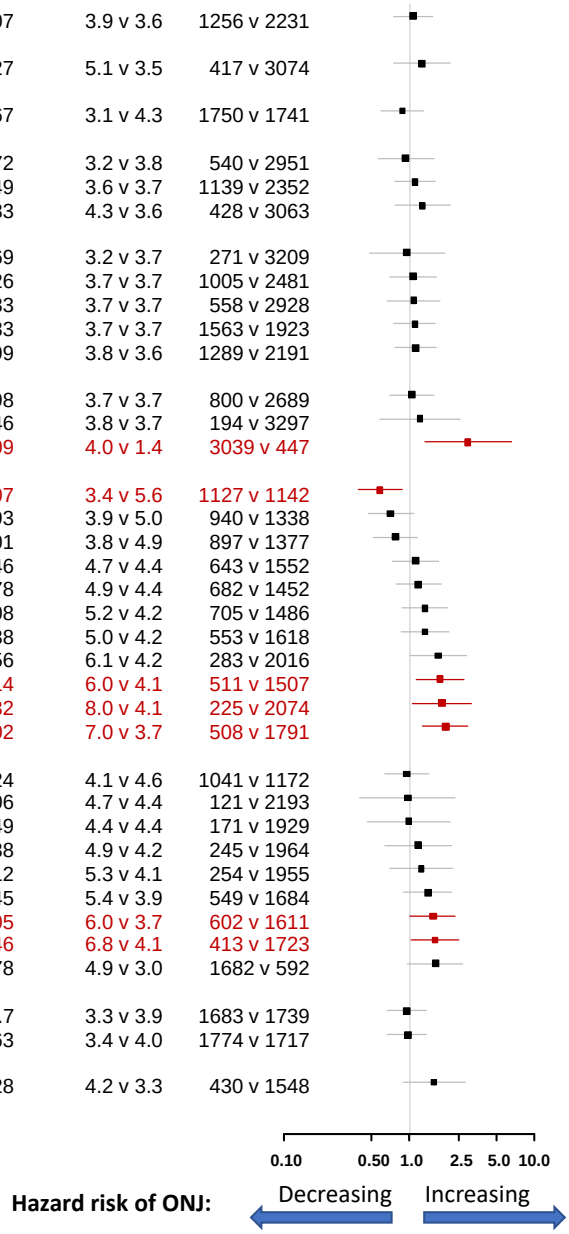
eFigure 3. Hazard Risk of Confirmed Plus Suspected ONJ by Baseline Predictors

