Robert Marx, DDS

Cancer Treatment Induced Bone Loss (CTIBL): RANK Ligand, Bisphosphonate, Anti-angiogenesis, and More

No financial relationships in the past twelve months by presenter or spouse/partner.

Non-Paid Consultant: Lenkbar

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Miami Cancer Meeting

Hilton Hotel

April 27, 2018

Drug Induced Osteonecrosis Of The Jaws (DIONJ)

A Problem That every Oncologist and Oral Surgeon Faces

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Director of Research

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Miller School of Medicine

Disclosure - Past

1. Novartis — Consultant
2. Merck Co. — Consultant
3. Amgen — Consultant

Disclosure - Active

International Game Fish Association

Goals Of This Presentation

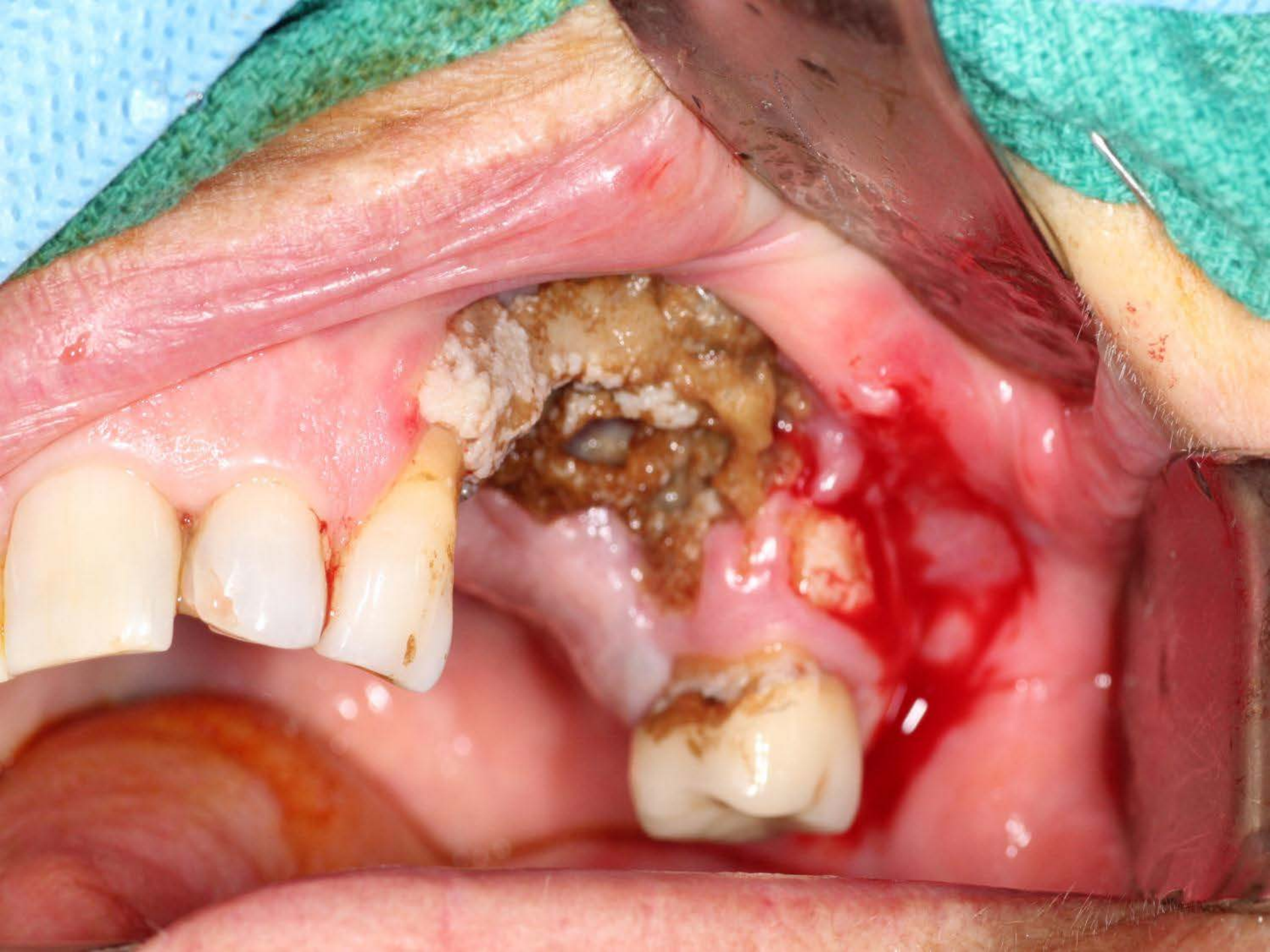
1. DIONJ is a real entity
2. We are on your side
3. We are on the patient's side
4. Review prevention and treatment protocol

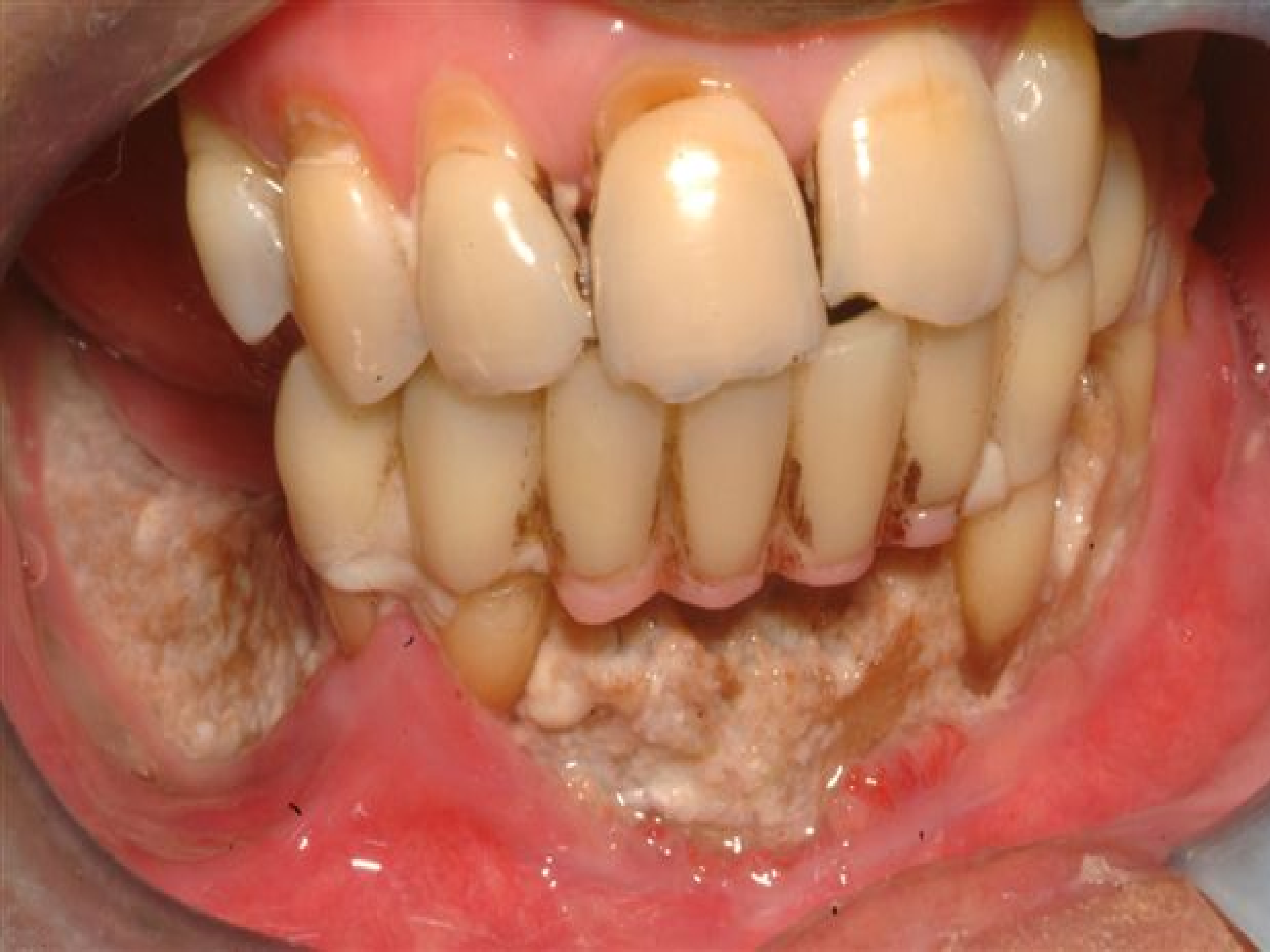
Marx RE.

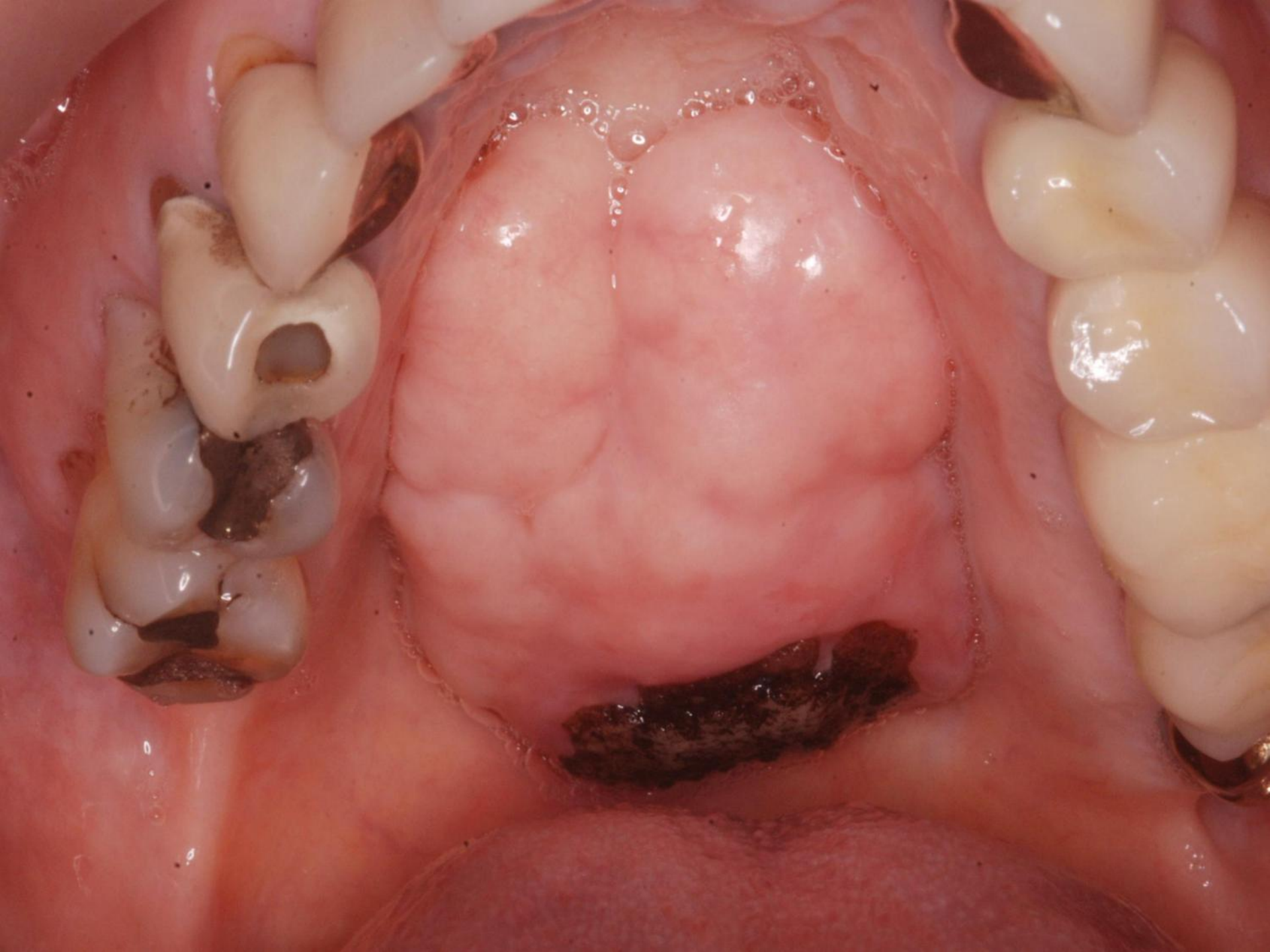
Pamidronate (Aredia) and Zoledronate (Zometa) induces avascular necrosis of the jaws. A growing epidemic.

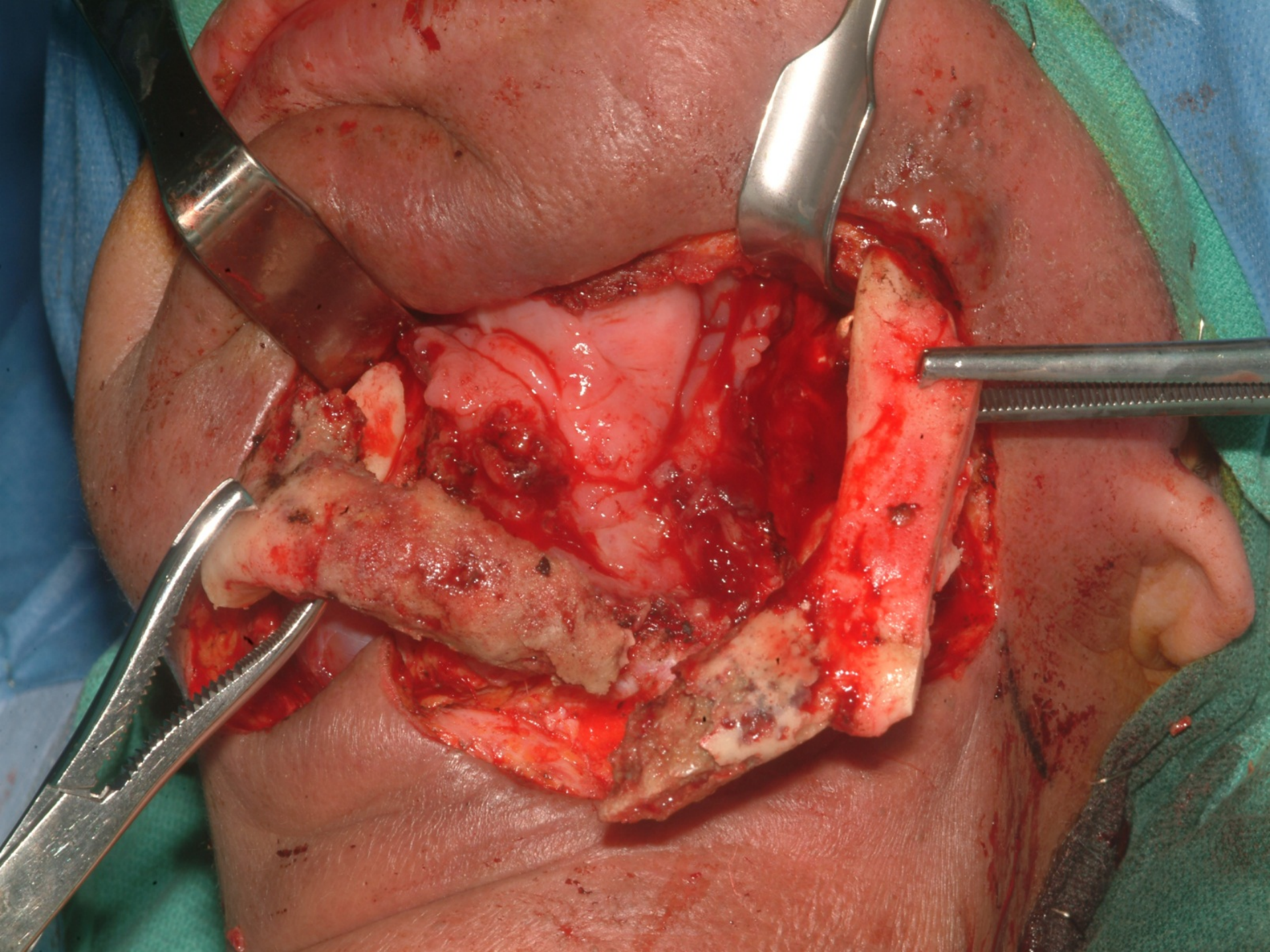
J Oral Maxillofac Surg 61:1115, 2003

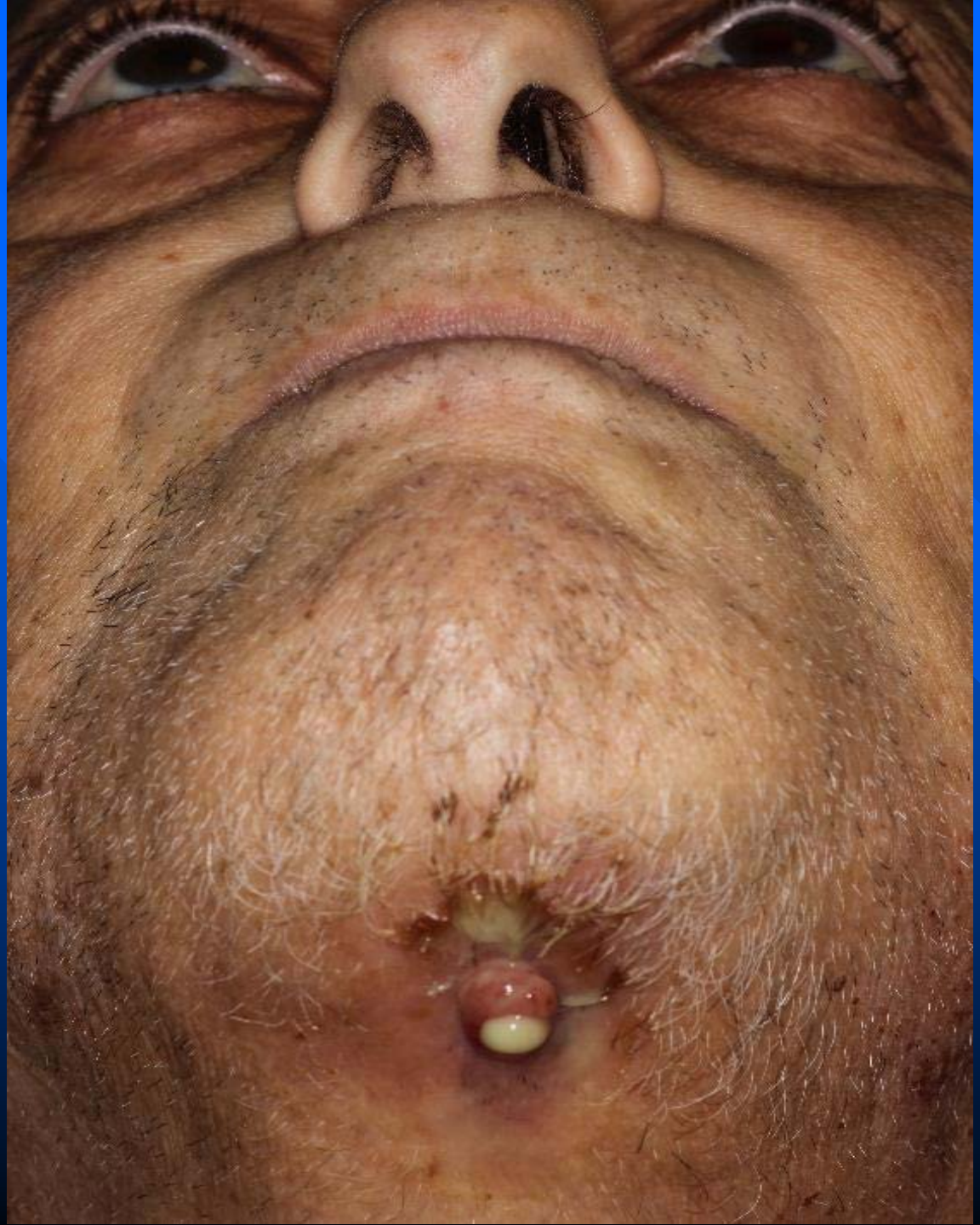
Drug Induced Osteonecrosis Of The Jaws: The Continuing Epidemic

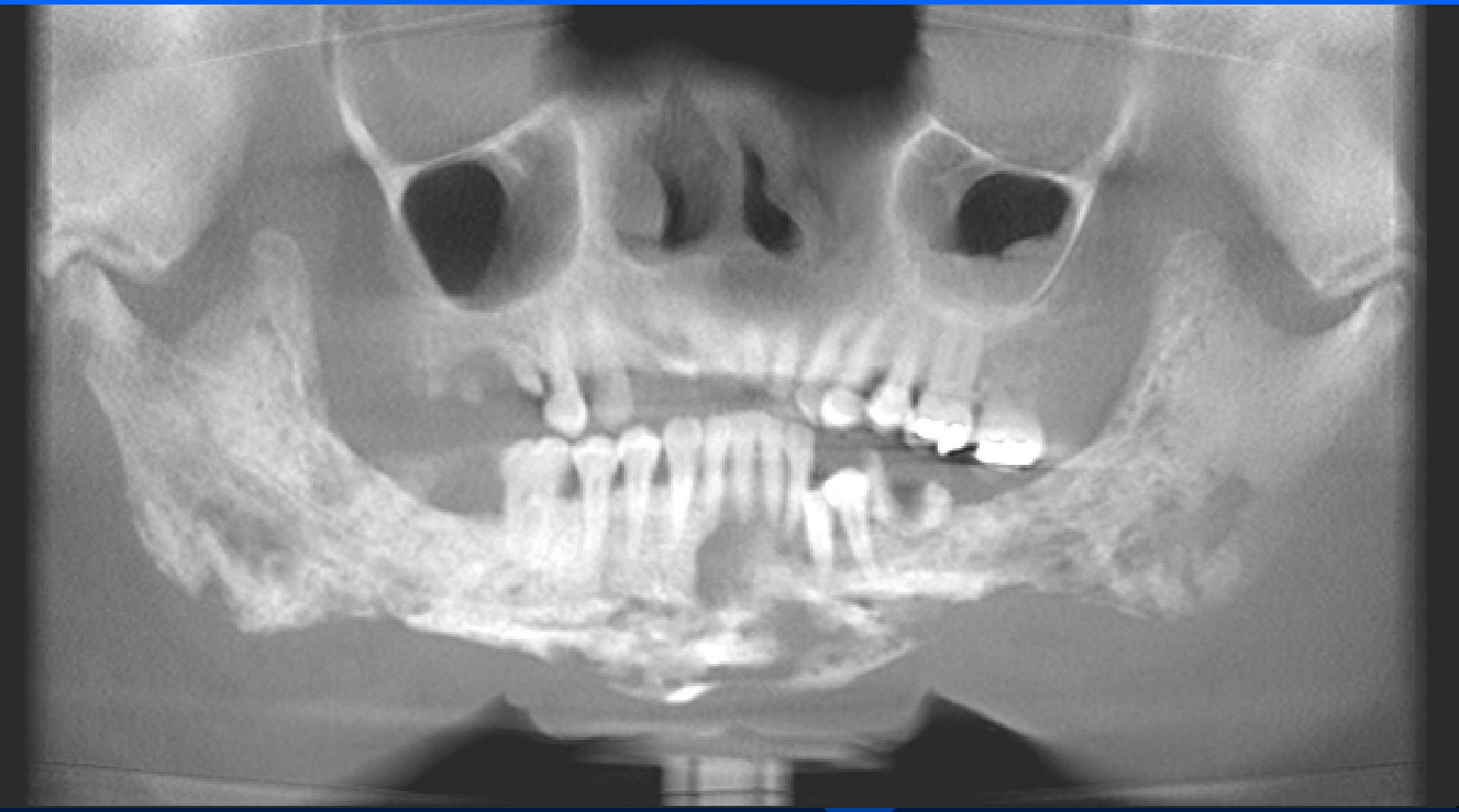












DIONJ is a real entity and should be prevented and treated.

Osteonecrosis Articles

Year	Number of Articles
1999 - 2002	0
2003	4
2004	7
2005	62
2006	136
2007	175
2008 - 2017	200+ each year

Oncology Related DIONJ Drugs

1.	Denosumab 120 mg/mo	=	High Risk
2.	Zolendronate 4 mg/mo	-	High Risk
3.	Alendronate 70 mg/wk	=	High Risk
4.	Sunitinib 25 mg/day	=	High Risk
5.	Pamidronate 90 mg/mo	=	Moderate Risk
6.	Bevacizumab 500 mg/2 wks	=	Low Risk

Other Chemotherapy Drugs Are Not Known To Cause DIONJ

Drug Types Known To Cause DIONJ

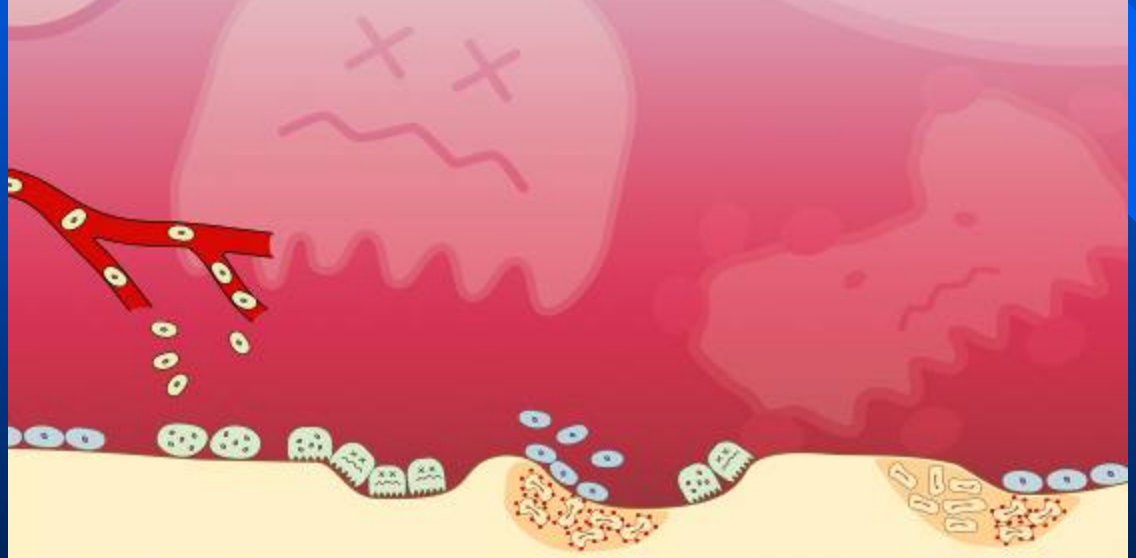
1. Bisphosphonates
2. RANK-L inhibitors
3. Antiangiogenic drugs
4. TRK Inhibitors
5. IL6 inhibitors

Drug Induced Osteonecrosis Of The Jaws

1. Over 20,000 cases reported in the literature so far
2. Over 13,300 cases reported to the FDA
3. Over 2,200 publications to date
4. More than 12 organizations posting position papers
5. Numerous lectures and courses

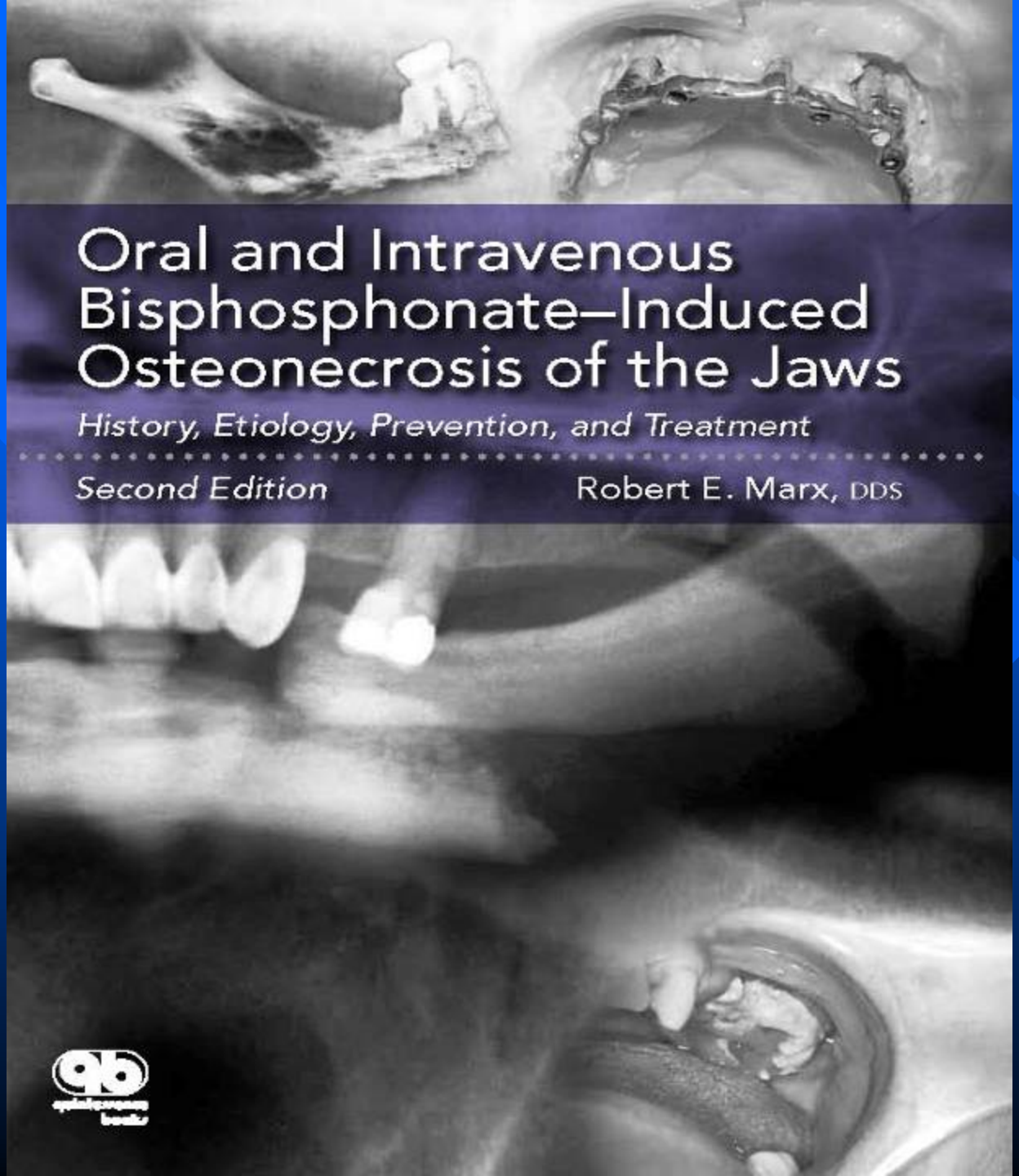
Oral & Intravenous Bisphosphonate-Induced Osteonecrosis of the Jaws

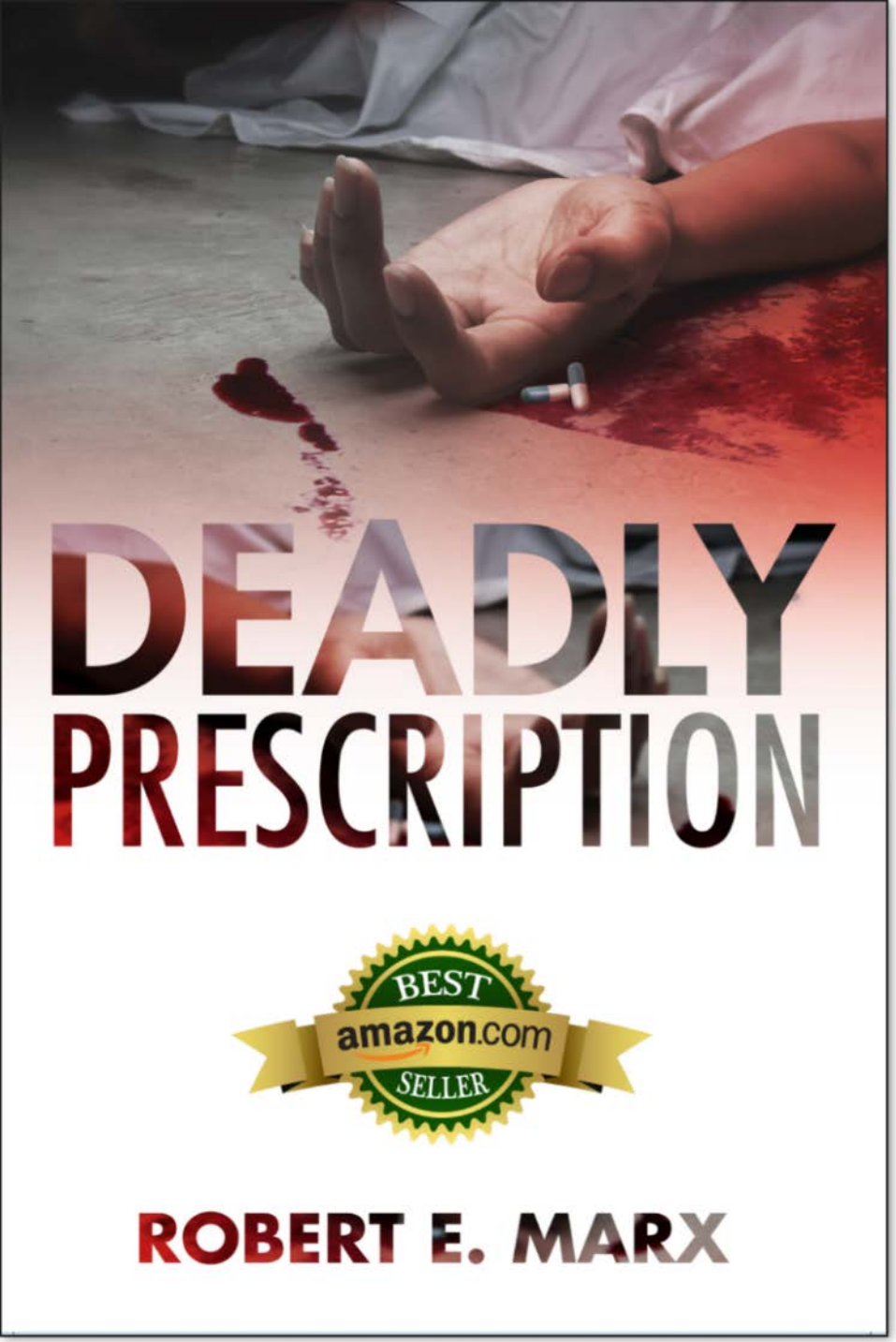
History, Etiology, Prevention, and Treatment



Robert E. Marx, DDS

quintessence books


Oral and Intravenous Bisphosphonate–Induced Osteonecrosis of the Jaws
History, Etiology, Prevention, and Treatment
Second Edition
Robert E. Marx, DDS



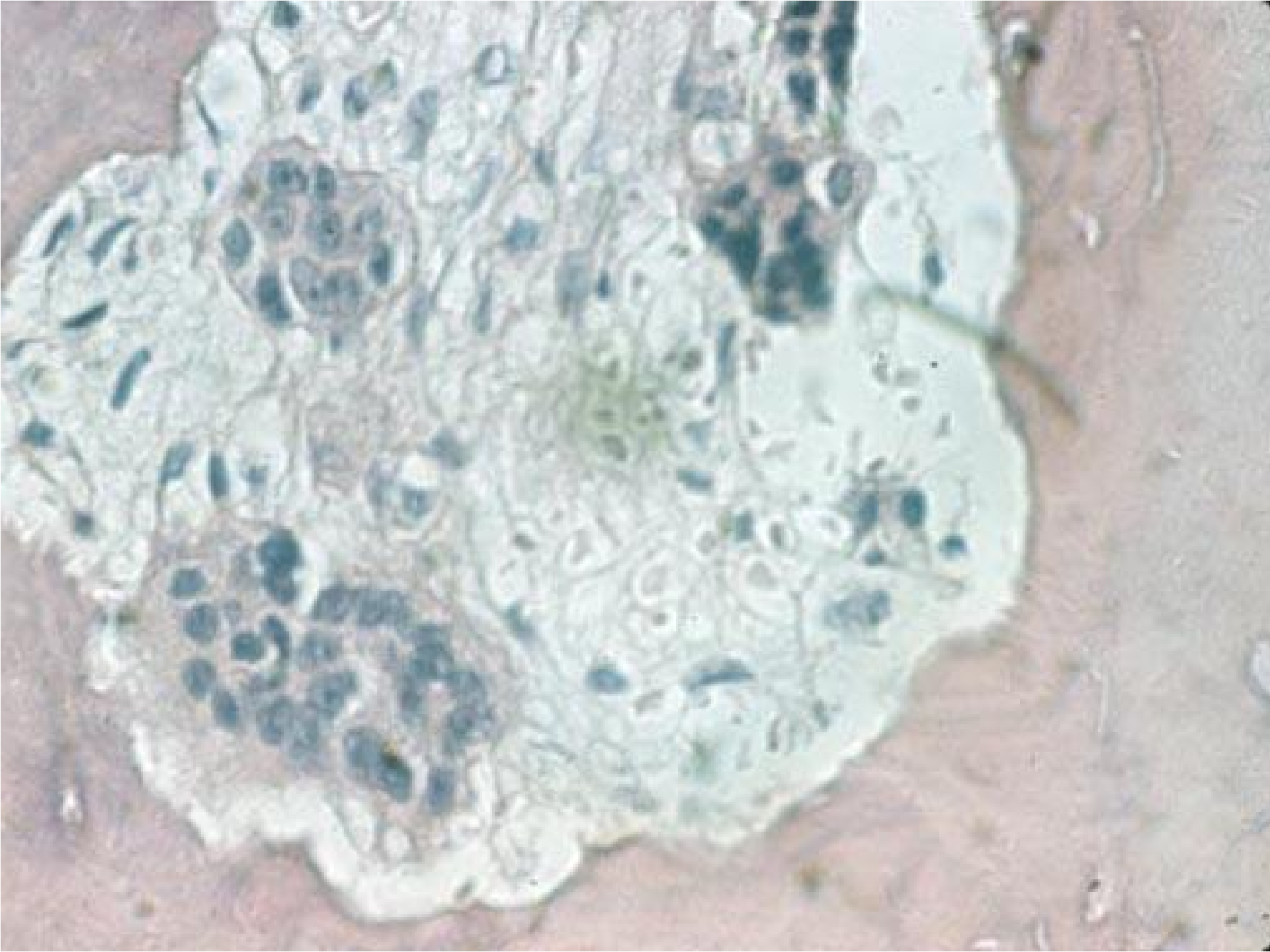
How far will some men go for money and power? Deadly Prescription shows what happens when profit becomes more important than life. Author Dr. Robert E. Marx tells a riveting story so lifelike, you'll wonder whether it really happened or not. The twists and turns will catch you off guard, and the details will keep you on the edge of your seat,. The story tells of tainted drug studies and side-effects plus numerous coverups by two pharmaceutical giants. The protagonist confronts these giants by defending his patients as a forensic expert in lawsuits against these companies. Their ruthless team of lawyers will stop at nothing to quiet any noisemaker. See how men of greed actually think and act. After all, what's a few thousand lives destroyed when billions of dollars are being made as a result?

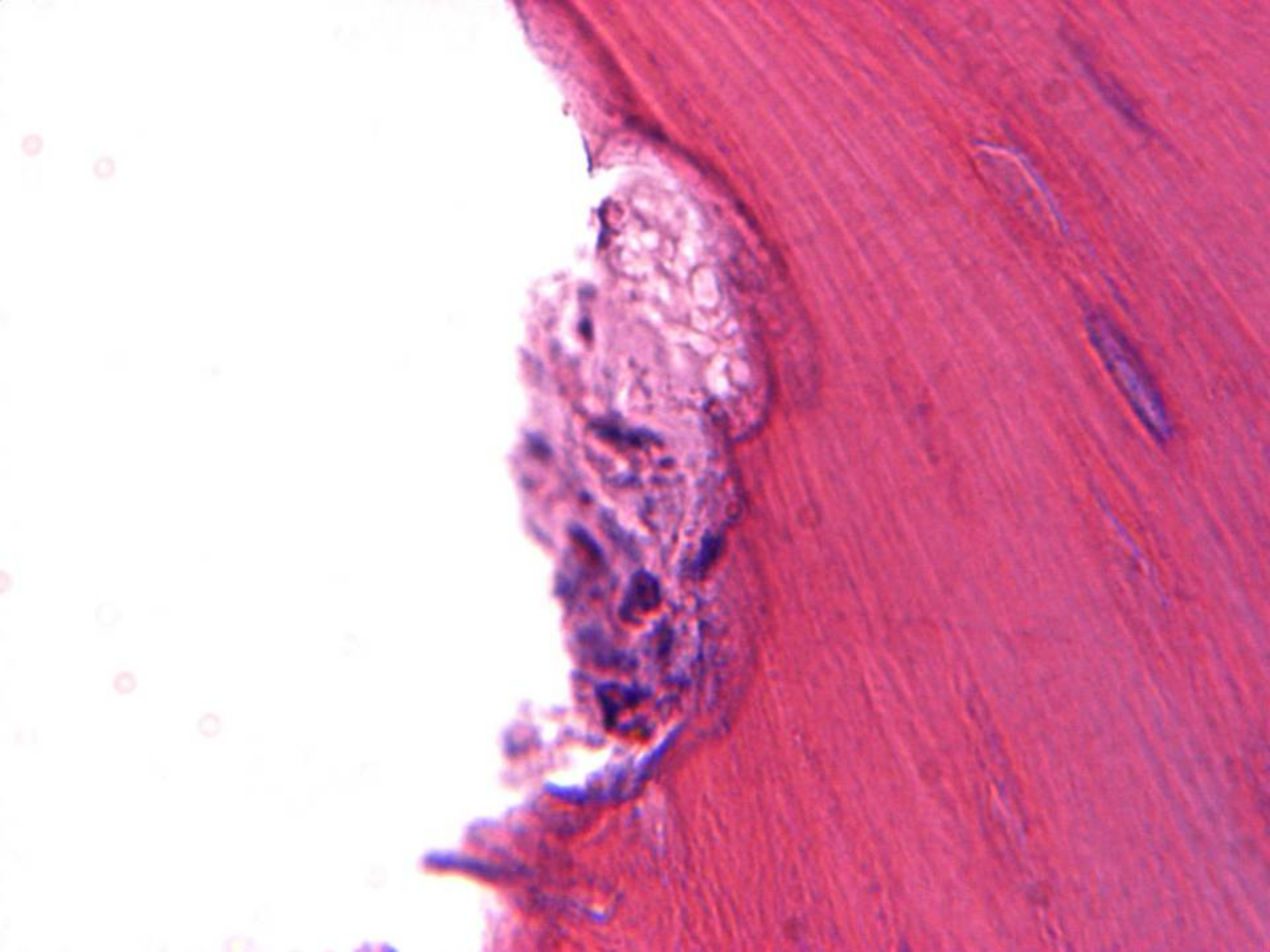
Drug induced osteonecrosis is the only correct term because bisphosphonates and Denosumab are the cause of exposed bone osteonecrosis in the jaws

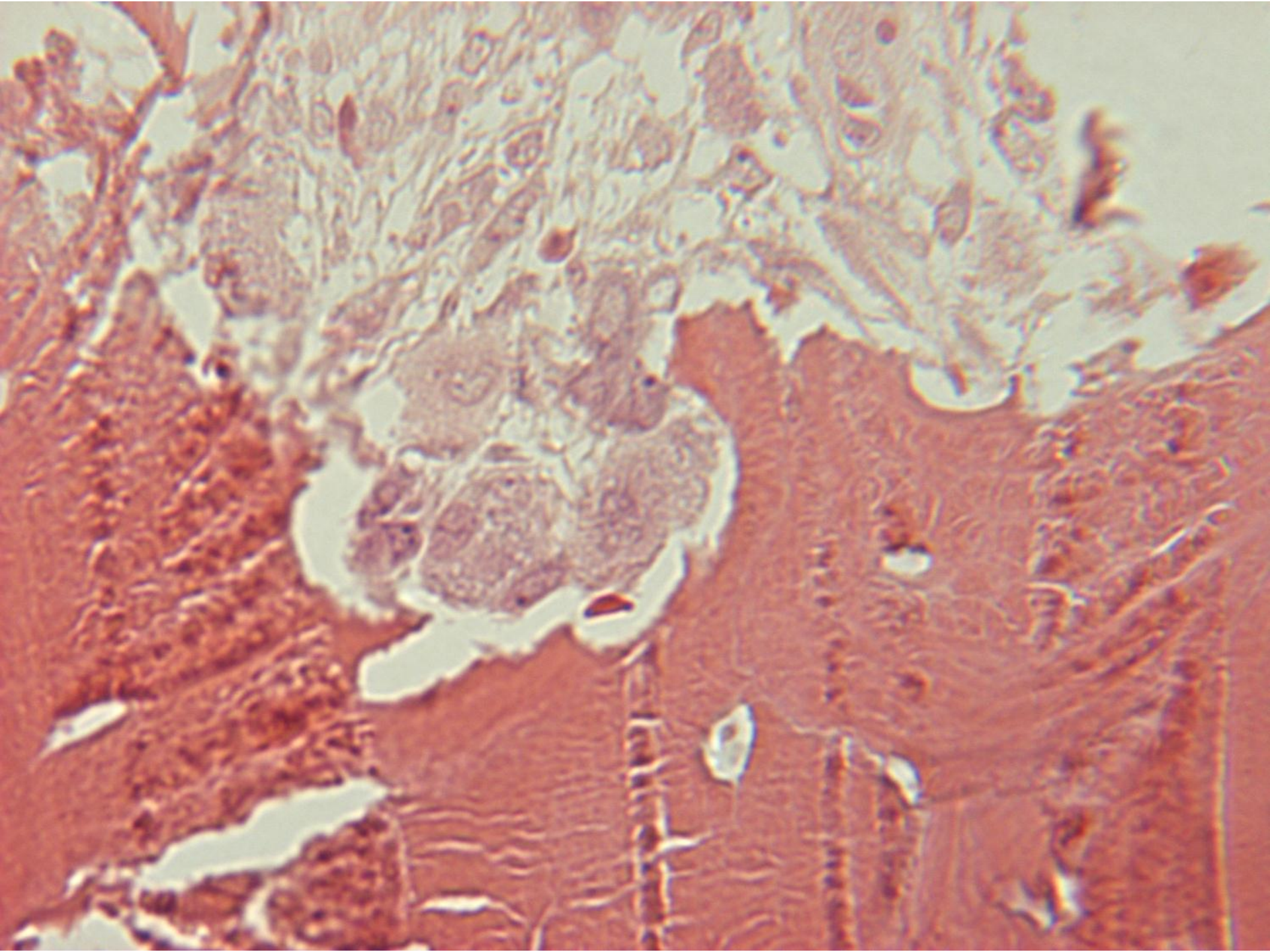
Drug Induced Osteonecrosis Of The Jaws (DIONJ) is the only scientifically correct term and is consistent with the AMA ICD- 10 M 87.10

Mechanism Of Action Bisphosphonate

1. Mostly Osteoclast death at resorption sites
2. To a lesser degree Osteoclast precursor inhibition and death in bone marrow

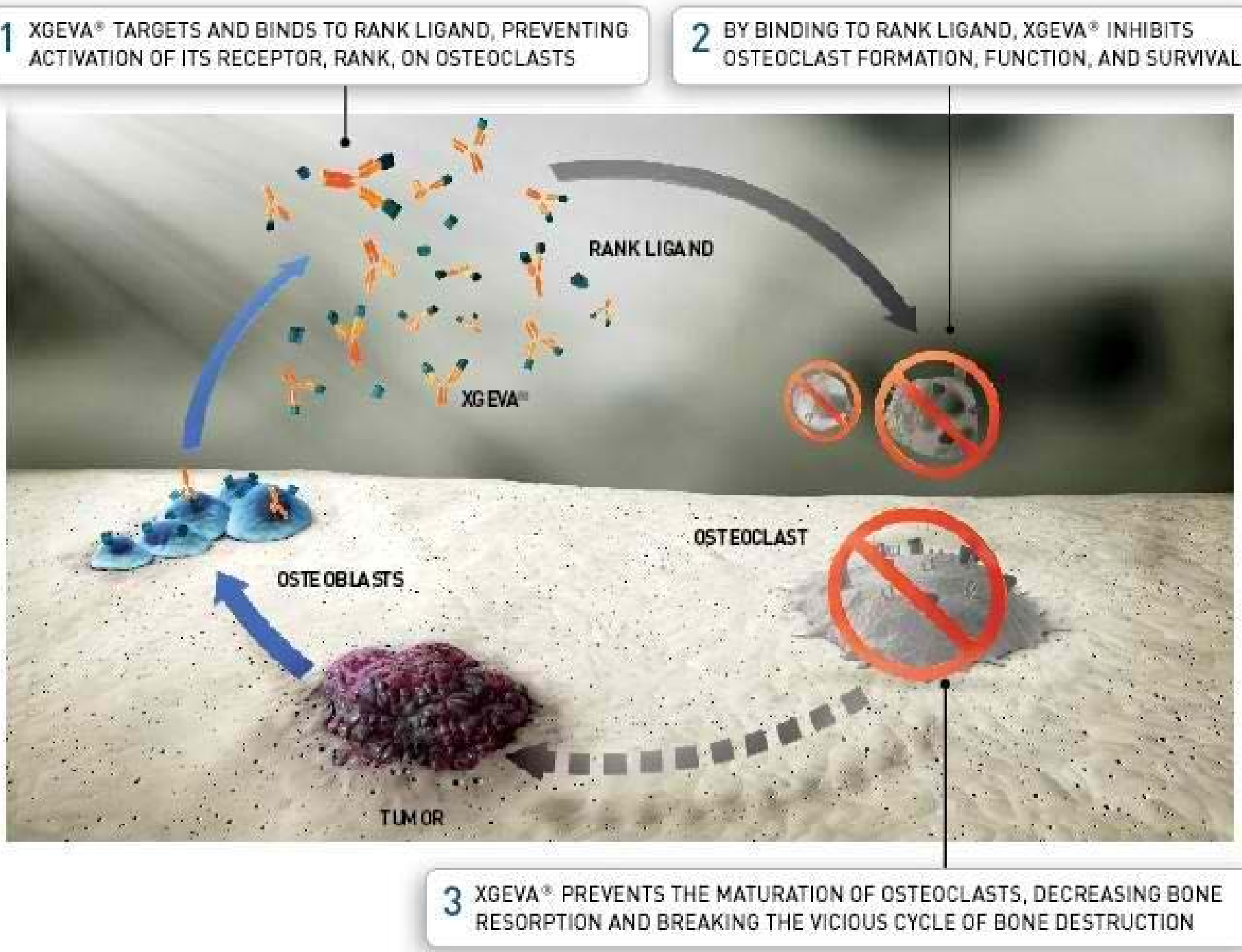


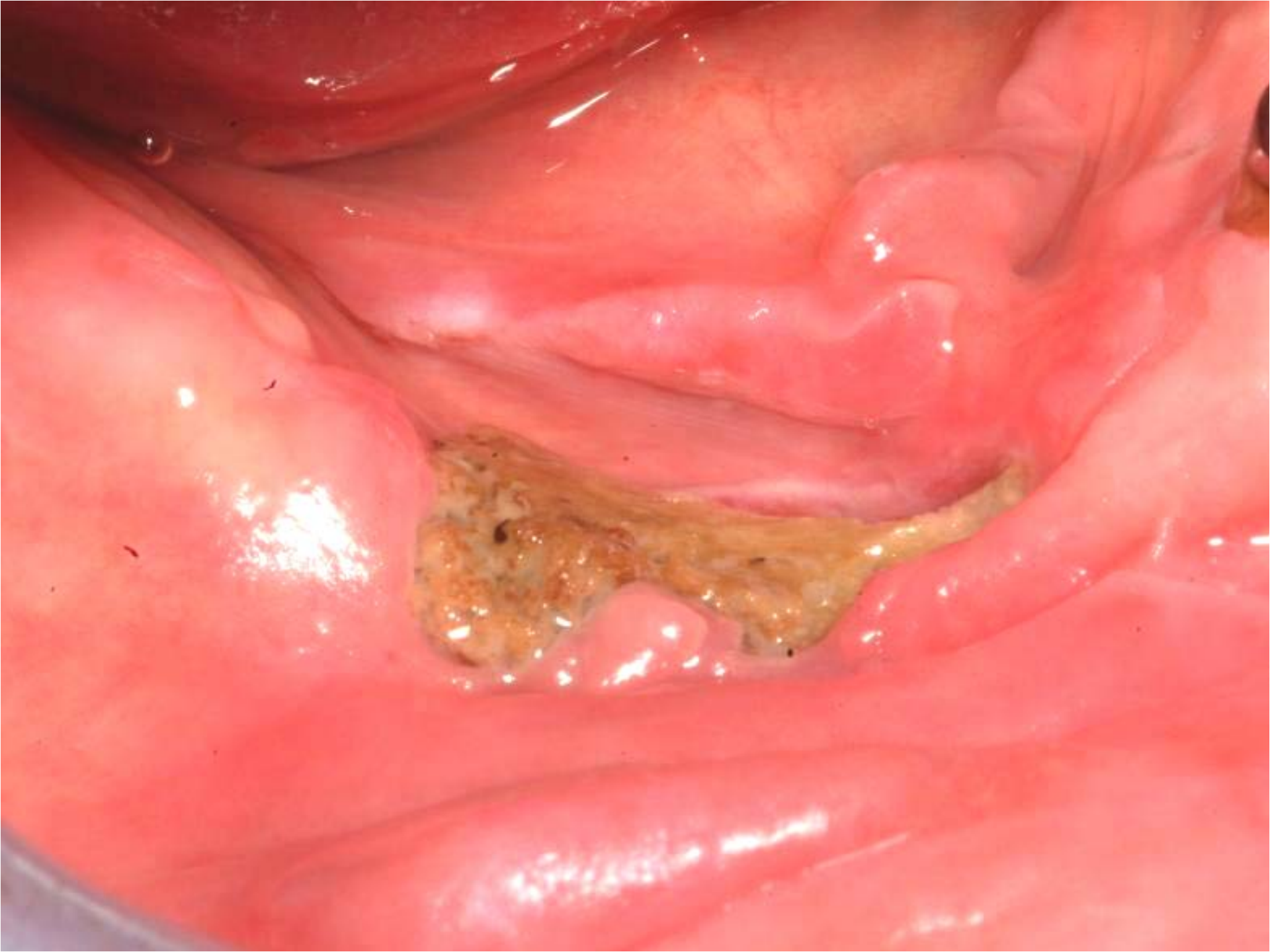


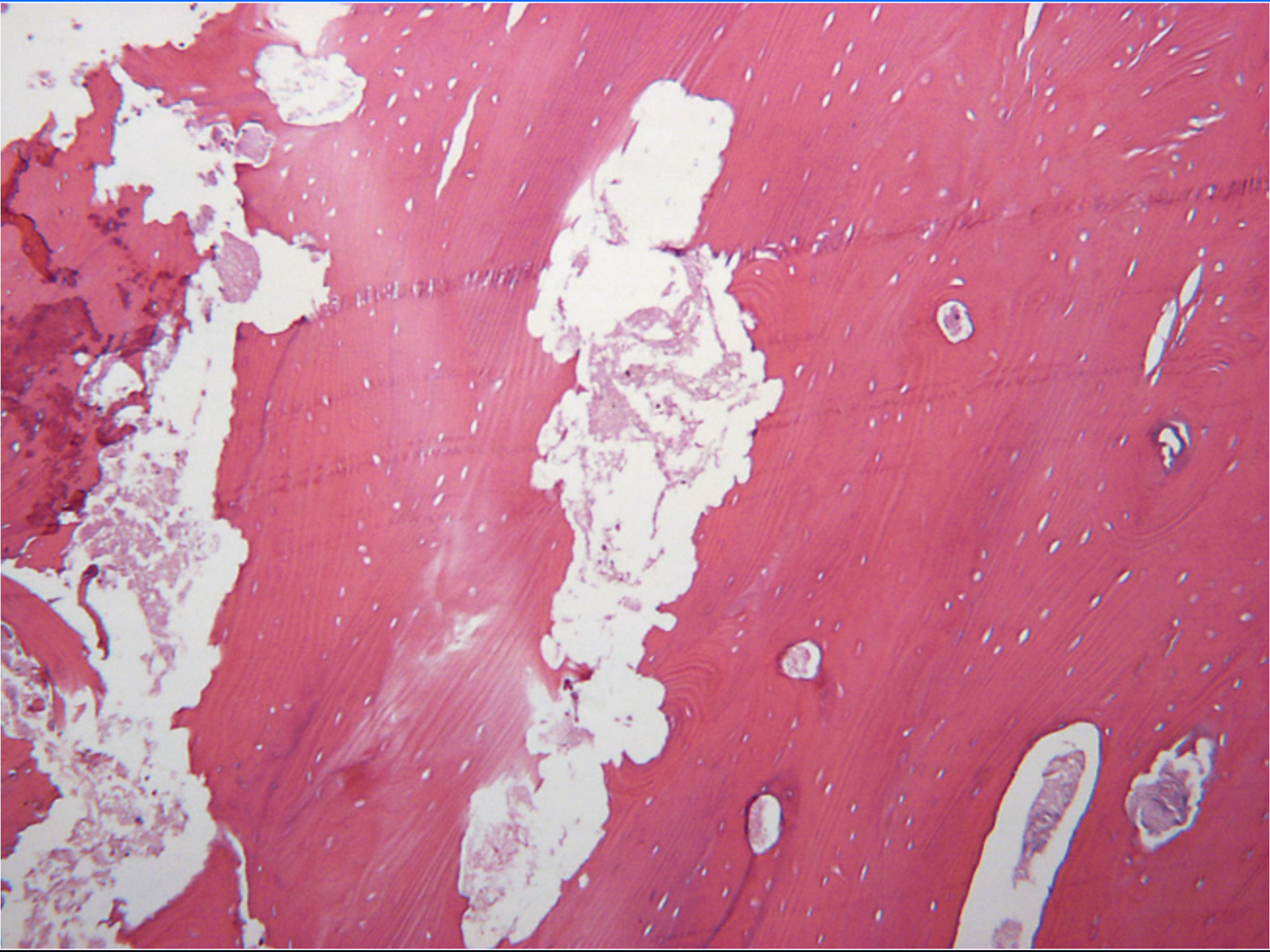


Mechanism Of Action Denosumab

1. Osteoclast inhibition at resorption sites
2. Osteoclast inhibition in blood and tissue spaces
3. Osteoclast precursor inhibition in bone marrow