CATEGORY and FACTOR	Hazard Ratio (95% CI)	p-value	3-Year CI (Yes vs. No, %)	Sample Sizes (Yes vs. No, N)
ALCOHOL USE				
Alcoholic drinks/yr > median	1.05 (0.72 - 1.52)	0.807	3.9 v 3.6	1256 v 2231
ANTI-ANGIOGENIC EXPOSURE				
Past Exposure to anti-angiogenic therapy	1.24 (0.73 - 2.13)	0.427	5.1 v 3.5	417 v 3074
CANCER HISTORY				
Time from dx to bone disease > median	0.86 (0.57 - 1.30)	0.467	3.1 v 4.3	1750 v 1741
COMORBID DISEASES				
Diabetes	0.92 (0.55 - 1.57)	0.772	3.2 v 3.8	540 v 2951
Any comorbidity	1.09 (0.74 - 1.61)	0.649	3.6 v 3.7	1139 v 2352
Osteoporosis or osteopenia	1.26 (0.75 - 2.12)	0.383	4.3 v 3.6	428 v 3063
CORTICOSTEROID THERAPY				
Steroids, >= 6 months	0.94 (0.46 - 1.93)	0.869	3.2 v 3.7	271 v 3209
Current steroids	1.05 (0.67 - 1.64)	0.826	3.7 v 3.7	1005 v 2481
Past steroids	1.07 (0.65 - 1.76)	0.783	3.7 v 3.7	558 v 2928
Any steroids	1.09 (0.73 - 1.61)	0.683	3.7 v 3.7	1563 v 1923
Steroids, < 6 months	1.11 (0.75 - 1.66)	0.599	3.8 v 3.6	1289 v 2191
OSTEOCLAST INHIBITOR EXPOSURE				
Planned ZA duration<=2 yrs	1.03 (0.67 - 1.57)	0.898	3.7 v 3.7	800 v 2689
Prior osteoclast inhibitor	1.20 (0.56 - 2.58)	0.646	3.8 v 3.7	194 v 3297
Planned ZA dosing interval=Q 3-4 wks	3.00 (1.31 - 6.86)	0.009	4.0 v 1.4	3039 v 447
PRE-EXISTING DENTAL DISEASE				
Number of teeth (total) > median	0.56 (0.37 - 0.86)	0.007	3.4 v 5.6	1127 v 1142
Number of mandibular teeth > median	0.69 (0.45 - 1.06)	0.093	3.9 v 5.0	940 v 1338
Number of maxillary teeth > median	0.75 (0.49 - 1.16)	0.201	3.8 v 4.9	897 v 1377
Calculus moderate or severe	1.11 (0.71 - 1.74)	0.646	4.7 v 4.4	643 v 1552
Number of caries > median	1.17 (0.76 - 1.81)	0.478	4.9 v 4.4	682 v 1452
Dental plaque moderate or severe	1.32 (0.86 - 2.02)	0.208	5.2 v 4.2	705 v 1486
Gingivitis moderate or severe	1.32 (0.83 - 2.10)	0.238	5.0 v 4.2	553 v 1618
Complete dentures	1.70 (0.99 - 2.92)	0.056	6.1 v 4.2	283 v 2016
Periodontal disease moderate or severe	1.77 (1.13 - 2.79)	0.014	6.0 v 4.1	511 v 1507
Removable dentures	1.84 (1.05 - 3.20)	0.032	8.0 v 4.1	225 v 2074
Any dentures	1.96 (1.27 - 3.02)	0.002	7.0 v 3.7	508 v 1791
PRIOR DENTAL PROCEDURES				
>3 extractions	0.93 (0.61 - 1.41)	0.724	4.1 v 4.6	1041 v 1172
Any implants	0.95 (0.38 - 2.33)	0.906	4.7 v 4.4	121 v 2193
Prior orthodontics	0.97 (0.44 - 2.15)	0.949	4.4 v 4.4	171 v 1929
Minor periodontal treatments	1.16 (0.62 - 2.19)	0.638	4.9 v 4.2	245 v 1964
Intermediate periodontal treatments	1.23 (0.67 - 2.26)	0.512	5.3 v 4.1	254 v 1955
Any periodontal treatments	1.40 (0.89 - 2.20)	0.145	5.4 v 3.9	549 v 1684
1-3 extractions	1.54 (1.00 - 2.37)	0.05	6.0 v 3.7	602 v 1611
Tori	1.60 (1.01 - 2.54)	0.046	6.8 v 4.1	413 v 1723
Any oral surgery	1.61 (0.95 - 2.73)	0.078	4.9 v 3.0	1682 v 592
RADIOTHERAPY				
Total cGy > median	0.93 (0.64 - 1.35)	0.7	3.3 v 3.9	1683 v 1739
Any RT	0.95 (0.65 - 1.37)	0.763	3.4 v 4.0	1774 v 1717
SMOKING HISTORY				
Current smoker	1.57 (0.88 - 2.82)	0.128	4.2 v 3.3	430 v 1548



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eTable 1. Patient Characteristics by Baseline Dental Examination Status