1 XGEVA® TARGETS AND BINDS TO RANK LIGAND, PREVENTING ACTIVATION OF ITS RECEPTOR, RANK, ON OSTEOCLASTS
2 BY BINDING TO RANK LIGAND, XGEVA® INHIBITS OSTEOCLAST FORMATION, FUNCTION, AND SURVIVAL
RANK LIGAND
XGEVA®
OSTEOCLAST
OSTEOBLASTS
TUMOR
3 XGEVA® PREVENTS THE MATURATION OF OSTEOCLASTS, DECREASING BONE RESORPTION AND BREAKING THE VICIOUS CYCLE OF BONE DESTRUCTION





Key Differences

Bisphosphonates: most affect osteoclasts resorbing bone and some affect precursors in bone marrow

Denosumab, affects mature osteoclasts and their precursors everywhere

Key Difference Half Life In Bone

Bisphosphonates	11+ years
Denosumab	26 days

Oncology Related DIONJ Drugs

Denosumab	120 mg/month	= High risk
Zoledronate	4 mg/month	= High risk
Pamidronate	90 mg/month	= Moderate risk
Alendronate	70 mg/week	= Moderate risk

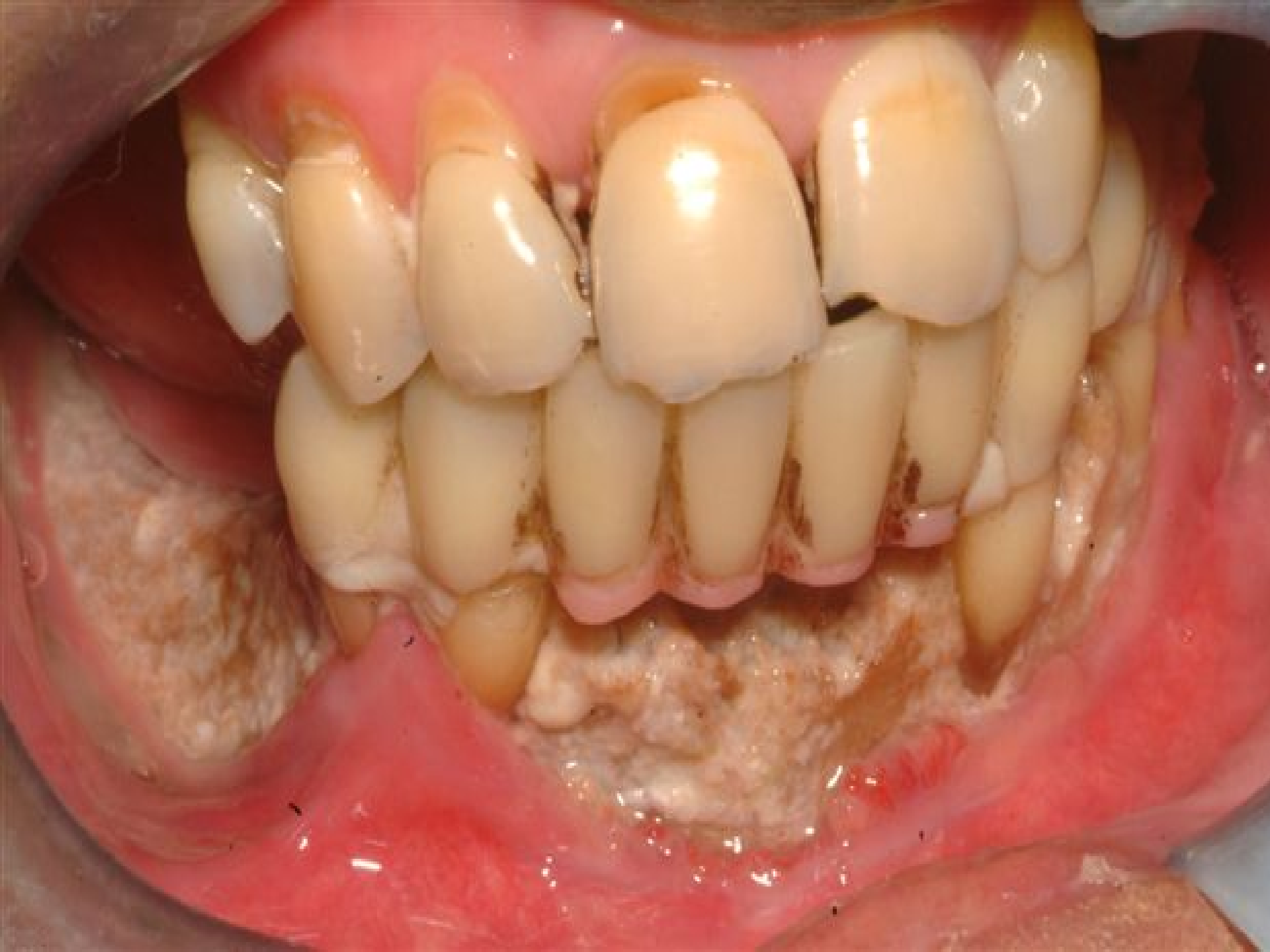
•

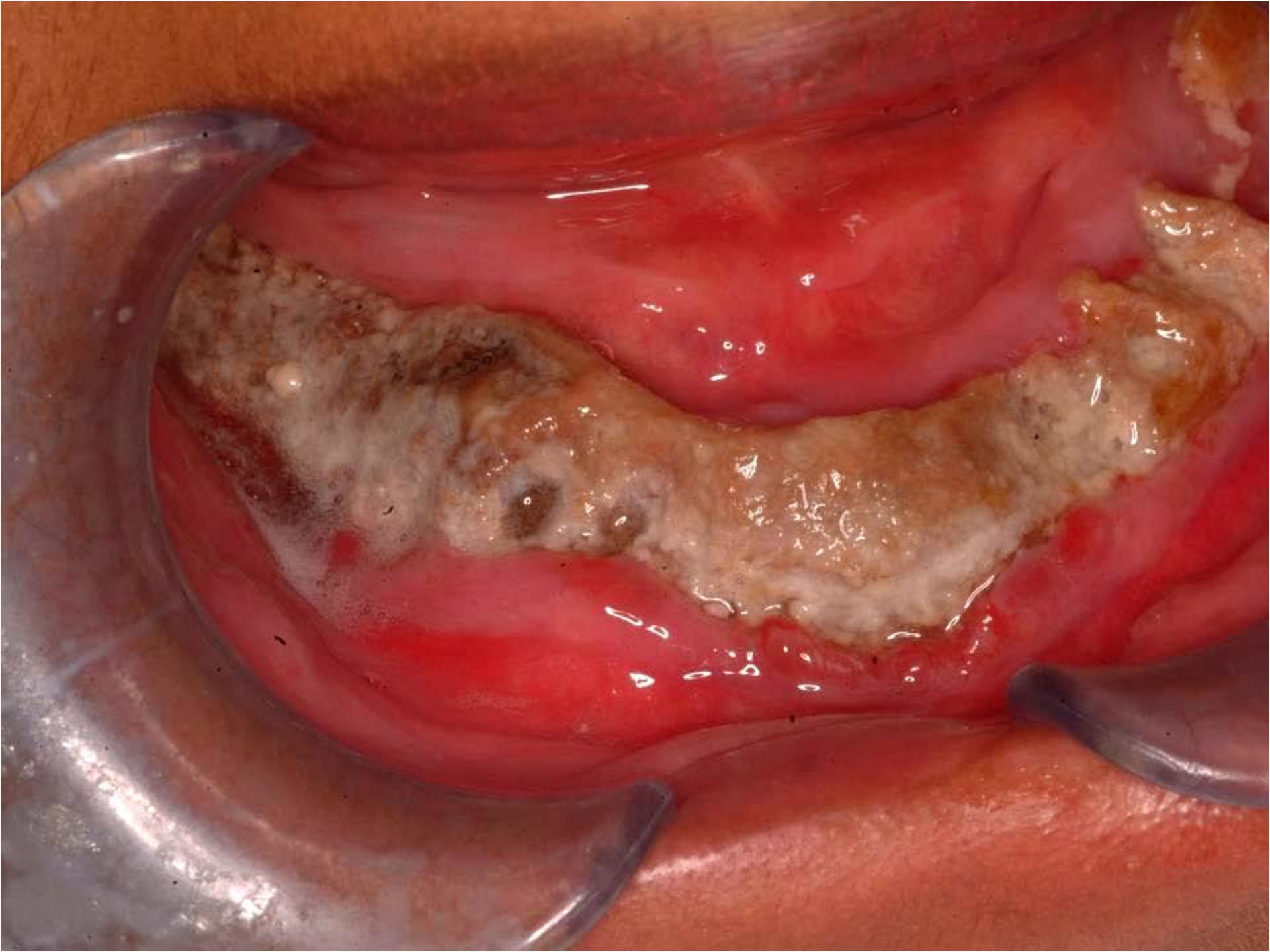
The New Addition To The Epidemic

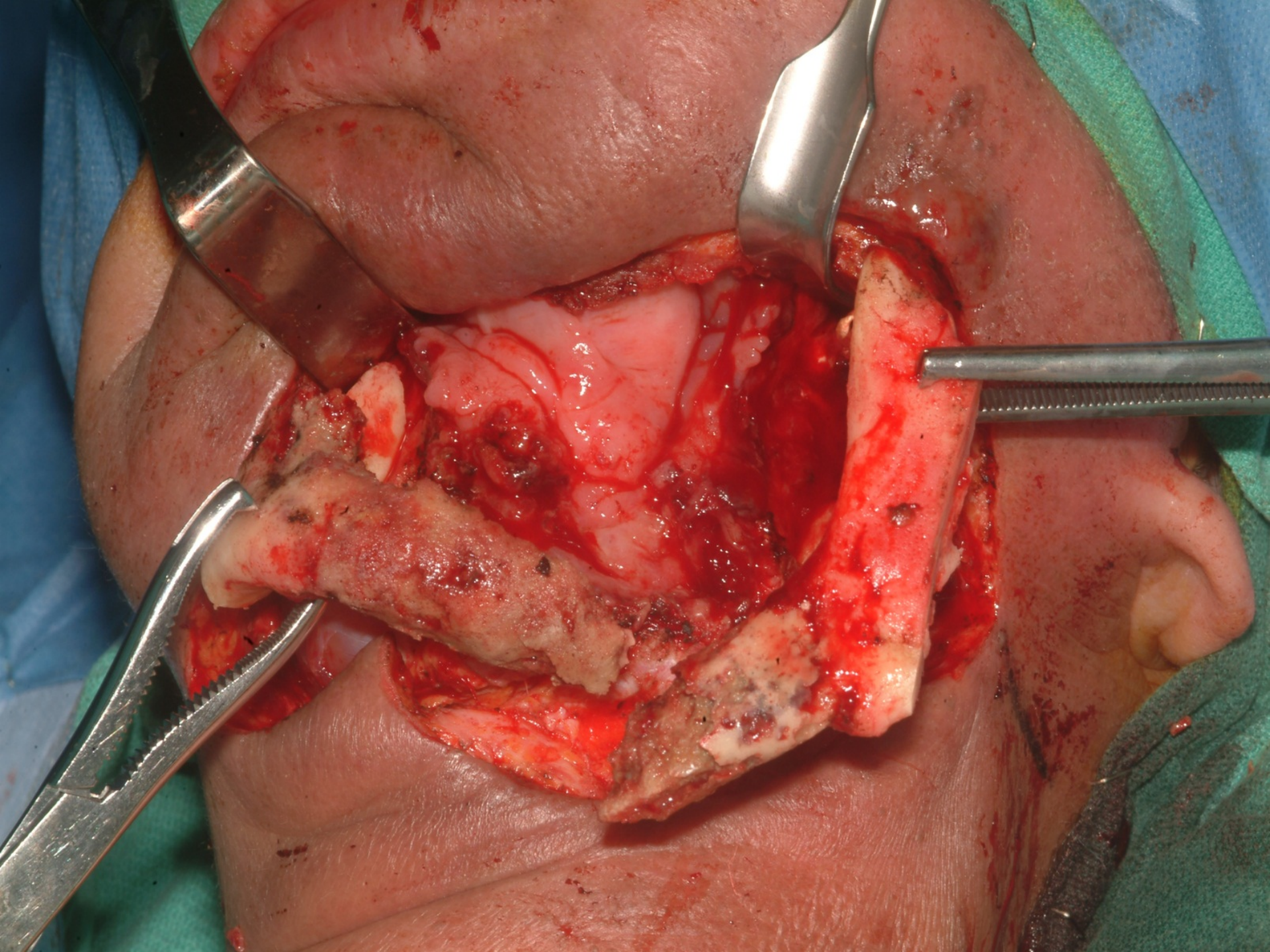
Bisphosphonate Followed By A RANKL Inhibitor

Bisphosphonate → RANKL Inhibitor

1. Rapid onset of ONJ
2. More extensive
3. More severe





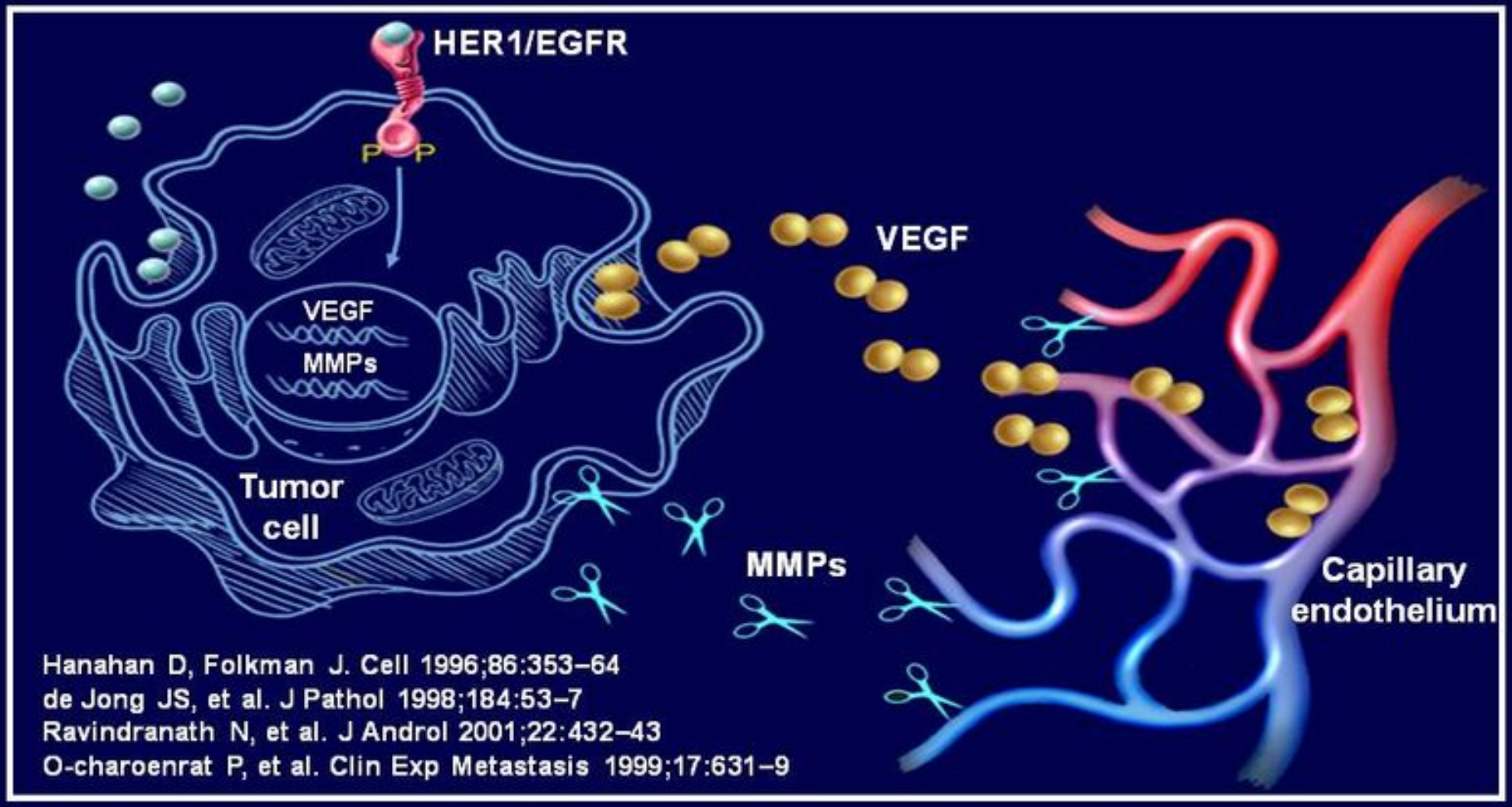


Mechanism Of Action Bevacizumab

1. Blocks the action of Vascular Endothelial Growth Factor (VEGF)

EGFR and Angiogenesis

- HER1/EGFR signaling increases vascular endothelial growth factor (VEGF) and matrix metalloproteinase (MMP) levels



Hanahan D, Folkman J. Cell 1996;86:353–64
de Jong JS, et al. J Pathol 1998;184:53–7
Ravindranath N, et al. J Androl 2001;22:432–43
O-charoenrat P, et al. Clin Exp Metastasis 1999;17:631–9

Mechanism Of Action Sunitinib

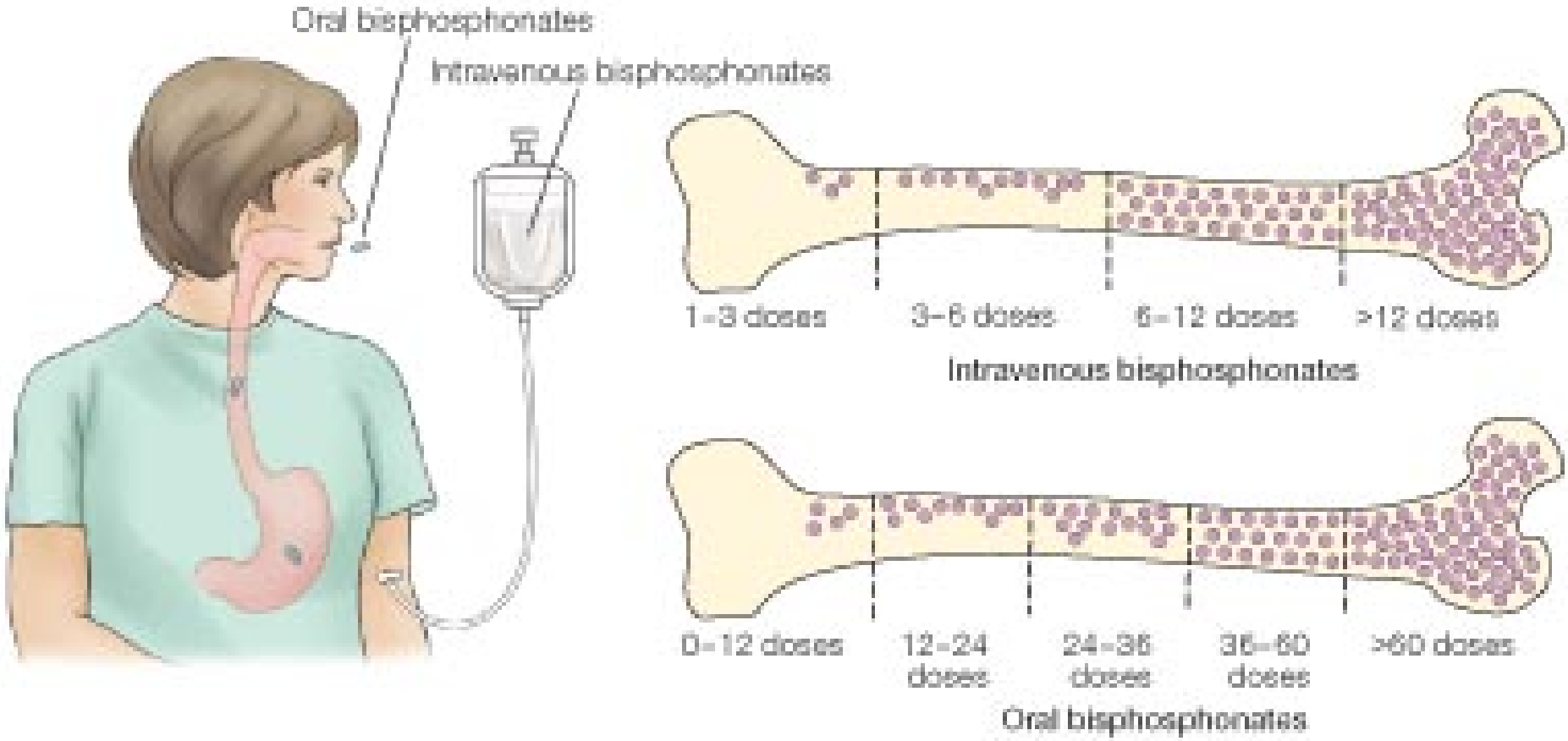
1. Blocks action of multiple growth factors i.e. VEGF, PDGF, TGF-b etc.

Case Experience

1. Intravenous bisphosphonate induced osteonecrosis: 299 cases
2. Oral bisphosphonate induced osteonecrosis: 139 cases
3. Subcutaneous RANKL cases: 84
4. Total: 522 cases

Four Critical Issues

1. Risk factors: Dose, potency, frequency, half life, duration of drug use


Oral bisphosphonates
Intravenous bisphosphonates
1–3 doses
3–6 doses
6–12 doses
>12 doses
Intravenous bisphosphonates
0–12 doses
12–24 doses
24–36 doses
36–60 doses
>60 doses
Oral bisphosphonates

The IV and SC routes have 140 times the bone bioavailability of an oral dose.

The Risk Factor Dose For IV or SC Begins:

1. Zoledronate - 4th dose
2. Pamidronate - 8th dose
3. Denosumab - 2nd dose
4. Bevacizumab - Unknown
5. Sunitinib - Unknown

Possible Prevention Strategies Observation

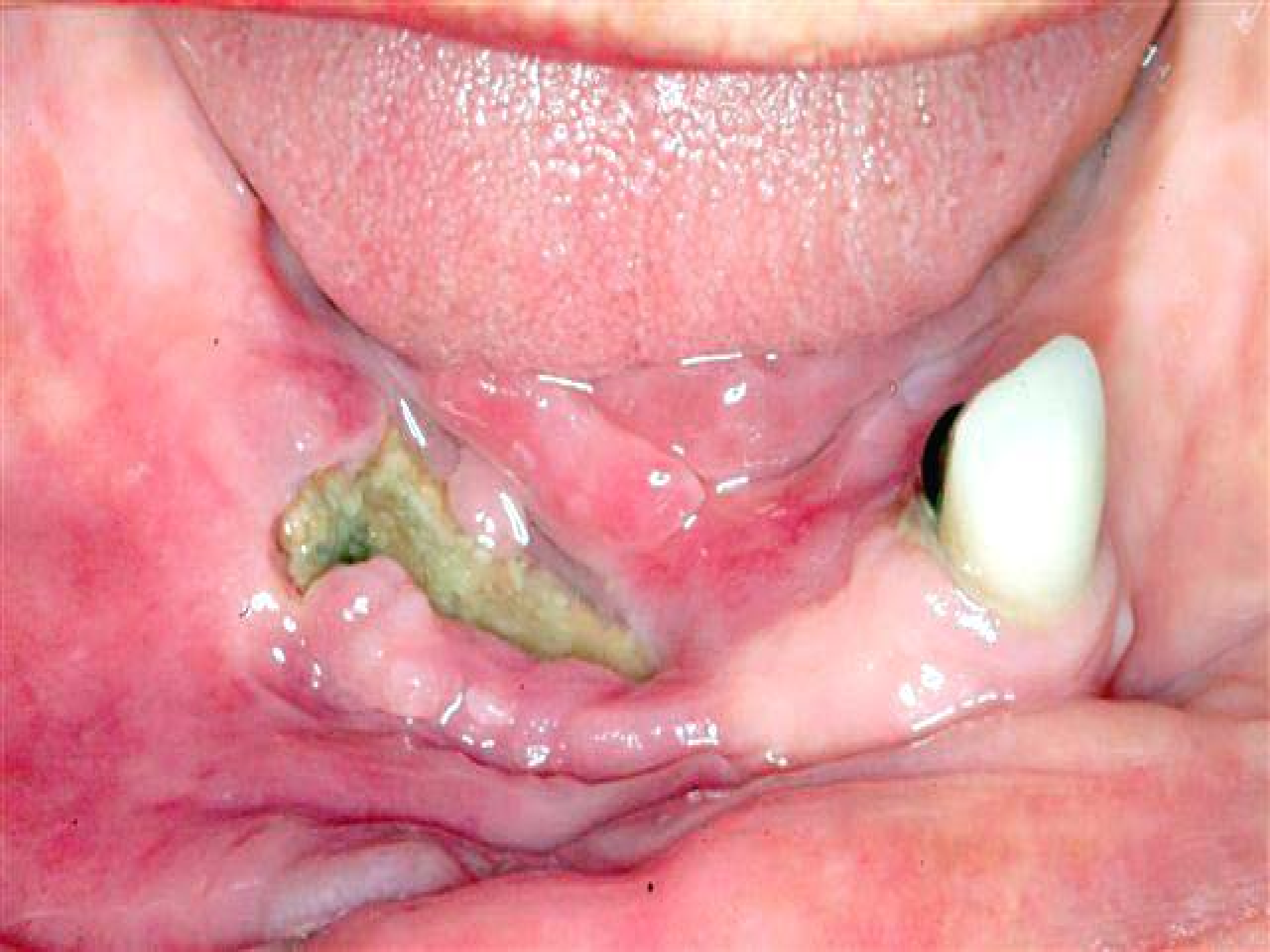
Reducing the frequency of the bisphosphonate or denosumab has seen a reduced incidence and severity.

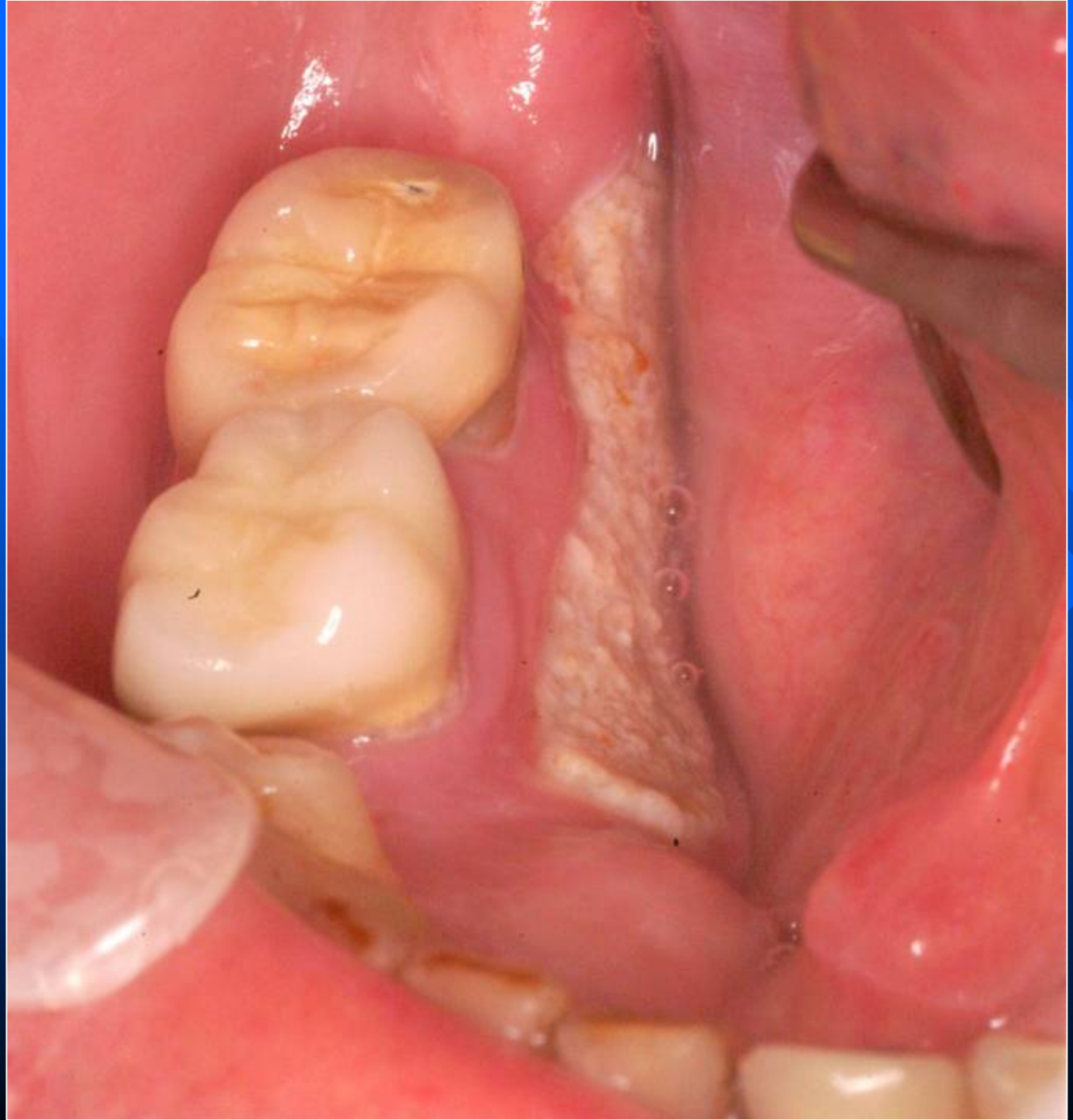
Four Critical Issues

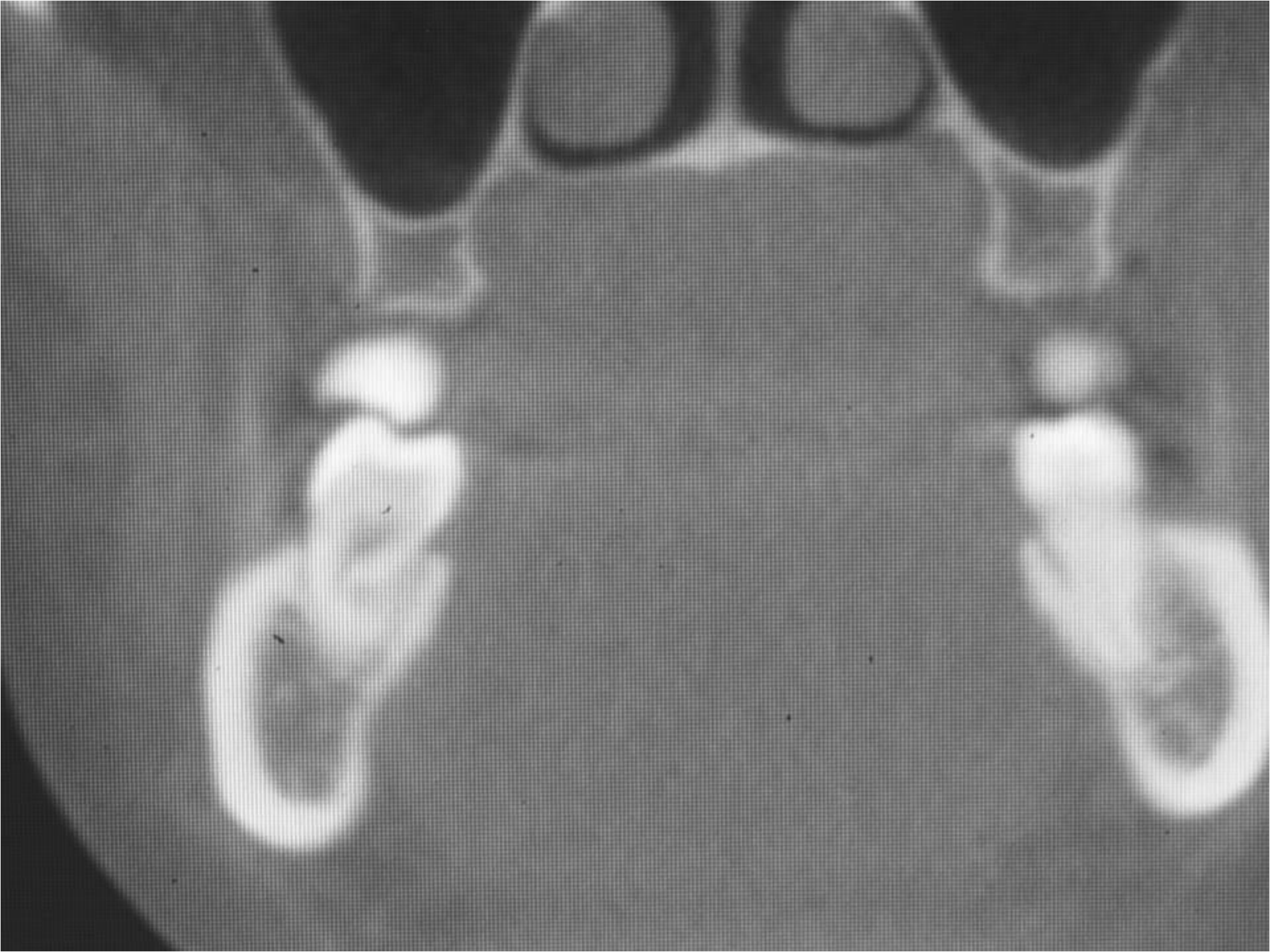
2. **Initiating factors: extractions, spontaneous, traumatic occlusion, other surgeries into alveolar bone ie. Dental implants**

Initiating Events

1.	Spontaneous	52/180	(29.0%)
2.	Tooth removal	111/180	(61.6%)
3.	Dental implant placement	4/180	(2.2%)
4.	Periodontal surgery	10/180	(5.6%)
5.	Biopsy	2/180	(1.1%)
6.	Apicoectomy	1/180	(0.59%)







Occlusion Plays A Significant Role In Initiating DIONJ

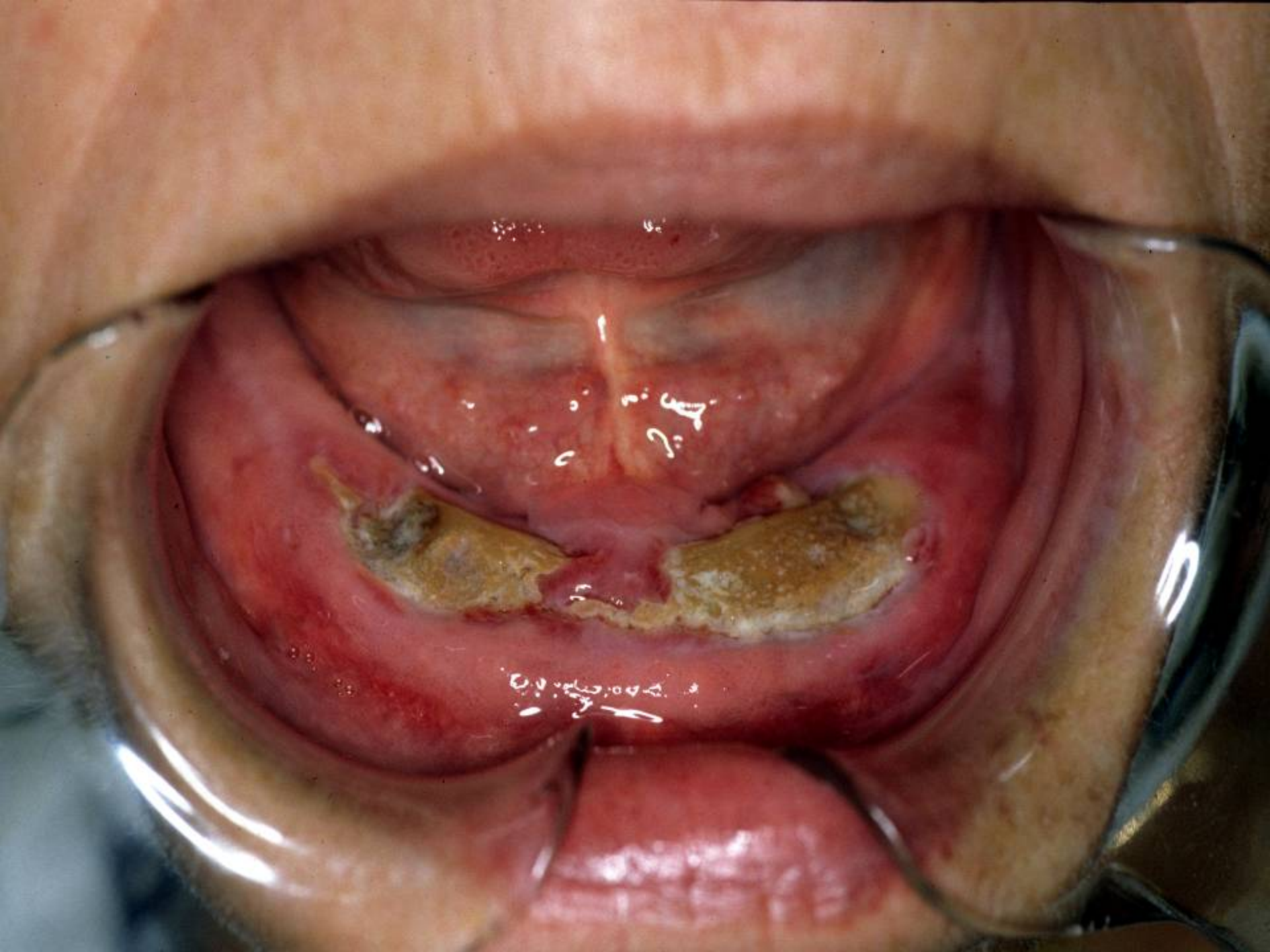
Marx RE, Sawatari Y, Fortin M, Broumand V.

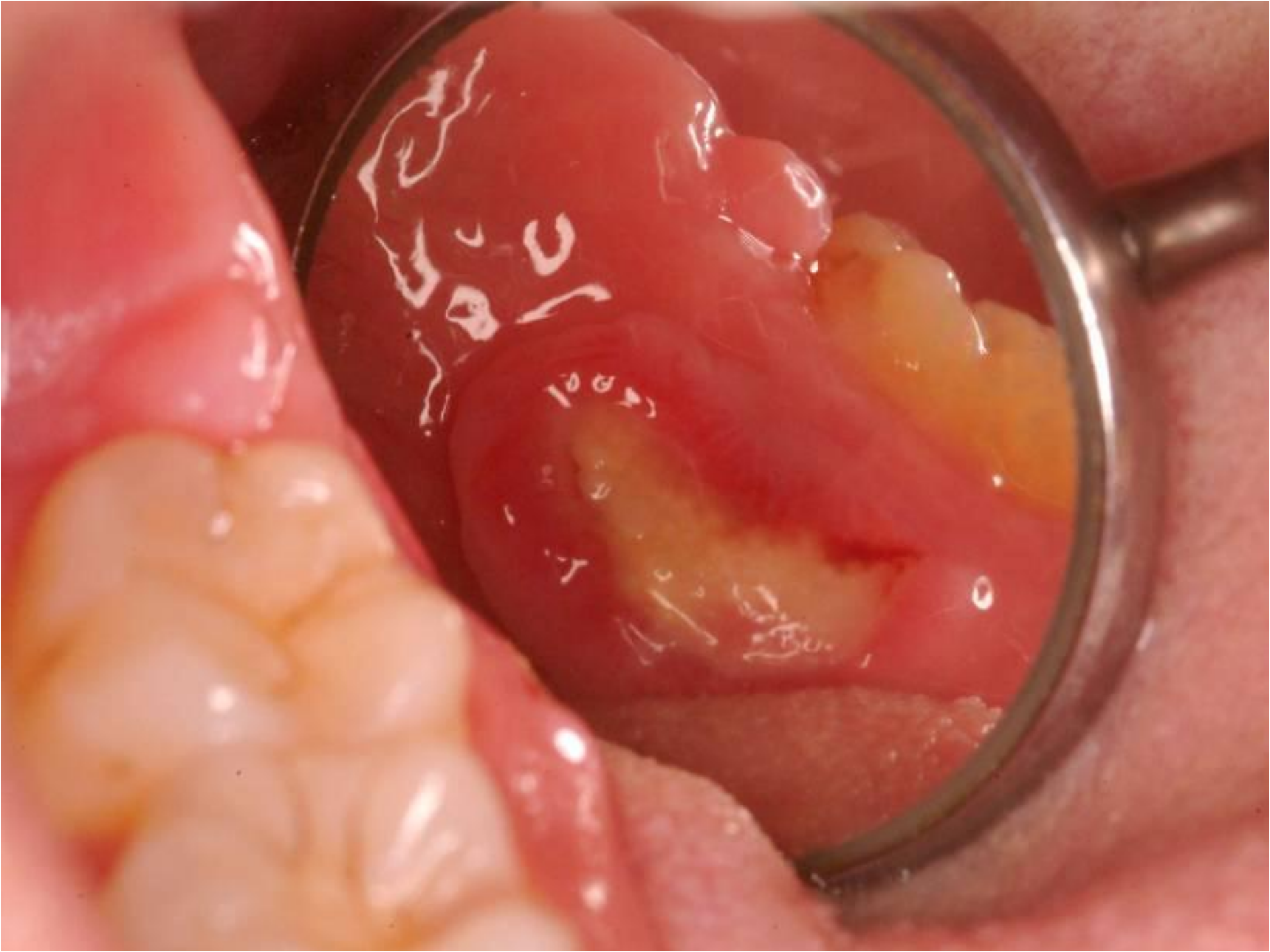
Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: Risk factors, recognition, prevention, and treatment.

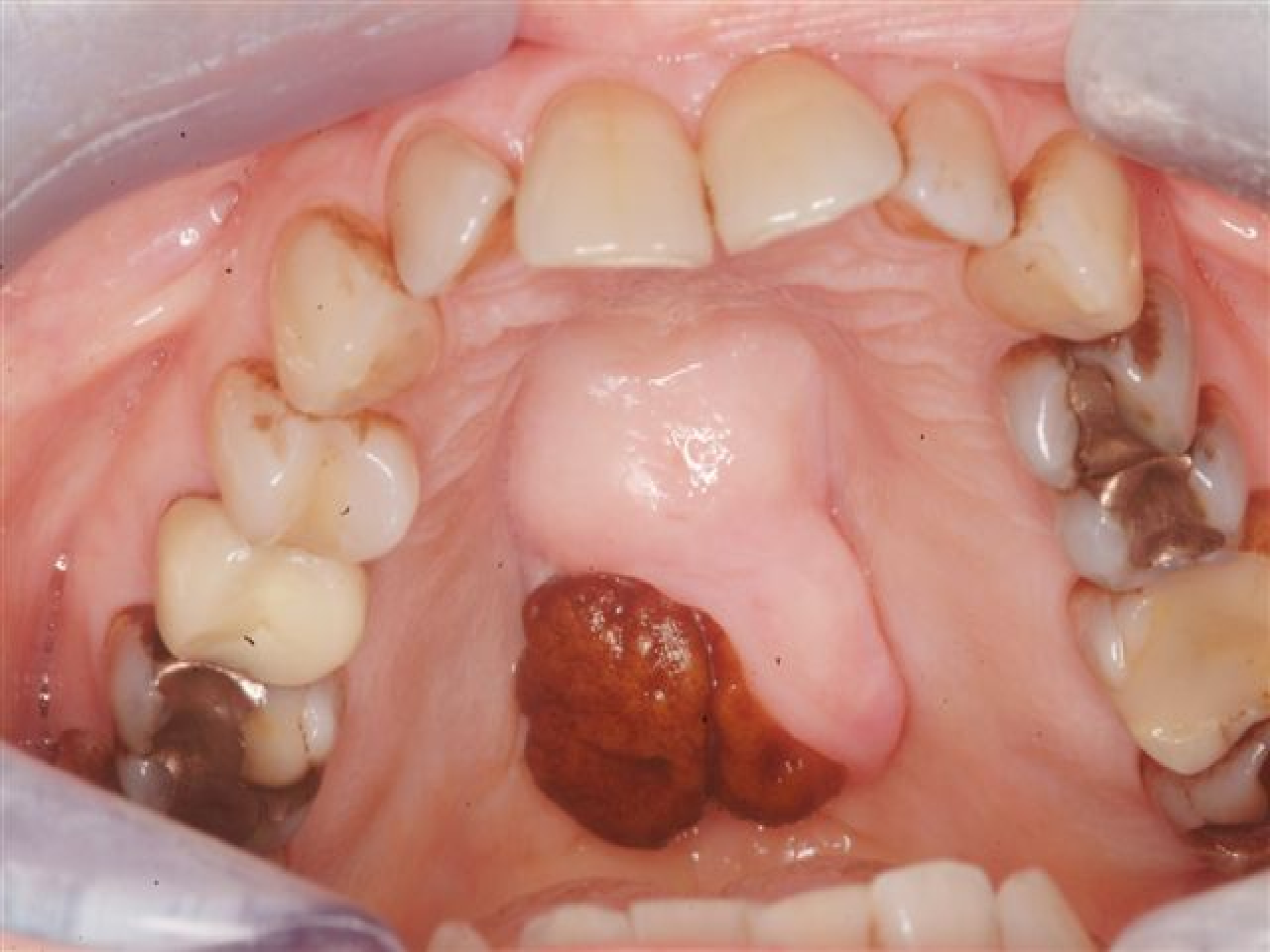
J Oral Maxillofac Surg 63:1567-1575, 2005

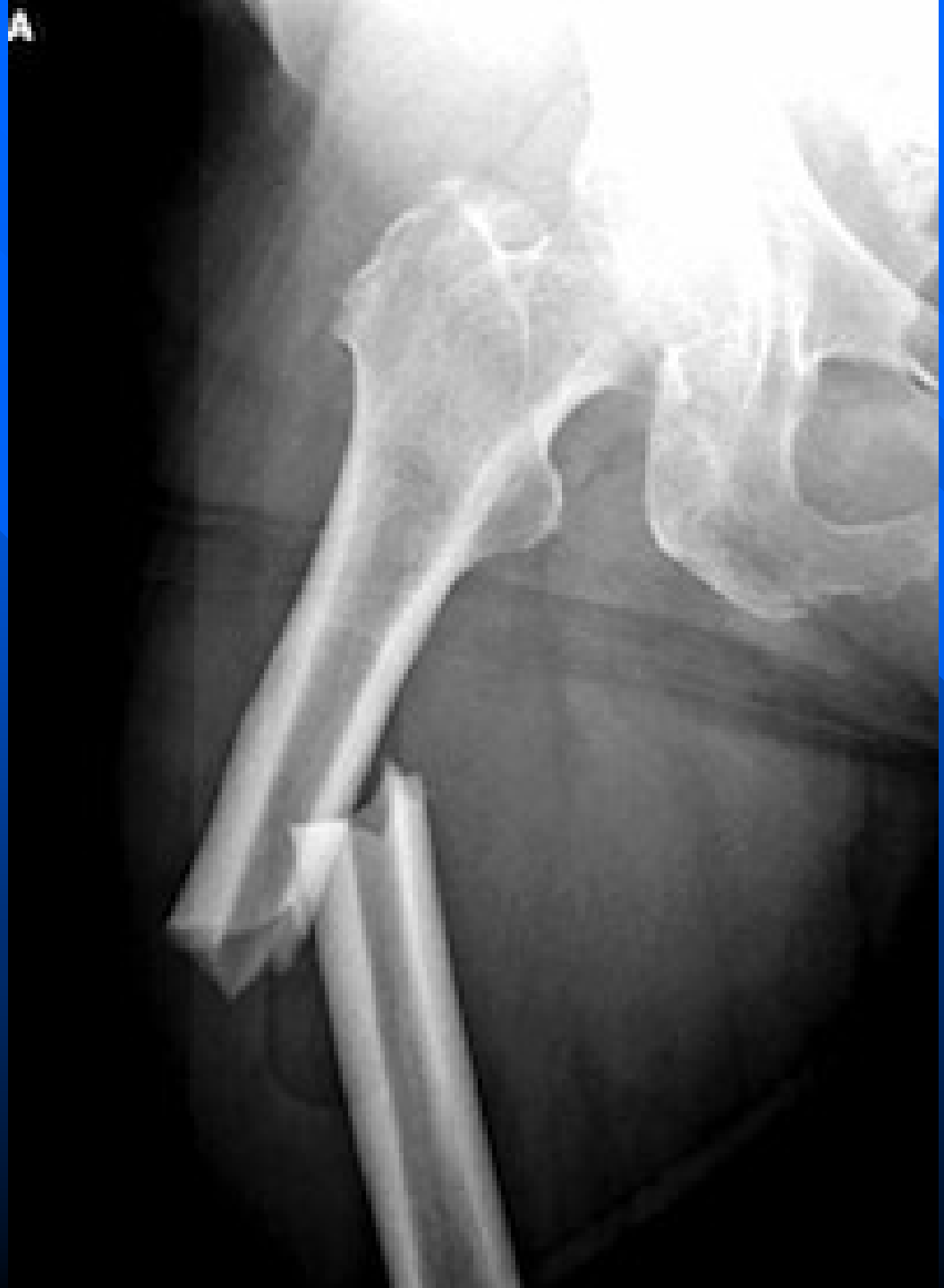
Four Critical Issues

3. **Vulnerable Sites: alveolar bone, tori, mandible > maxilla 2:1, lingual cortex .**





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Lenart BA, Lorich DG, Lane JM.

Atypical Fracture Of The Femoral Diaphasis In Postmenopausal Women Taking Alendronate.