		All eligible patients (n=3,491)		Exam done (n=2,263)		No exam done (n=1,228)		Exam vs No exam
		n	%	n	%	n	%	p[a]
Age, y (mean, sd)		63.1 (11.6)		63.3 (11.5)		62.6 (11.6)		0.074
Age, y (groups)								
	<55	763	21.9%	469	20.7%	294	23.9%	0.154
	55-59	538	15.4%	353	15.6%	185	15.1%	
	60-64	584	16.7%	371	16.4%	213	17.3%	
	65-69	587	16.8%	402	17.8%	185	15.1%	
	70-74	358	10.3%	234	10.3%	124	10.1%	
	>=75	661	18.9%	434	19.2%	227	18.5%	
Gender								
	Female	1,806	51.7%	1,187	52.5%	619	50.4%	0.248
	Male	1,685	48.3%	1,076	47.5%	609	49.6%	
Race								
	White	2,942	84.3%	1,939	85.7%	1,003	81.7%	<.001
	Black	368	10.5%	181	8.0%	187	15.2%	
	Asian	55	1.6%	43	1.9%	12	1.0%	
	Pacific Islander	5	0.1%	4	0.2%	1	0.1%	
	Native	18	0.5%	12	0.5%	6	0.5%	
	Multiracial	9	0.3%	5	0.2%	4	0.3%	
	Unknown race	94	2.7%	79	3.5%	15	1.2%	
Hispanic/Latino								
	Yes	190	5.4%	131	5.8%	59	4.8%	0.210
	No	3,184	91.2%	2,053	90.7%	1,131	92.1%	
	Missing/Unknown	117	3.4%	79	3.5%	38	3.1%	
Zubrod performance status								
	0	1,343	38.5%	924	40.8%	419	34.1%	<.001
	1	1,719	49.2%	1,117	49.4%	602	49.0%	
	2	351	10.1%	176	7.8%	175	14.3%	
	3	78	2.2%	46	2.0%	32	2.6%	
Alcohol use within past 3 months								
	None	2,231	63.9%	1,365	60.3%	866	70.5%	<.001
	1 per wk or fewer	542	15.5%	369	16.3%	173	14.1%	
	2-6 per wk	301	8.6%	221	9.8%	80	6.5%	
	1-3 per dy	204	5.8%	151	6.7%	53	4.3%	
	4 or more per dy	28	0.8%	18	0.8%	10	0.8%	
	Missing/Unknown	185	5.3%	139	6.1%	46	3.7%	
Cigarette smoking								
	Nonsmoker	1,545	44.3%	1,071	47.3%	474	38.6%	<.001
	Former smoker	1,513	43.3%	980	43.3%	533	43.4%	
	Current smoker	430	12.3%	209	9.2%	221	18.0%	
	Missing/Unknown	3	0.1%	3	0.1%	0	0.0%	
Patient reported dental pain/discomfort in last 3 months (mean,sd)[b]								
	Average pain	0.81 (1.84)		0.78 (1.78)		0.86 (1.96)		0.230
	Interference with eating	0.50 (1.55)		0.49 (1.54)		0.53 (1.57)		0.376
	Interference with smile	0.32 (1.36)		0.30 (1.33)		0.36 (1.42)		0.265
	Interference with speech	0.23 (1.07)		0.24 (1.09)		0.23 (1.02)		0.724
	Interference with quality of life	0.35 (1.28)		0.34 (1.29)		0.37 (1.28)		0.527

[a]P-values for categorical variables are from a chi-squared test (missing/unknown excluded); P-values for linear variables are from a t-test.
[b]Patient-reported outcomes are based on the brief pain inventory and are rated from 0 (No pain/Has not interfered) to 10 (Pain as bad as you can imagine/Completely interfered).

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eTable 2. Cumulative Incidence of ONJ

Cancer type	Point estimate (95% CI) by study year		
	1	**2**	**3**
Confirmed ONJ			
All	0.8 (0.5-1.1)	2.0 (1.5-2.5)	2.8 (2.3-3.5)
Breast	0.3 (0.1-0.8)	1.4 (0.8-2.3)	2.4 (1.5-3.4)
Lung	0.9 (0.4-1.9)	2.2 (1.3-3.6)	2.7 (1.6-4.2)
Myeloma	0.9 (0.3-1.9)	2.9 (1.7-4.5)	4.3 (2.8-6.4)
Prostate	1.2 (0.6-2.2)	1.9 (1.1-3.2)	2.9 (1.7-4.5)
Confirmed plus suspected ONJ			
All	1.1 (0.8-1.5)	2.6 (2.1-3.2)	3.7 (3.1-4.4)
Breast	0.5 (0.2-1.1)	1.7 (1.0-2.6)	2.9 (2.0-4.1)
Lung	1.4 (0.7-2.5)	2.8 (1.7-4.3)	3.5 (2.2-5.1)
Myeloma	1.0 (0.4-2.2)	3.6 (2.3-5.4)	5.3 (3.6-7.5)
Prostate	1.3 (0.6-2.4)	2.5 (1.5-3.9)	3.8 (2.5-5.5)

Abbreviation: ONJ, osteonecrosis of the jaw.