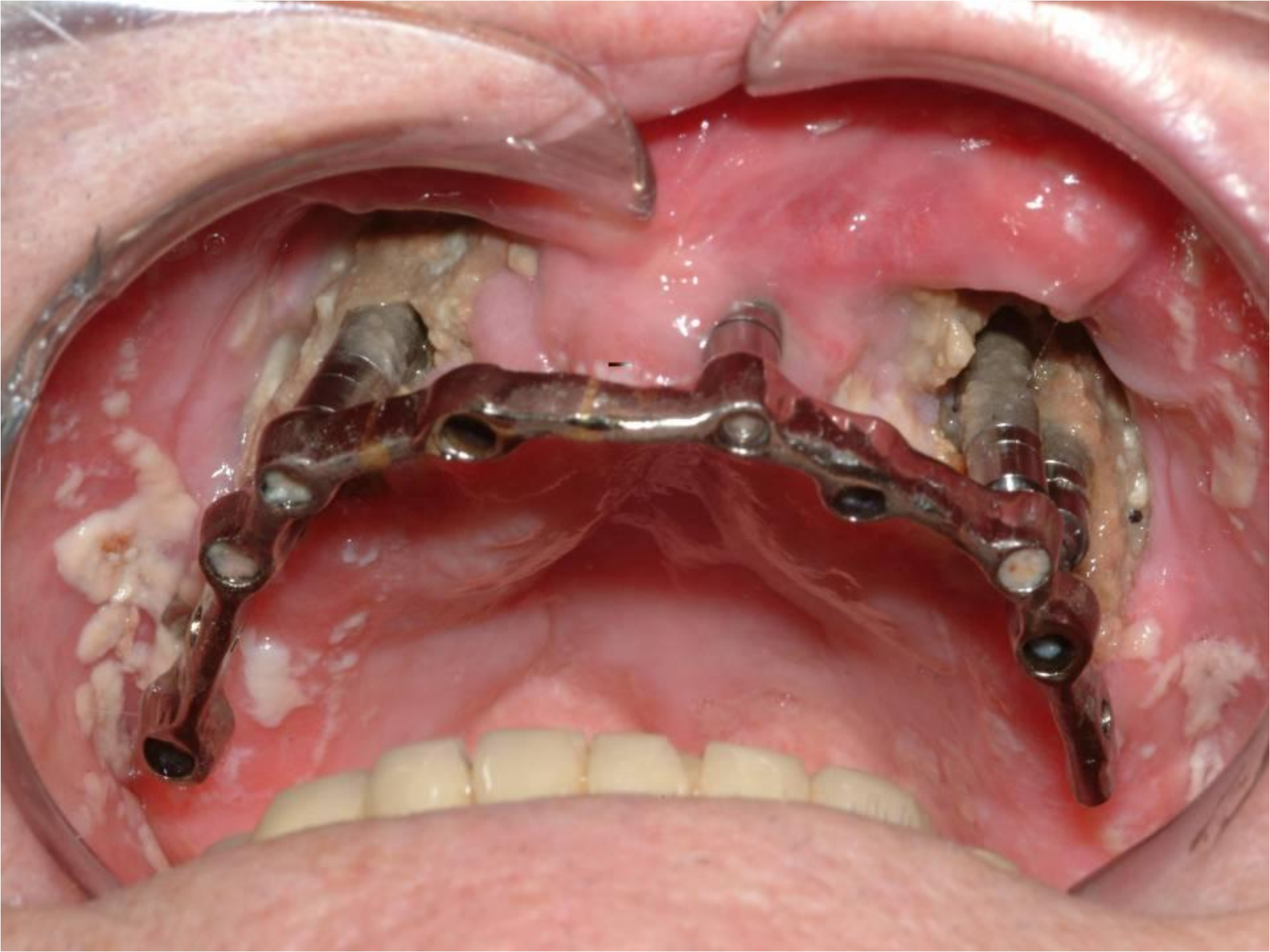
N Engl J Med
358:1304 - 1305, 2008

Four Critical Issues

4. Co-morbidities: other drugs i.e. steroids chemotherapy; obesity diabetes, smoking, cancer, peridontitis etc.

Comorbidities

1. Do not cause ONJ
2. Make ONJ occur sooner
3. Make ONJ more severe
4. Make ONJ more extensive

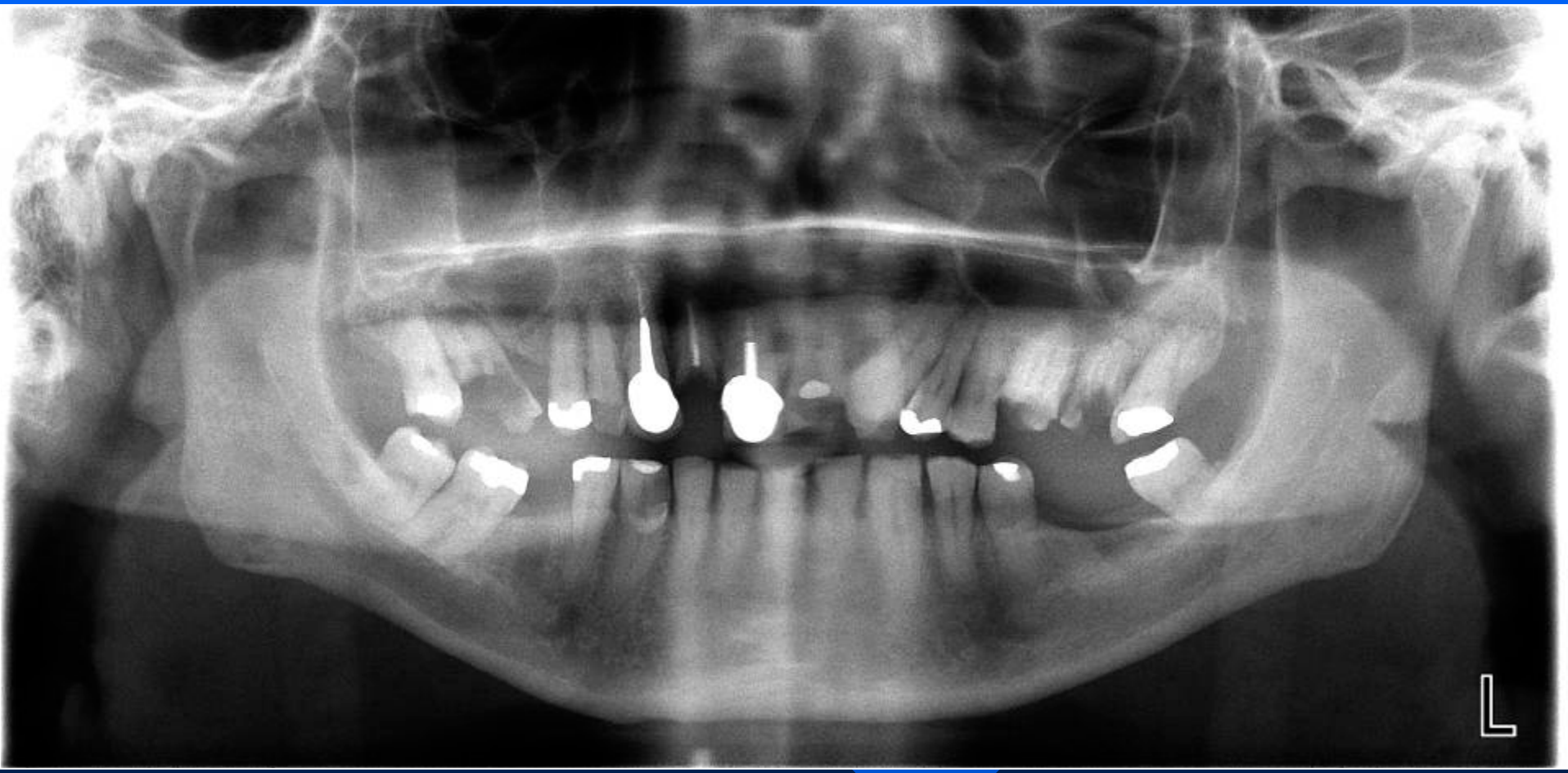


Prevention Of ONJ In Cancer Patients Taking Pamidronate, Zoledronate, or Denosumab

Extraction, Traumatic Occlusion, Periodontal Disease Are The Main Initiators Of Oral DIONJ

IV Bisphosphonates
Recommendations Before Therapy

1. Remove unsalvageable teeth
2. Prophylaxis
3. Treat caries
4. Treat periodontitis
5. Defer bisphosphonates for 2 months
6. Occlusal adjustment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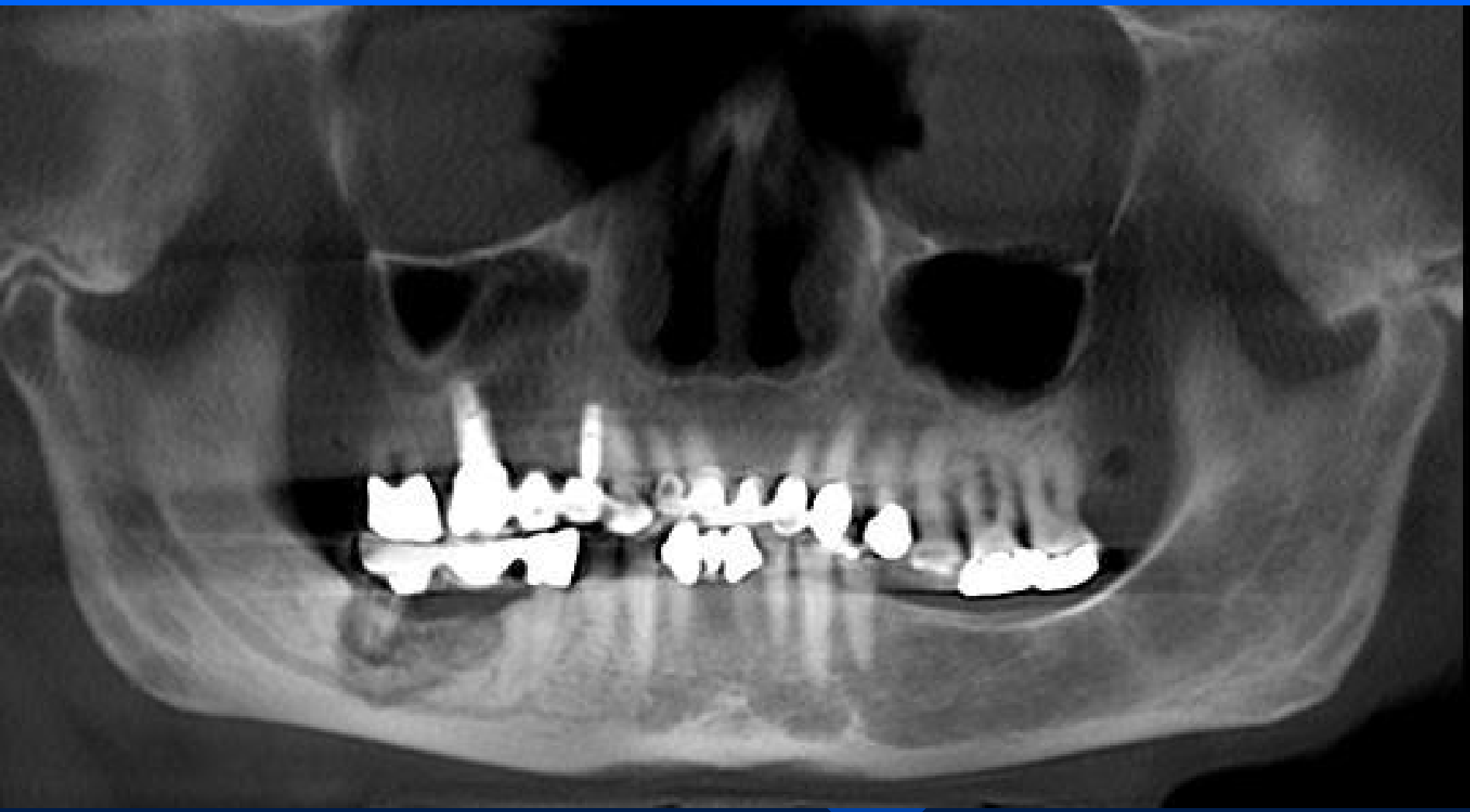


Recommend

Prior to or early in BP or Denosumab therapy, refer to a dentist or an oral maxillofacial surgeon.

IV Bisphosphonates
Recommendations During Therapy

1. Avoid invasive procedures (extractions, periosurgery, implants)
2. Treat caries: if needed, RCT and amputate crown
3. Supragingival scaling
4. Splint mobile teeth
5. If extractions are unavoidable, provide informed consent of increased risk

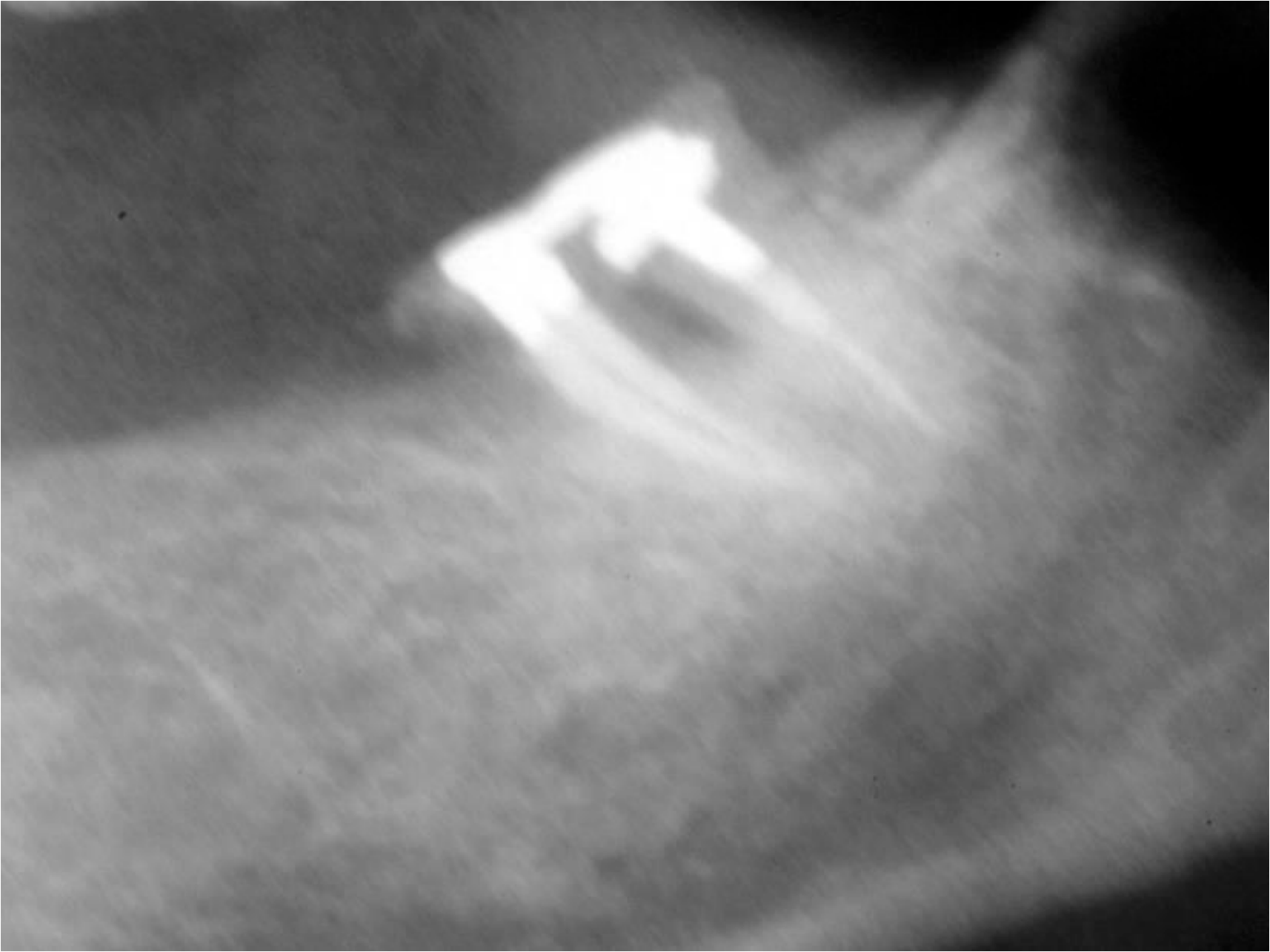
Recommend

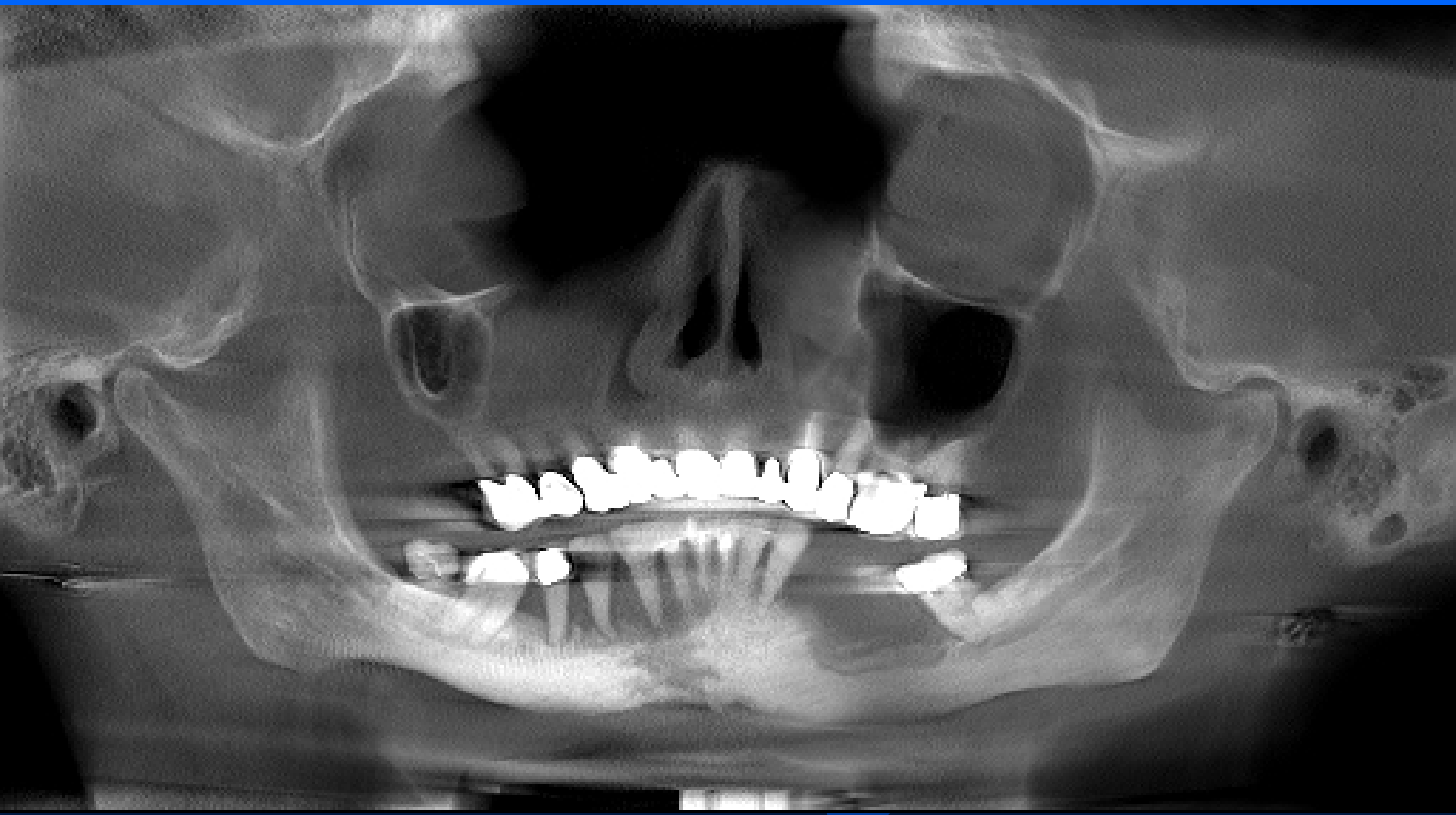
During BP or Denosumab therapy be alert for:

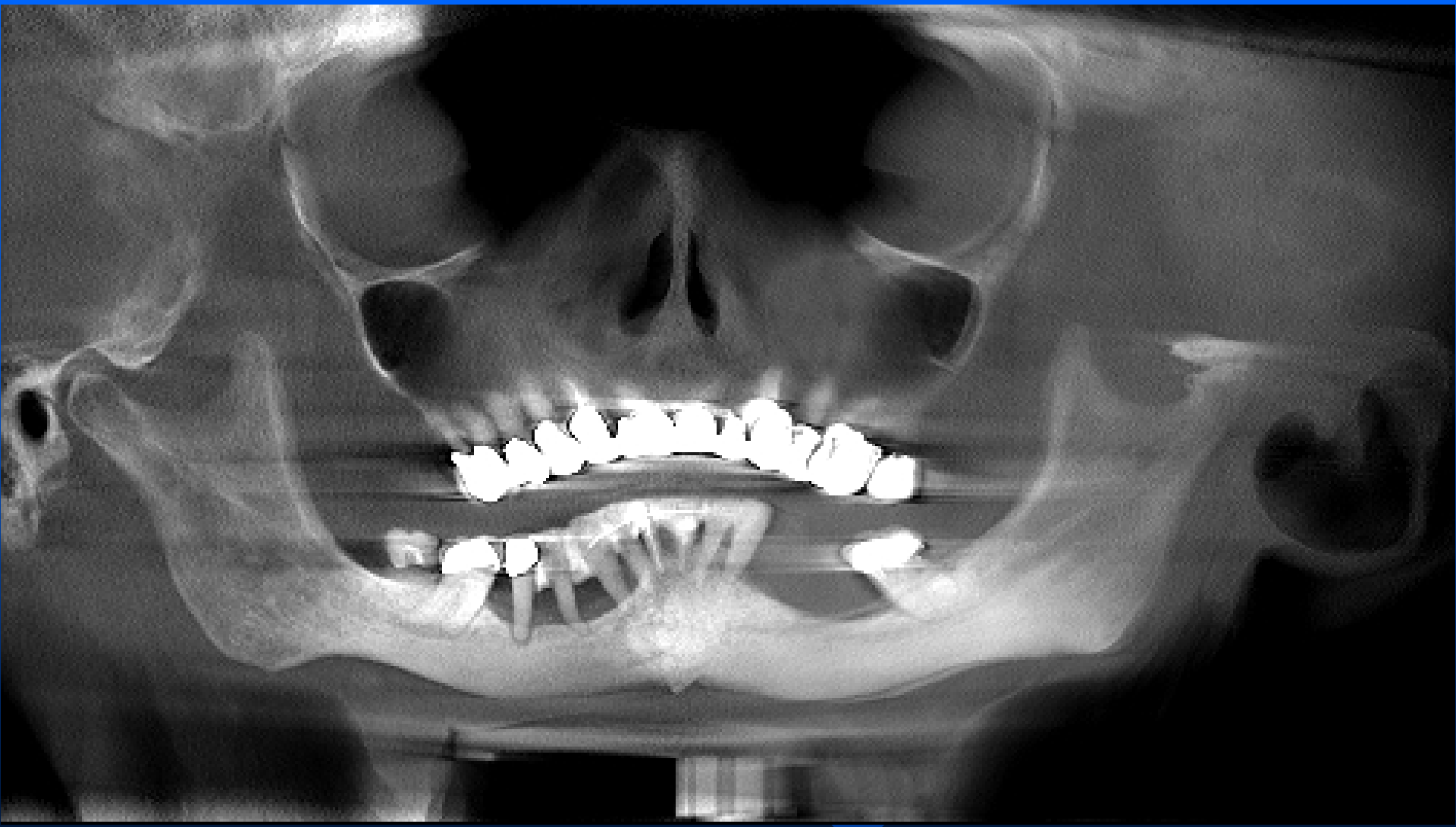
1. Jaw pain
2. Tooth pain
3. Facial selling
4. Fistulas
5. Exposed bone

Recommend

During BP or Denosumab therapy, refer to an oral maxillofacial surgeon for evaluation.







Treatment Options For ONJ Patients Treated For Cancer Metastasis Specific For Each Drug

Presenting Findings

1. Asymptomatic exposed bone
   52/180 (29%)
2. Painful exposed bone
   128/180 (71%)

Cancer Patients With DIONJ

1. Avoid debridements
2. Smooth sharp edges
3. Treat with PCN VK 500 mg qid or doxycycline 100 mg qd and Peridex tid

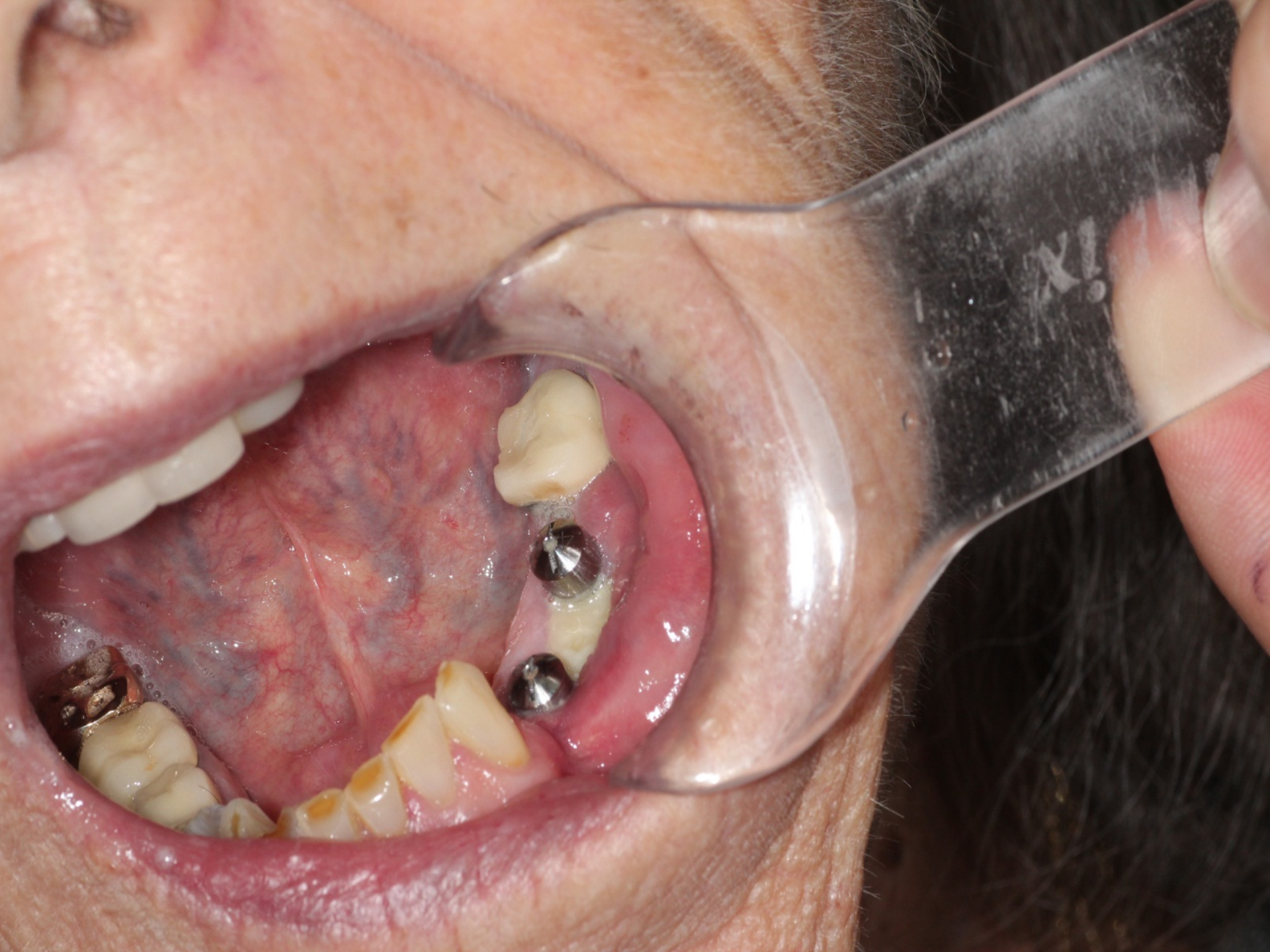
Cancer Patients With DIONJ

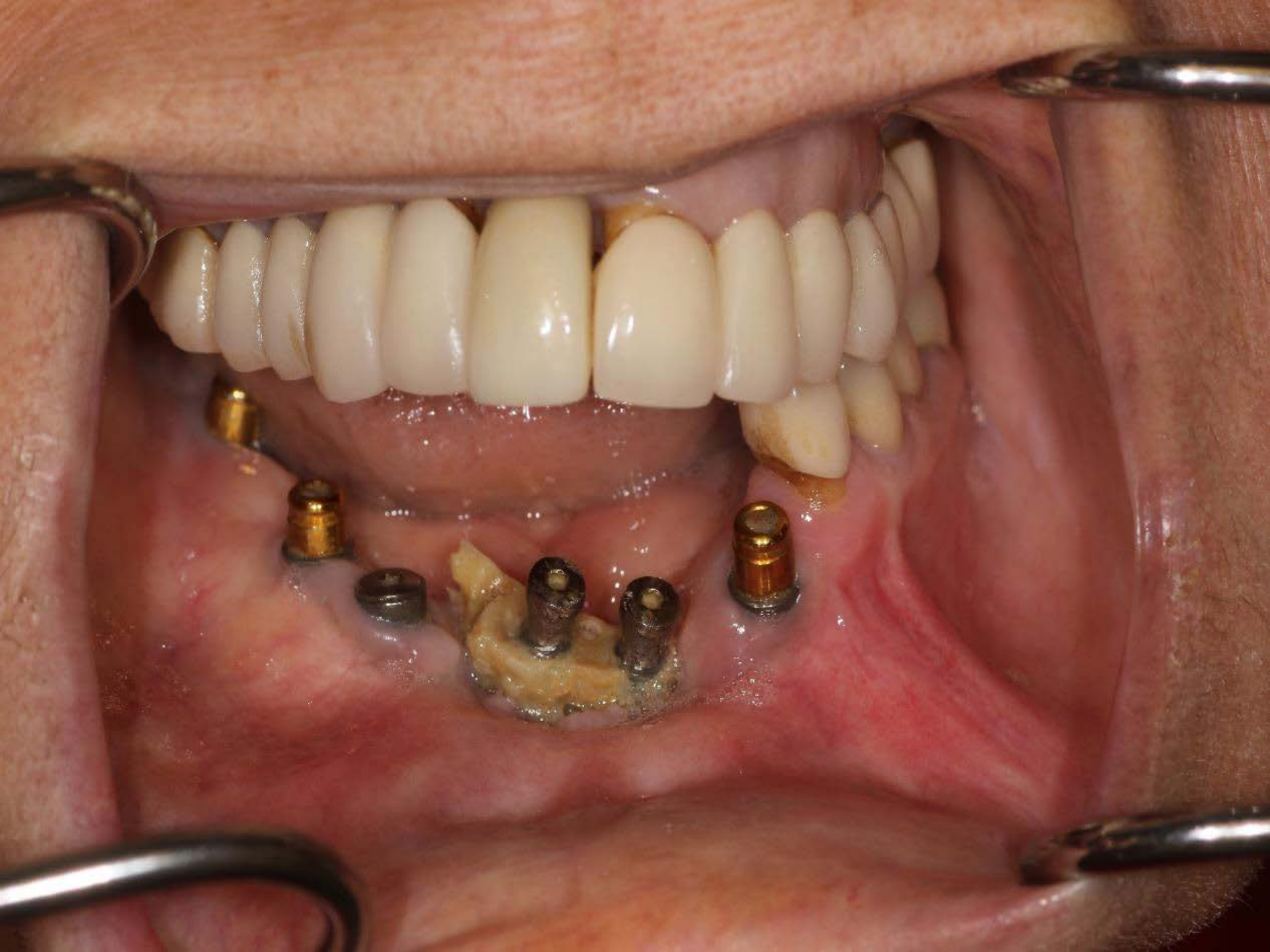
4. Doxycycline in PCN allergic patients
5. Add metronidazole 500 mg tid x 10 day in refractory cases
6. If surgery unavoidable, alveolectomy or continuity resection

Note!