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eTable 3. Description of Lesions[1]

Description of Lesions						
	Lesion 1		Lesion 2		Lesion 3	
Factors	**N**	**%/(IQR)**	**N**	**%/(IQR)**	**N**	**%/(IQR)**
Type						
Follow-up	36	45.6%	6	50.0%	1	100.0%
New	43	54.4%	6	50.0%		
Symptom severity						
Asymptomatic	33	45.2%	4	36.4%		
Mild	26	35.6%	3	27.3%		
Moderate	11	15.1%	4	36.4%	1	100.0%
Severe	3	4.1%	0	0%		
Lesion-associated periodontal infection						
No	59	84.3%	9	81.8%		
Yes	11	15.7%	2	18.2%	1	100.0%
Lesion-associated dental extraction						
No	41	58.6%	7	63.6%	1	100.0%
Yes	29	41.4%	4	36.4%		
Lesion-associated denture trauma						
No	63	90.0%	8	72.7%		
Yes	7	10.0%	3	27.3%	1	100.0%
Lesion-associated other dental surgery						
No	67	95.7%	11	100.0%	1	100.0%
Yes	3	4.3%				
Lesion-associated trauma (other)						
No	66	94.3%	11	100.0%	1	100.0%
Yes	4	5.7%				
Any associated factors above[2]						
No	28	40.0%	4	36.4%		
Yes	42	60.0%	7	63.6%	1	100.0%

IQR = intra quartile range

[1] Percentages shown among those with known data.

[2] Associated factors are periodontal infection, dental extraction, denture trauma, other dental surgery, or other trauma that were indicated by the patient's dentist as associated with the lesion (the factors are also individually listed).

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eTable 4. Patient-Reported Outcomes of Oral Health–Related Quality of Life[1]

	Patient reported dental pain/discomfort using items adapted from the Brief Pain Inventory (mean/sd)						
	Baseline			Follow-up[2]		P-value	
PRO Item[3]	All patients (N=1703)	Patients who developed ONJ (N=83)	Patients who did not develop ONJ (N=1620)	ONJ cases (N=83)	Non-cases (N=1620)	Comparing baseline values[4]	Comparing follow-up score minus baseline[5]
Average pain	0.71 (1.69)	0.60 (1.67)	0.71 (1.69)	2.72 (3.40)	0.64 (1.69)	.57	<.001
Interference with eating	0.39 (1.32)	0.54 (1.64)	0.38 (1.30)	2.80 (3.58)	0.45 (1.30)	.40	<.001
Interference with smile	0.23 (1.13)	0.28 (1.23)	0.23 (1.12)	1.32 (2.84)	0.31 (1.12)	.71	.004
Interference with speech	0.17 (0.85)	0.20 (0.80)	0.16 (0.85)	1.15 (2.60)	0.22 (1.08)	.73	.001
Interference with quality of life	0.23 (0.93)	0.36 (1.30)	0.22 (0.91)	2.22 (3.34)	0.34 (1.33)	.38	<.001

[1] Compared the change in PRO scores for each item between baseline and FU. Only patients with both baseline and follow-up PRO scores included.
[2] For patients with ONJ, the follow-up PRO score was assessed at the time of initial diagnosis. For patients without ONJ (non-cases), the follow-up PRO score closest to the median diagnosis time of 521 days for ONJ cases was used.
[3] Scale of 0-10; 0 is no symptom, 10 is maximum symptom
[4] T-tests comparing baseline values between cases and noncases.
[5] Paired T-tests comparing the difference between cases and non-cases in the change between baseline and follow-up scores.

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