Non-invasive dentistry is safe at all times, i.e. restorations, crowns, bridges, dentures, root canal treatments, non-osseous perio surgery.

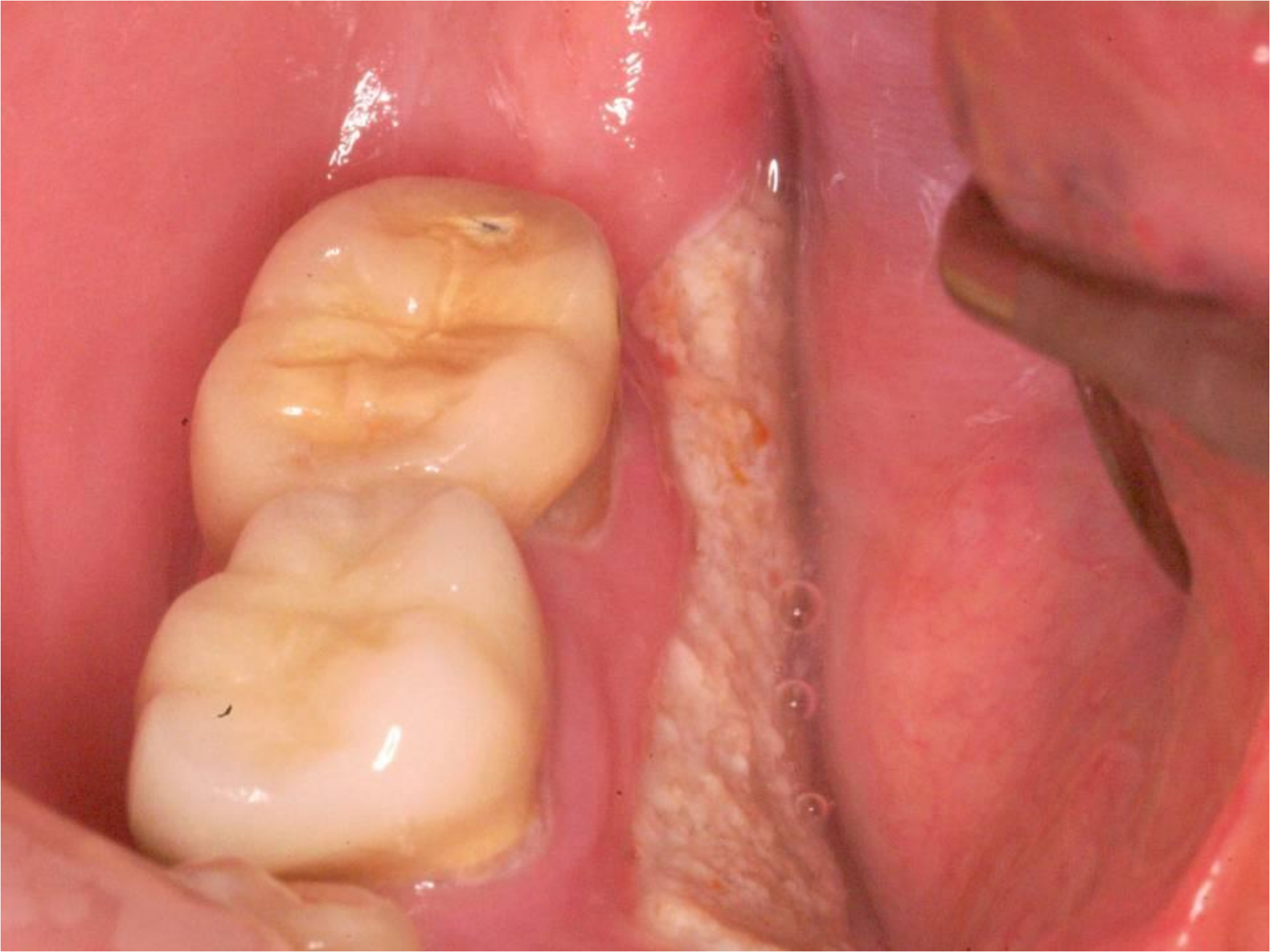
Dental implants in cancer patients on bisphosphonates or Denosumab is a *high* risk for DIONJ.





If the BP or Denosumab remains a therapeutic advantage, continue it.

We will manage the DIONJ.



Microorganisms Most Commonly Found In Bisphosphonate Induced Osteonecrosis

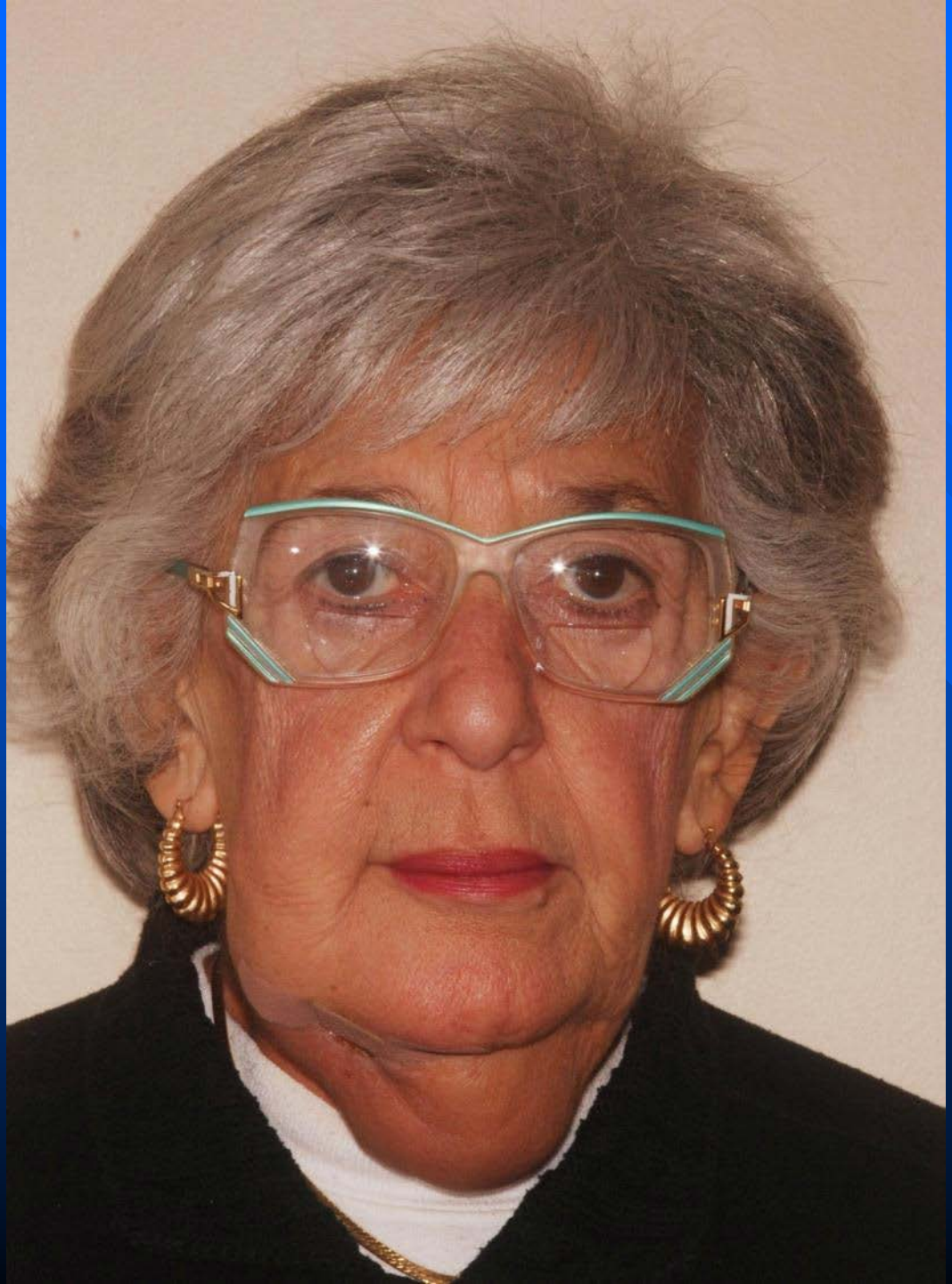
1. Actinomyces
2. Veillonella
3. Eikenella
4. Moraxella

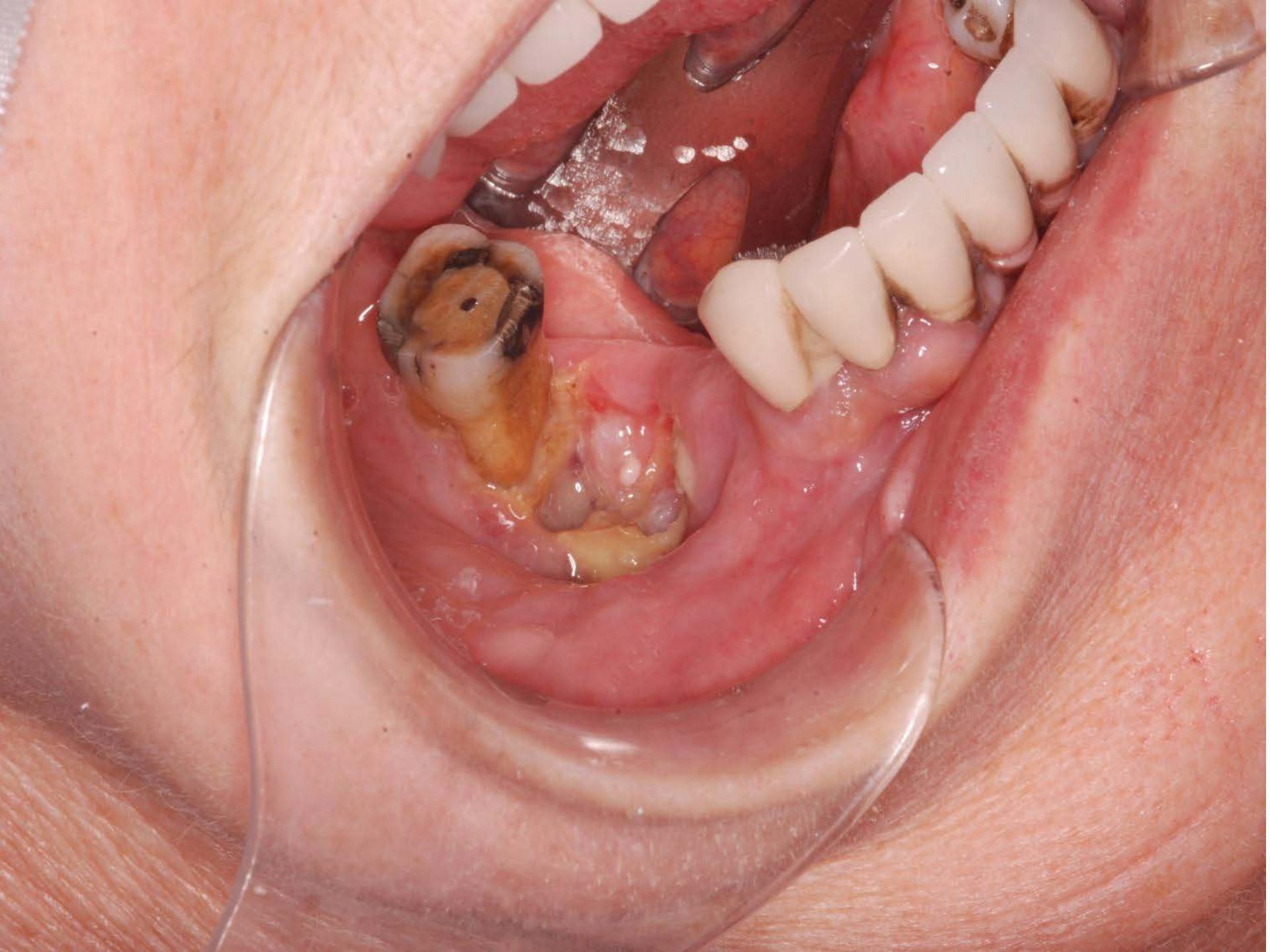
Ineffective Therapies Frequently Recommended For ONJ

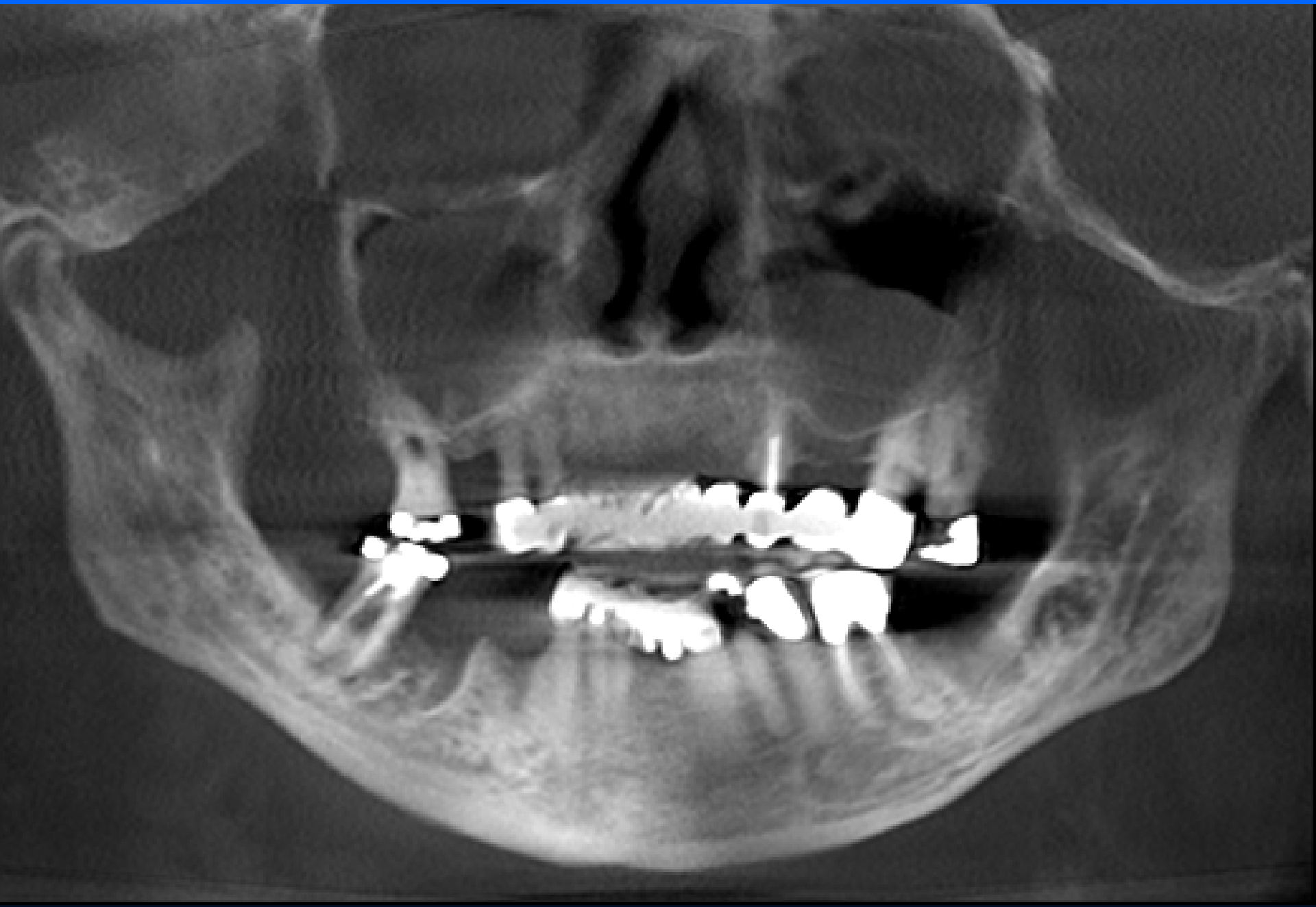
1. Clindamycin
2. Hyperbaric oxygen
3. Ozone
4. Laser

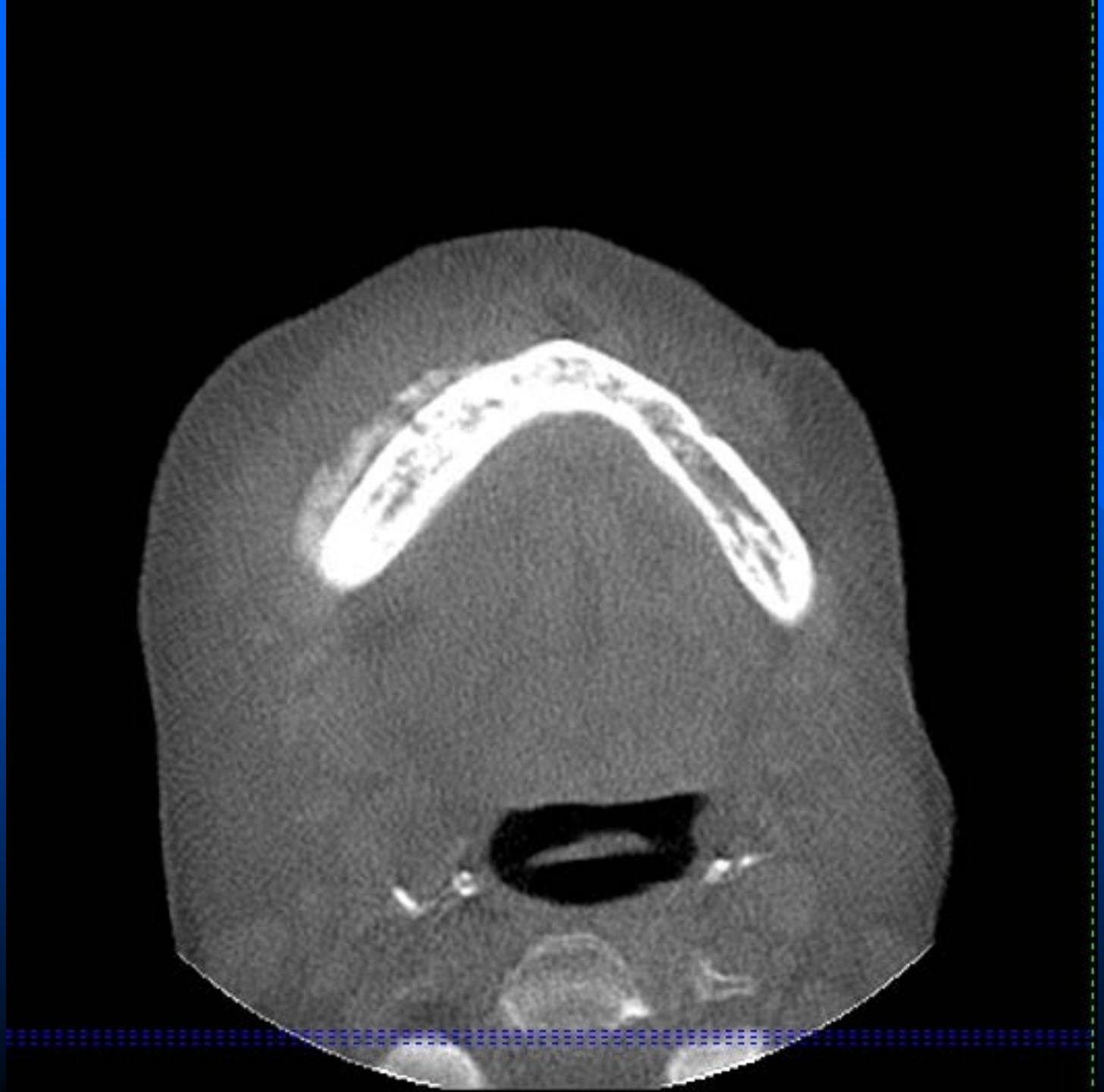
Indications For Resection

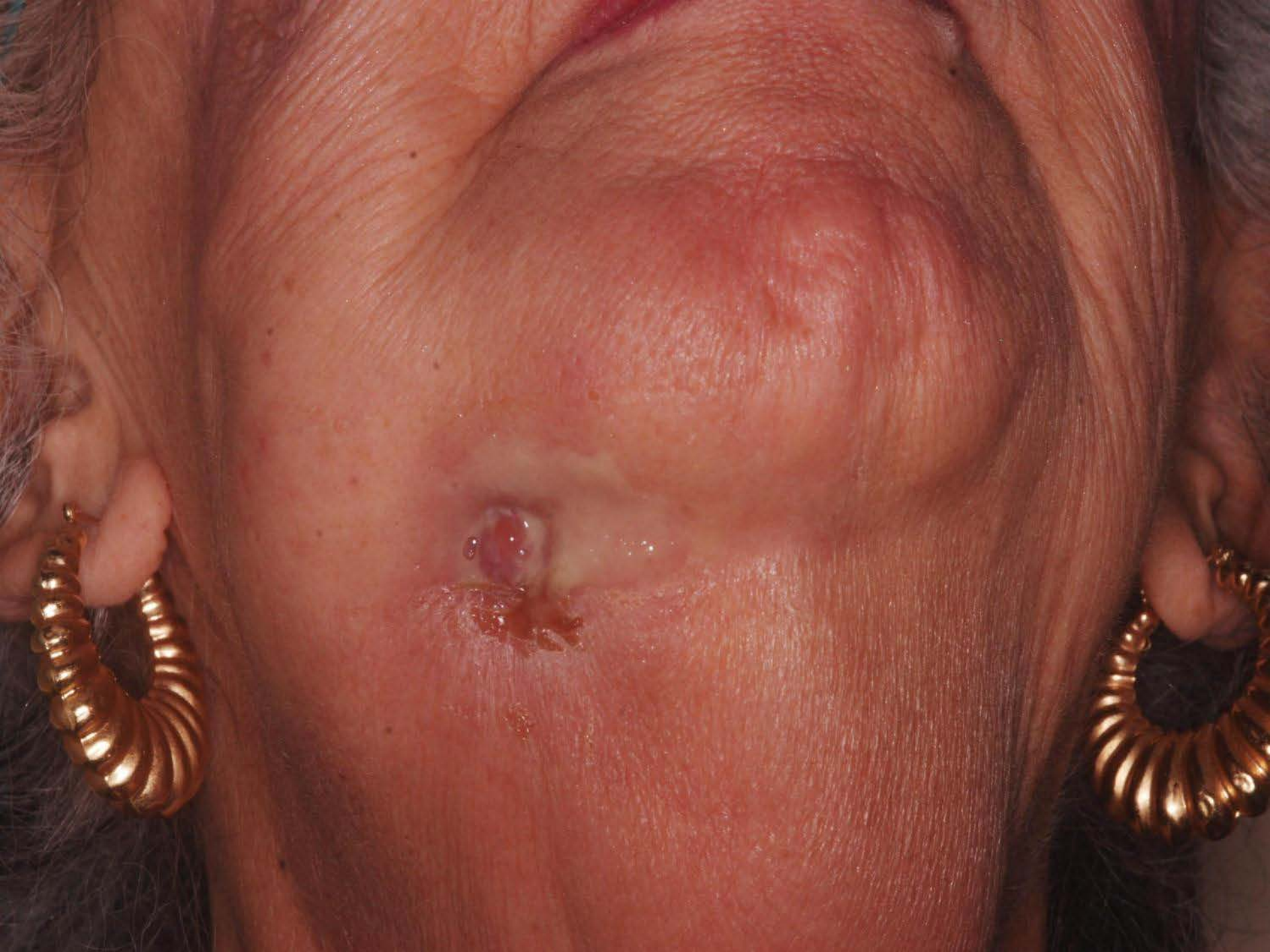
1. Symptomatic cases refractory to nonsurgical treatment
2. Pathologic fractures
3. Direct sinus communication

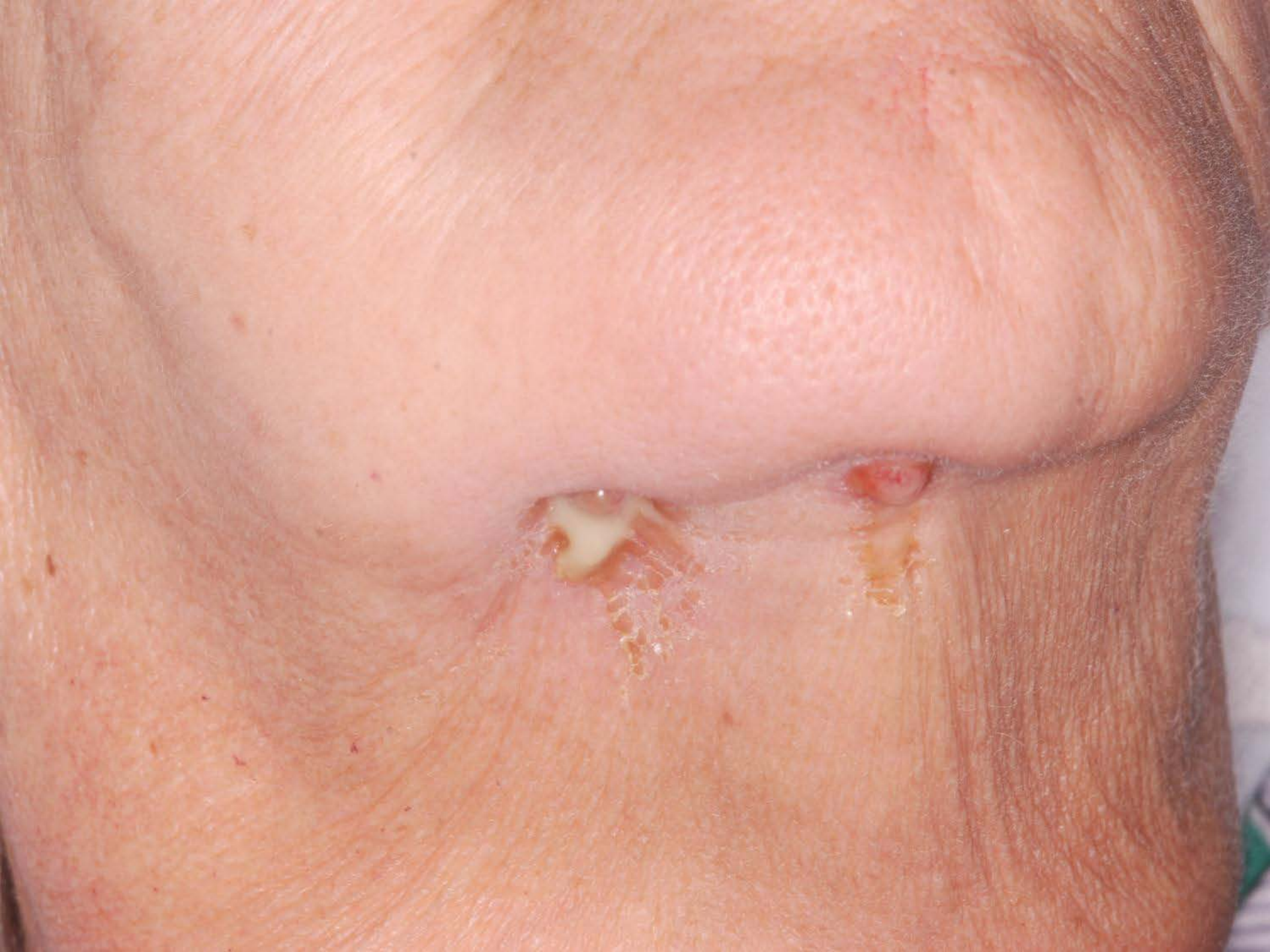


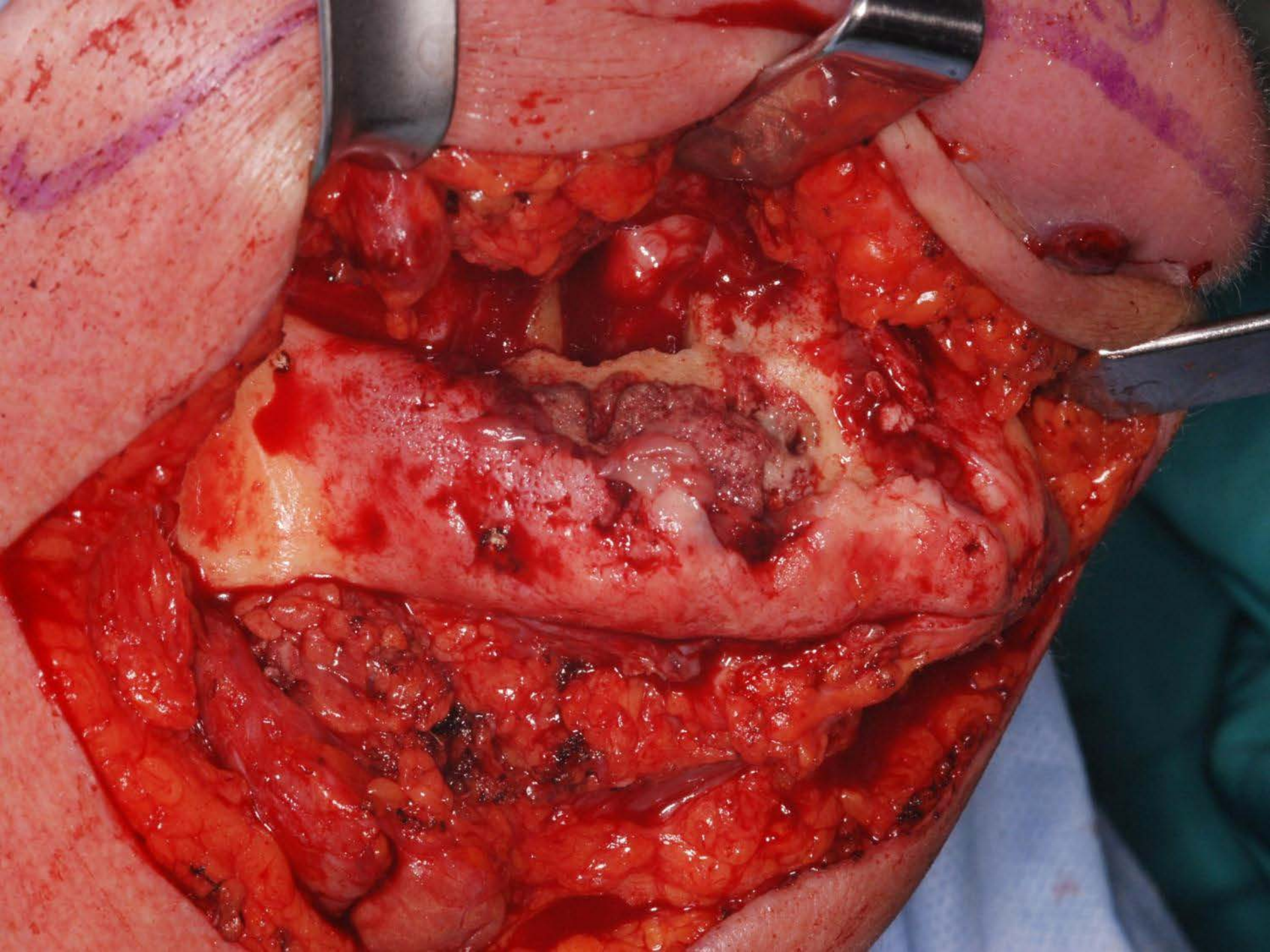


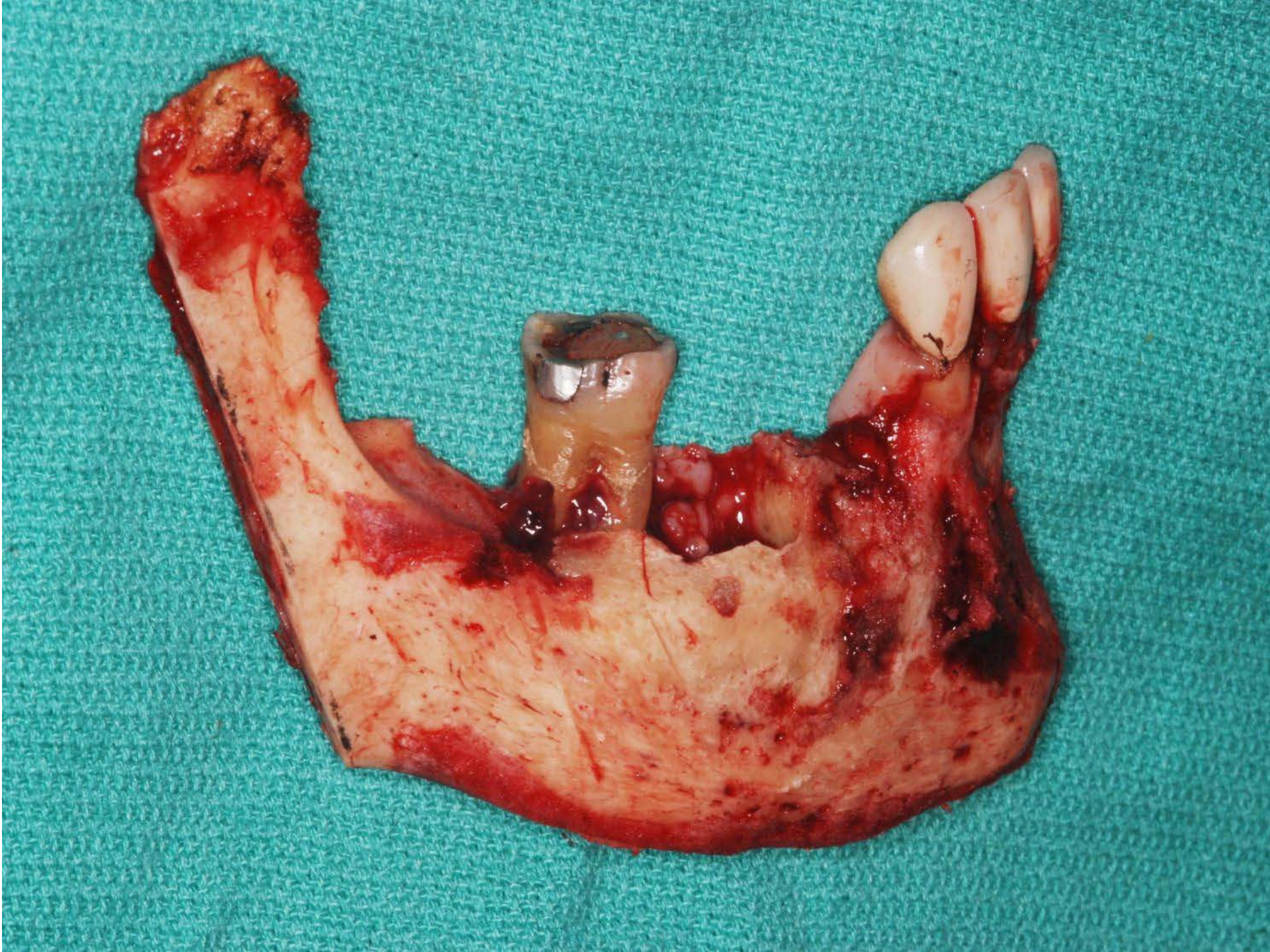


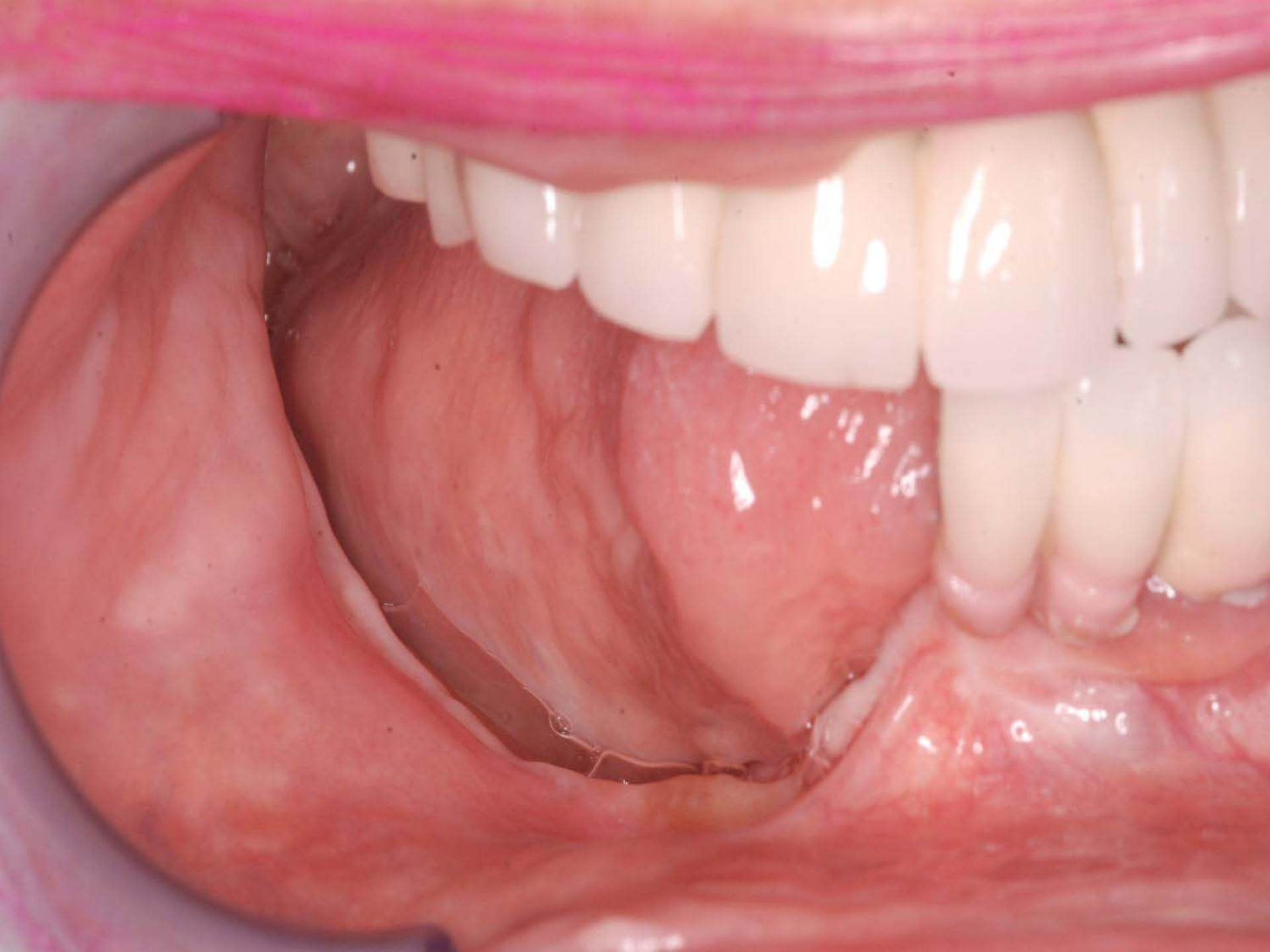


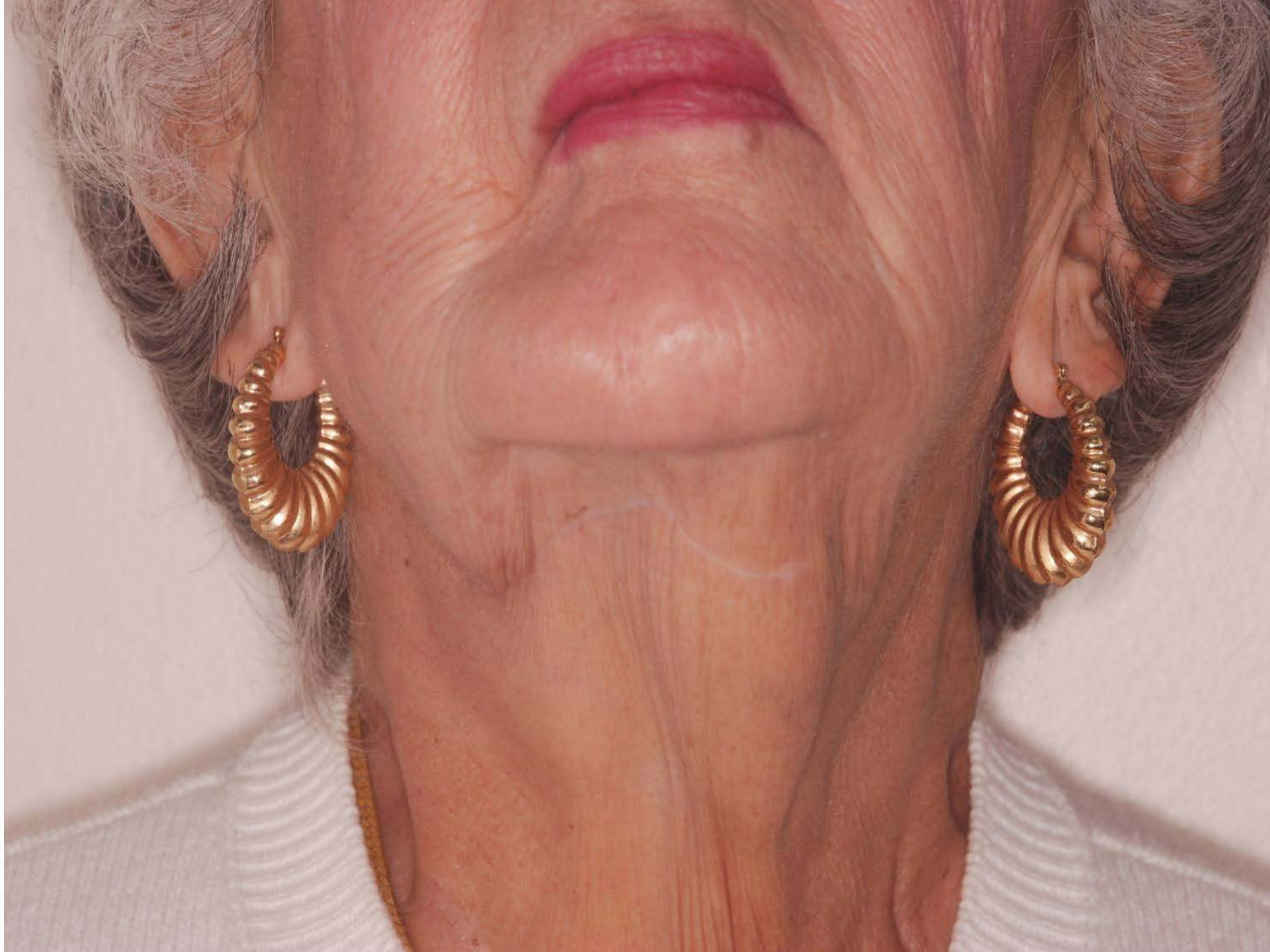


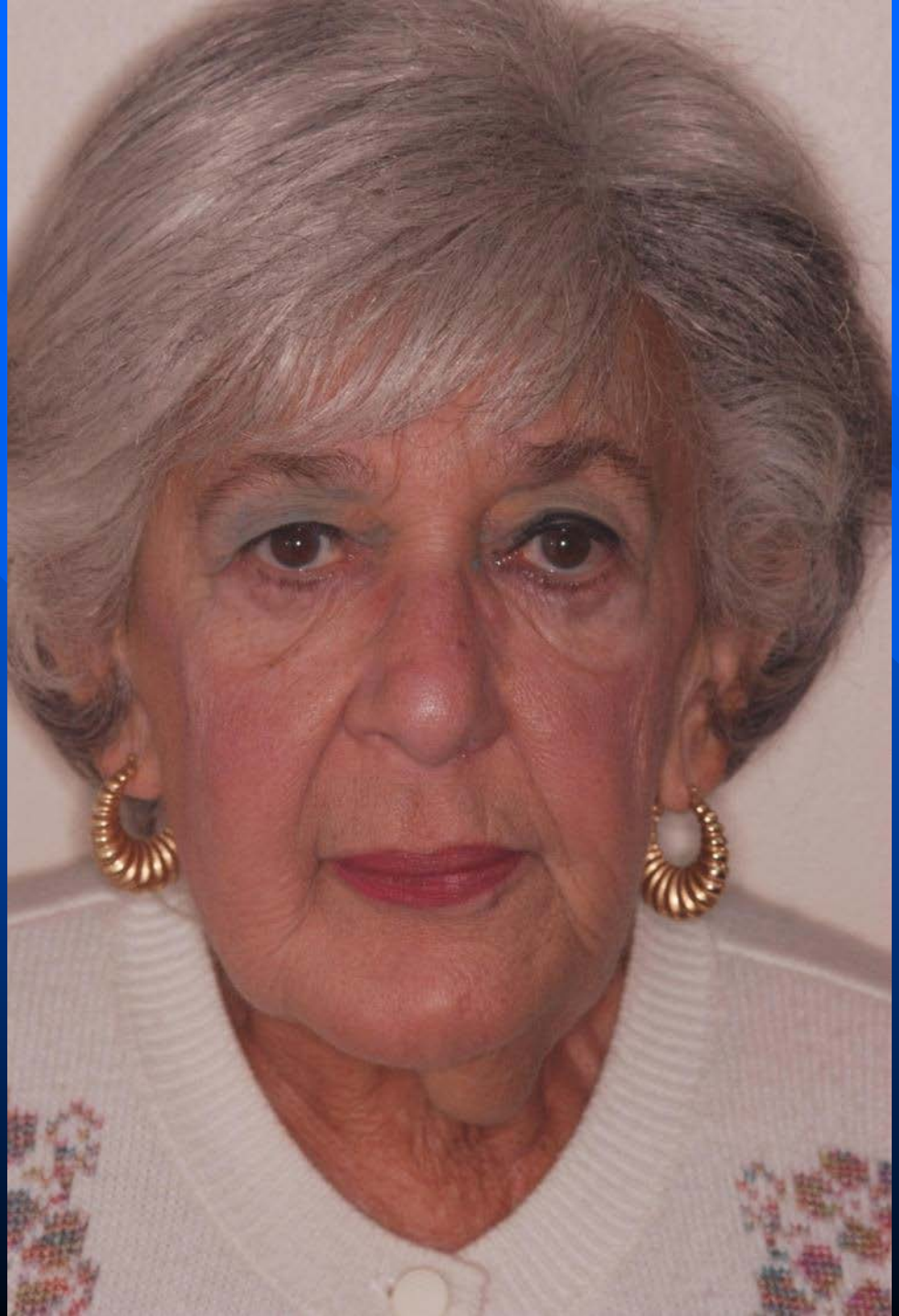


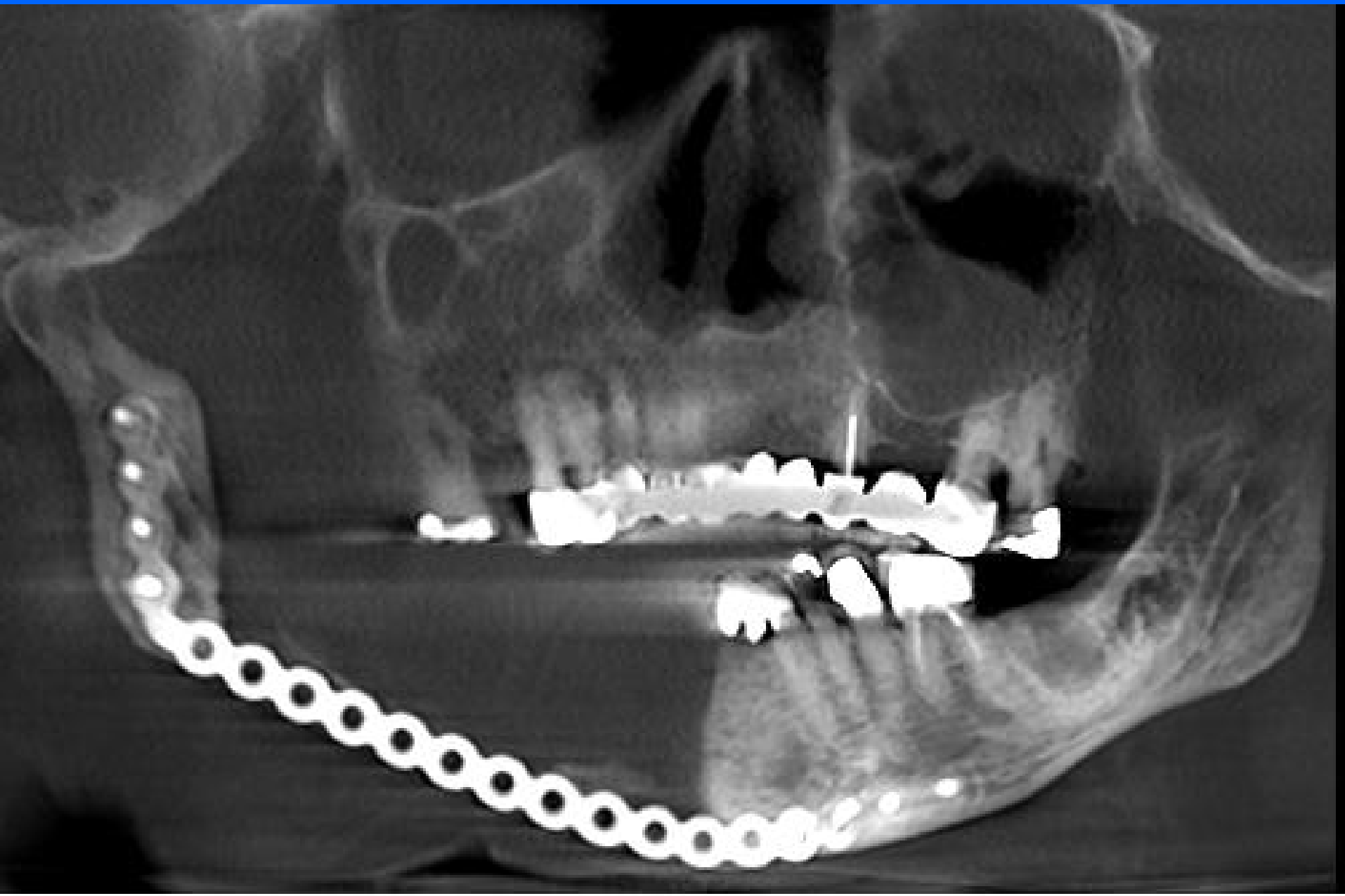


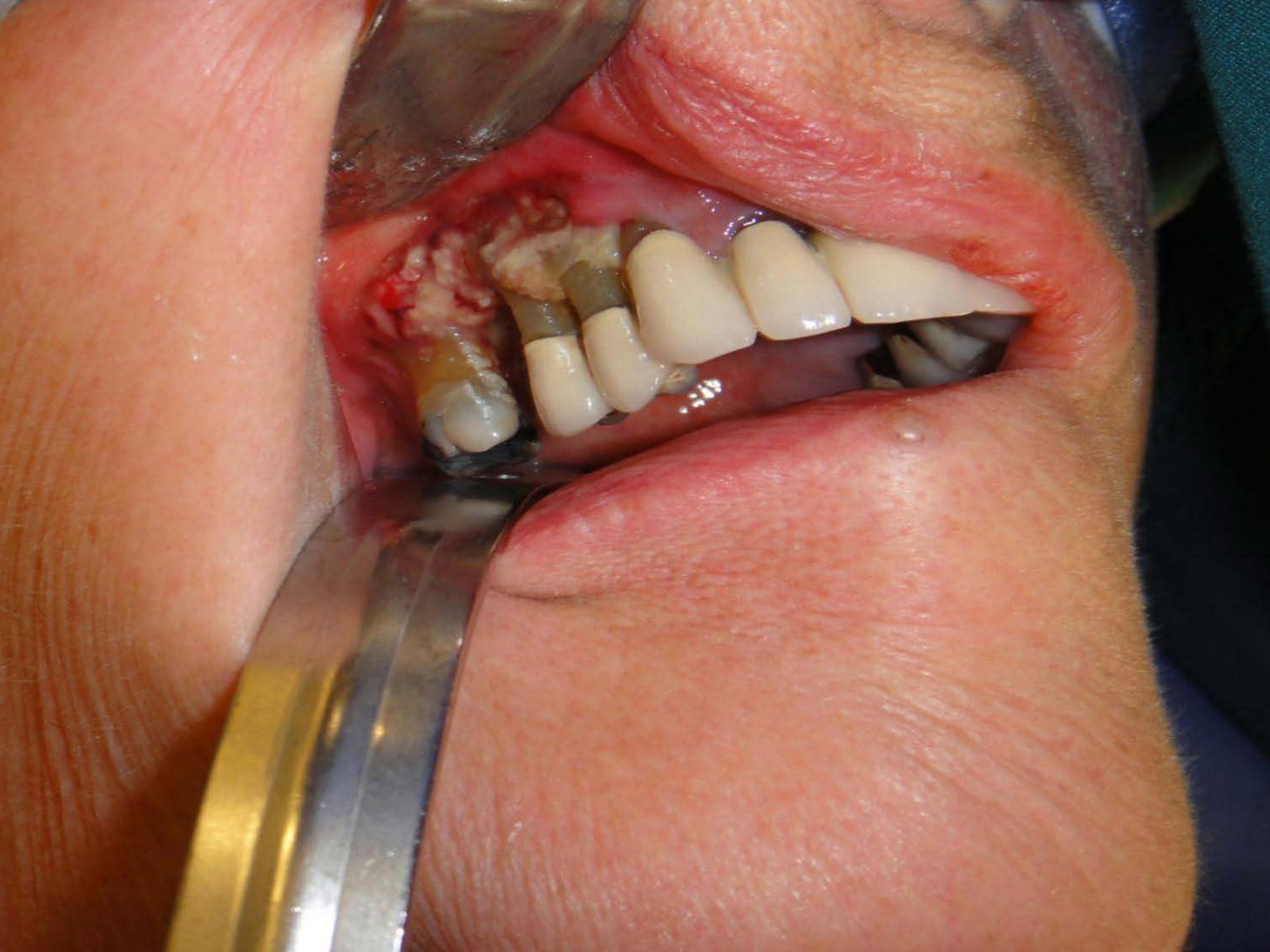


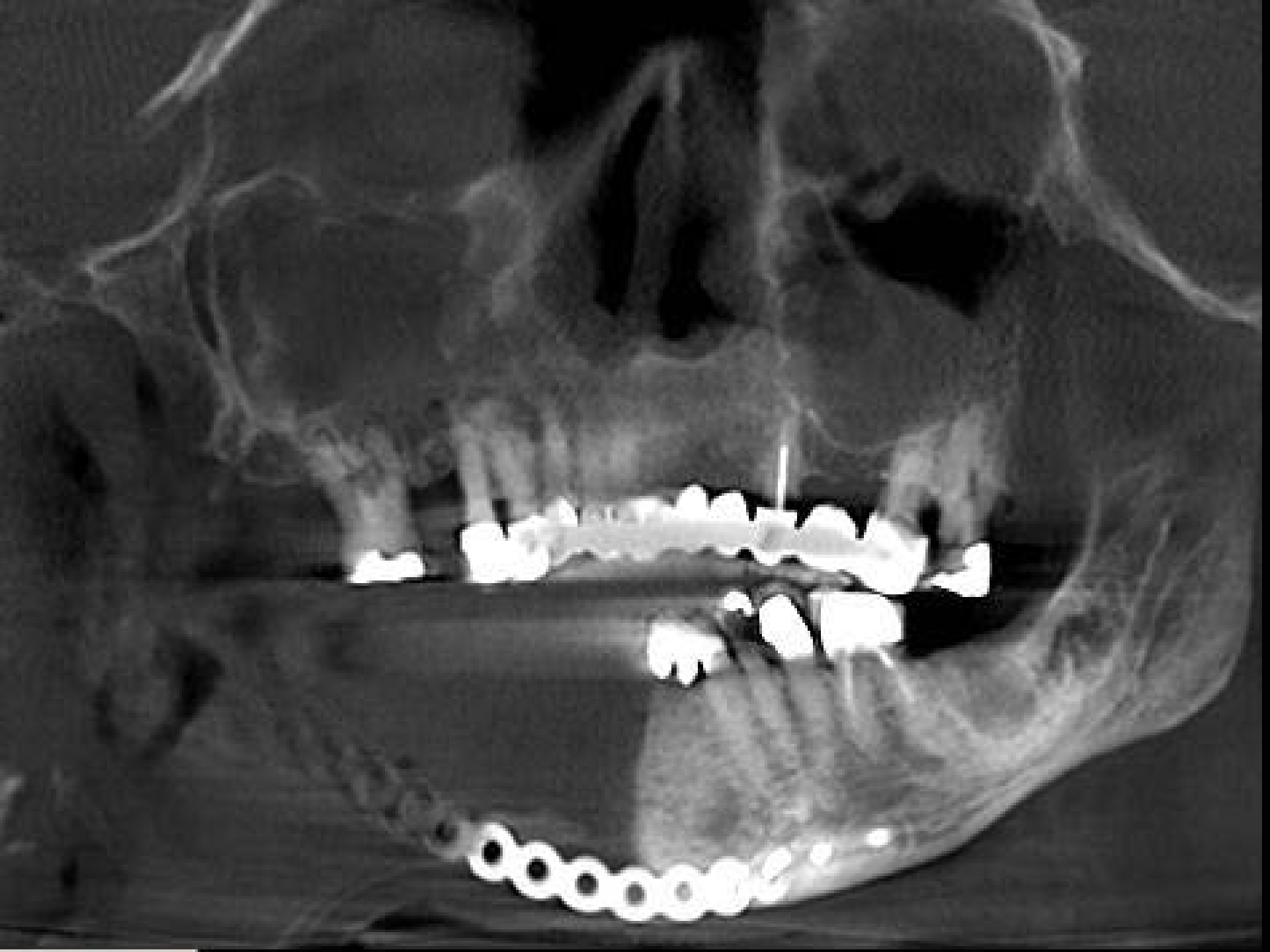


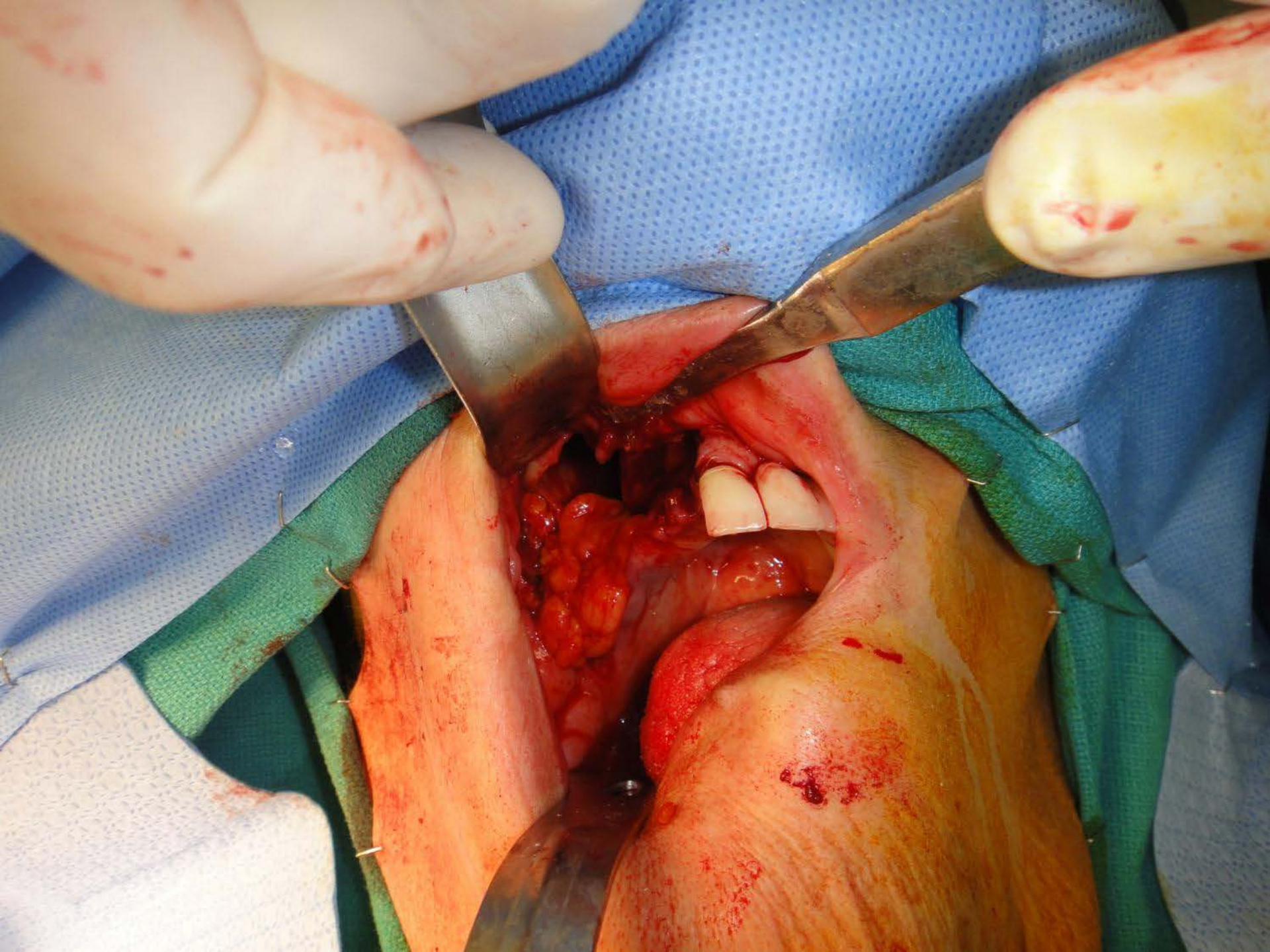


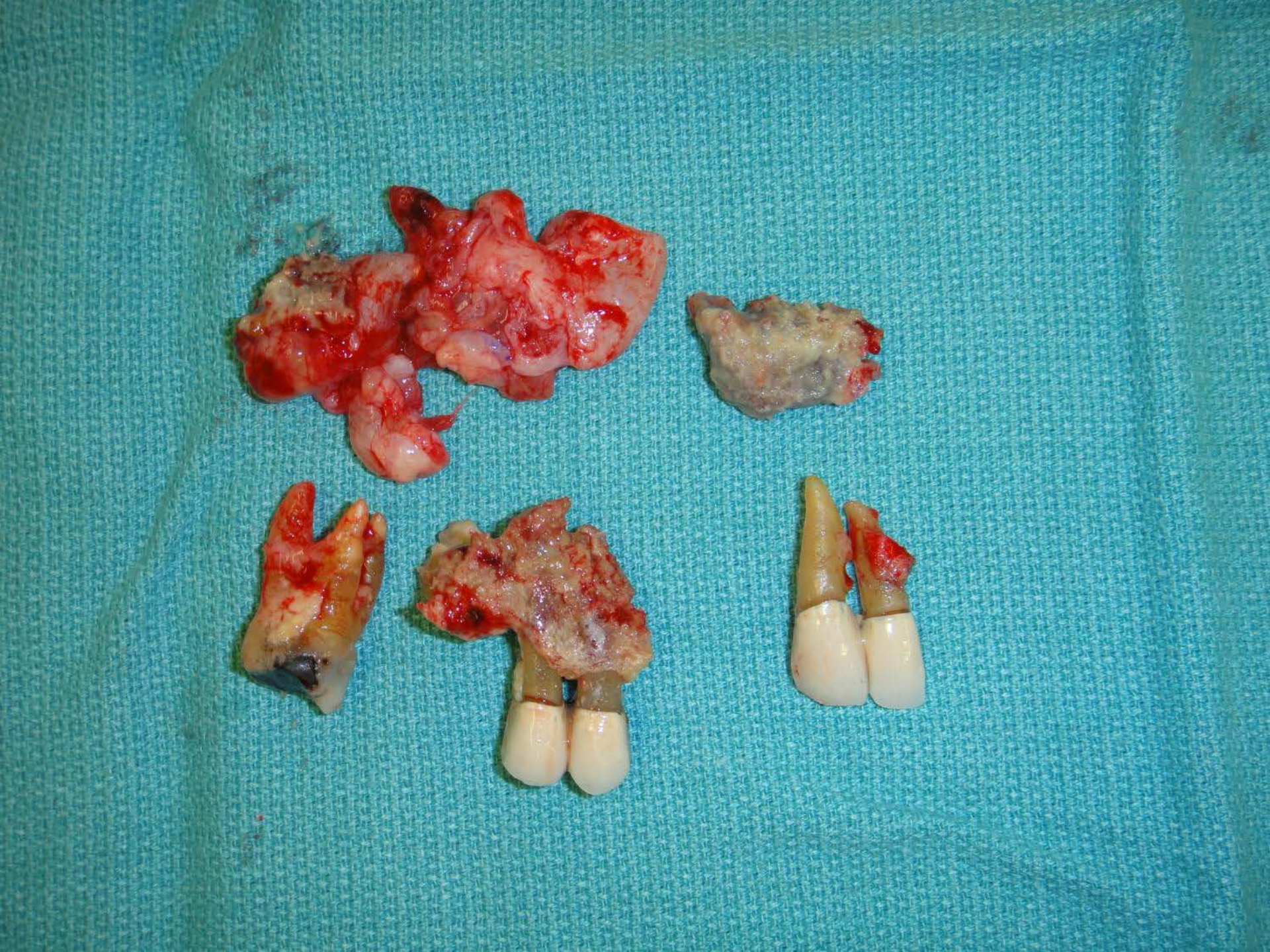


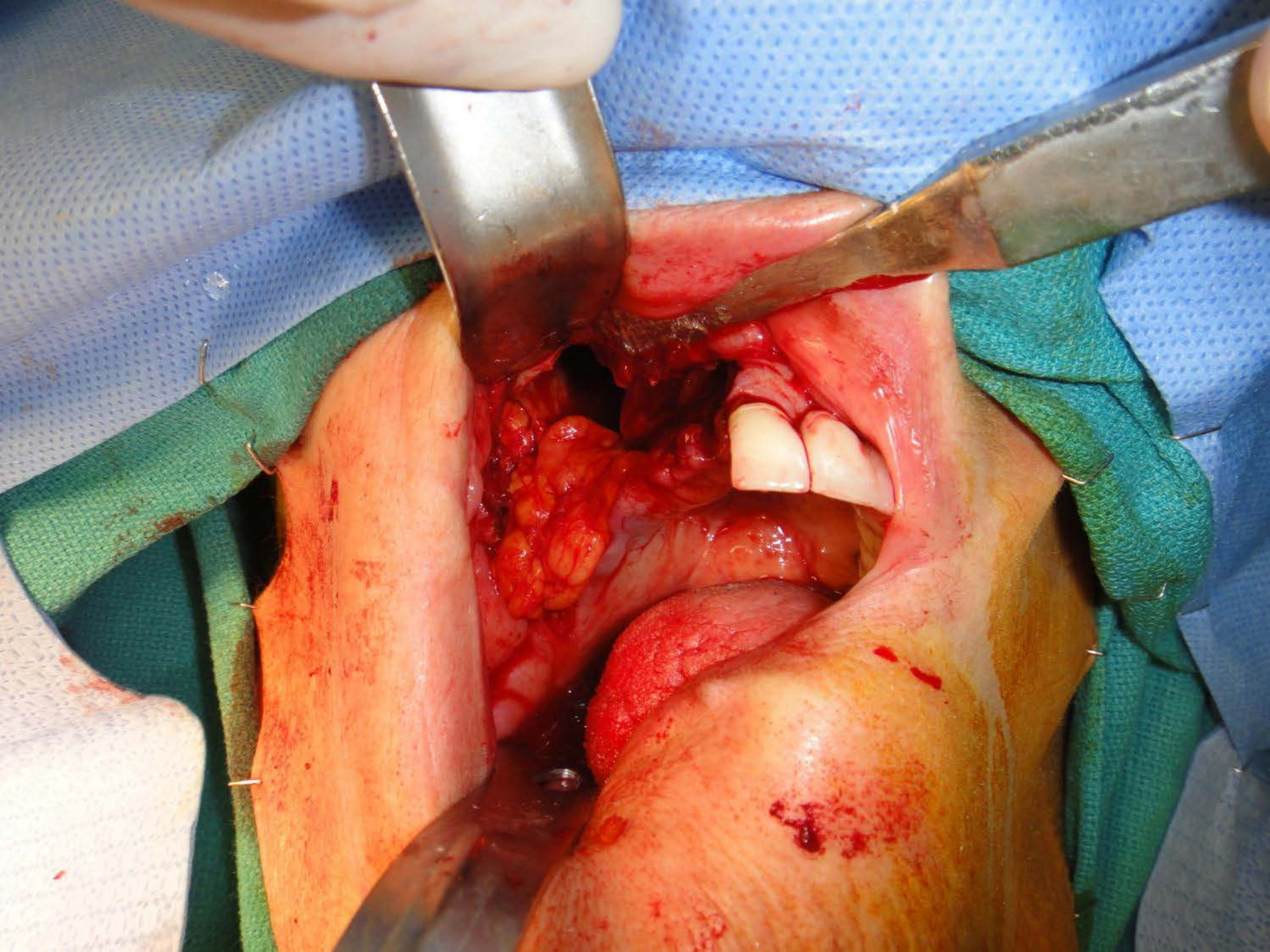


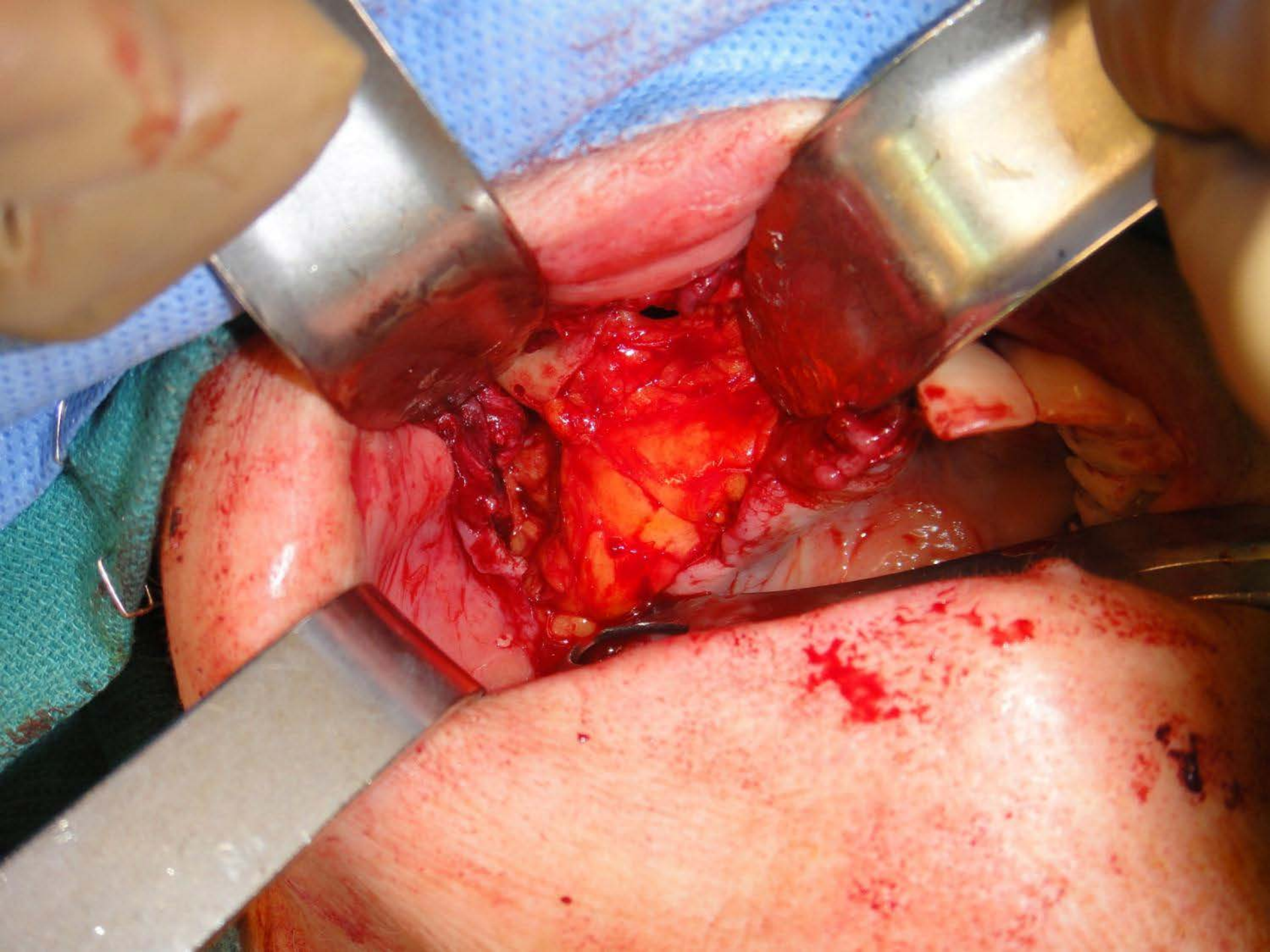


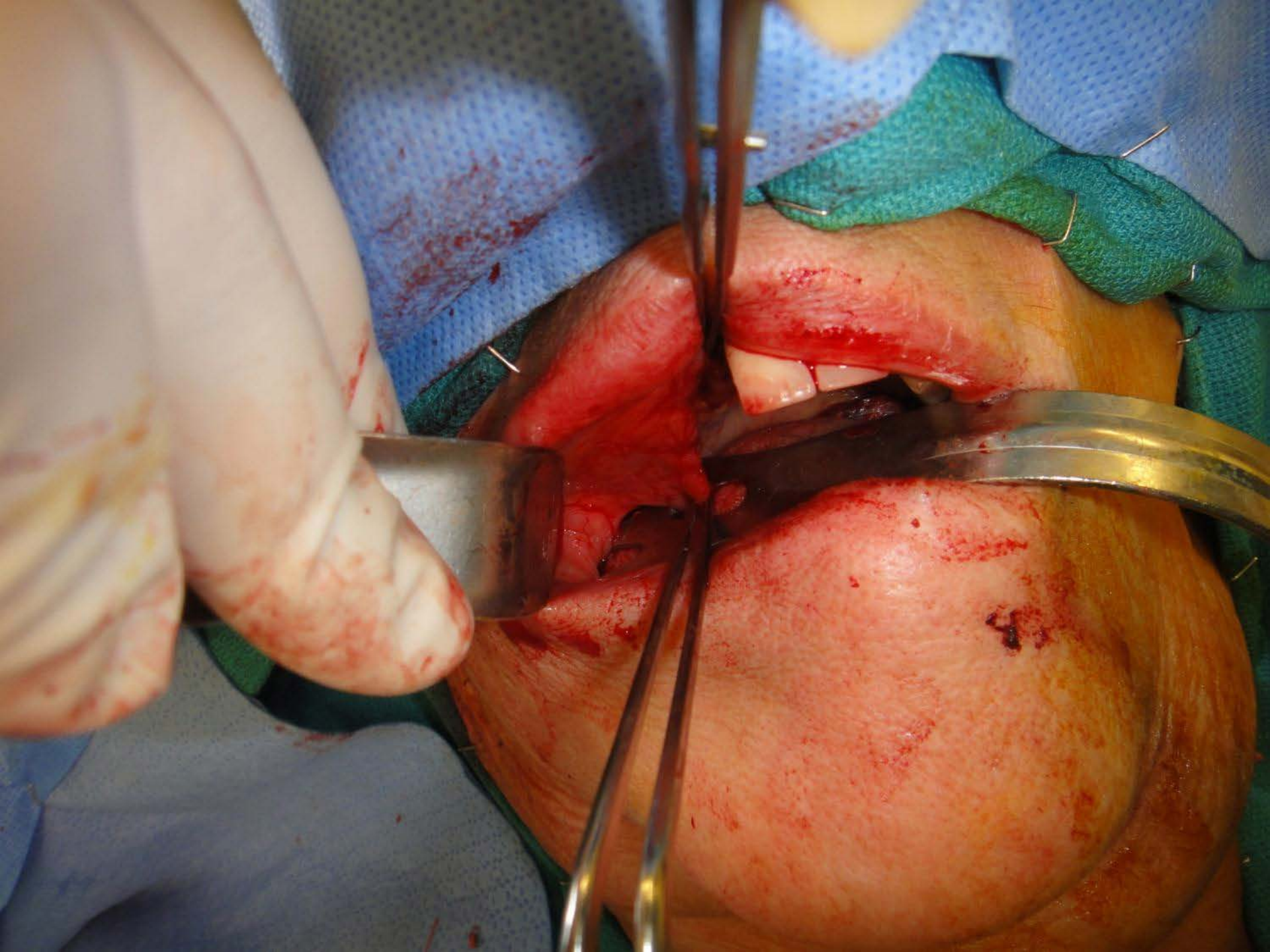


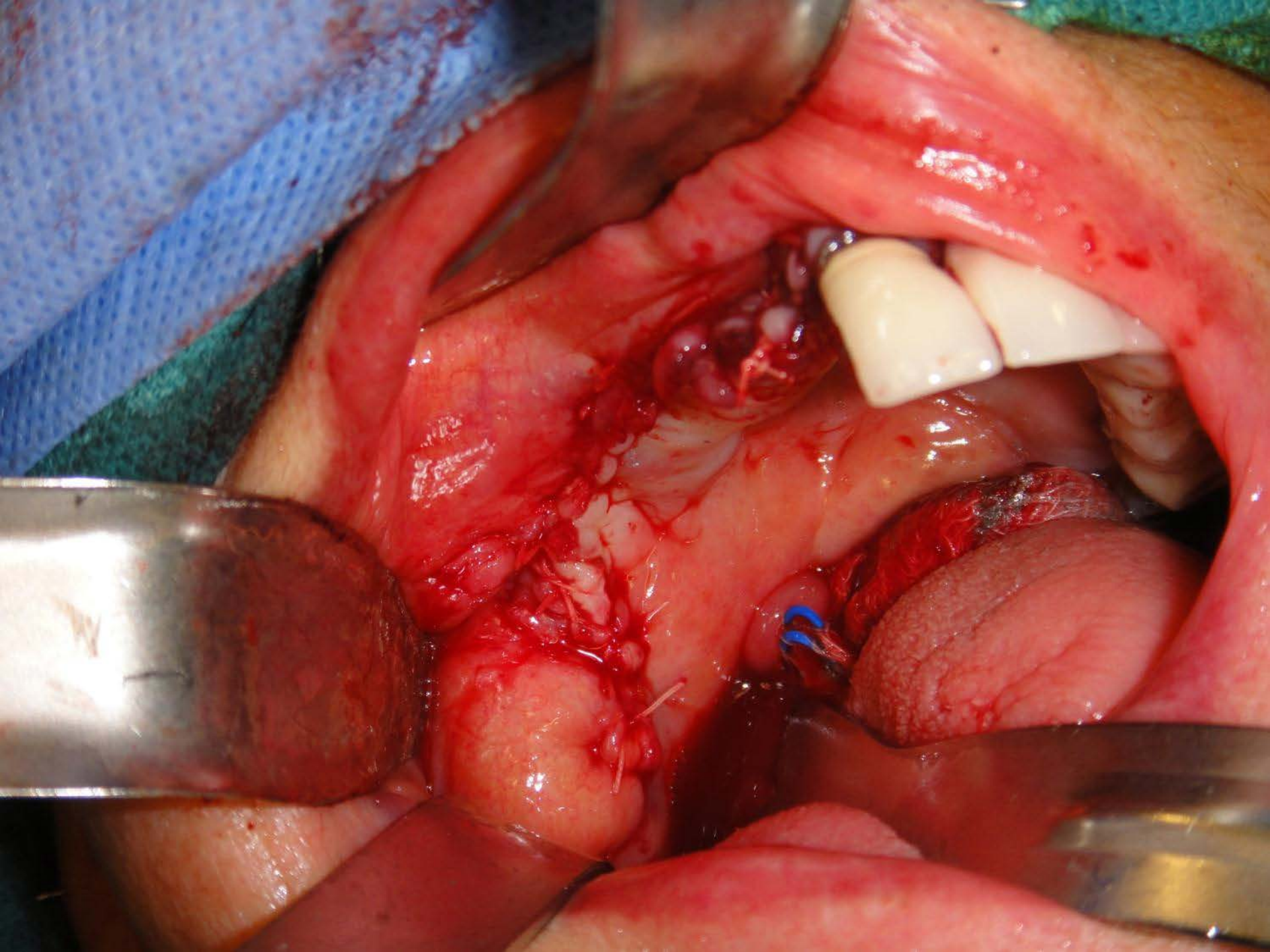


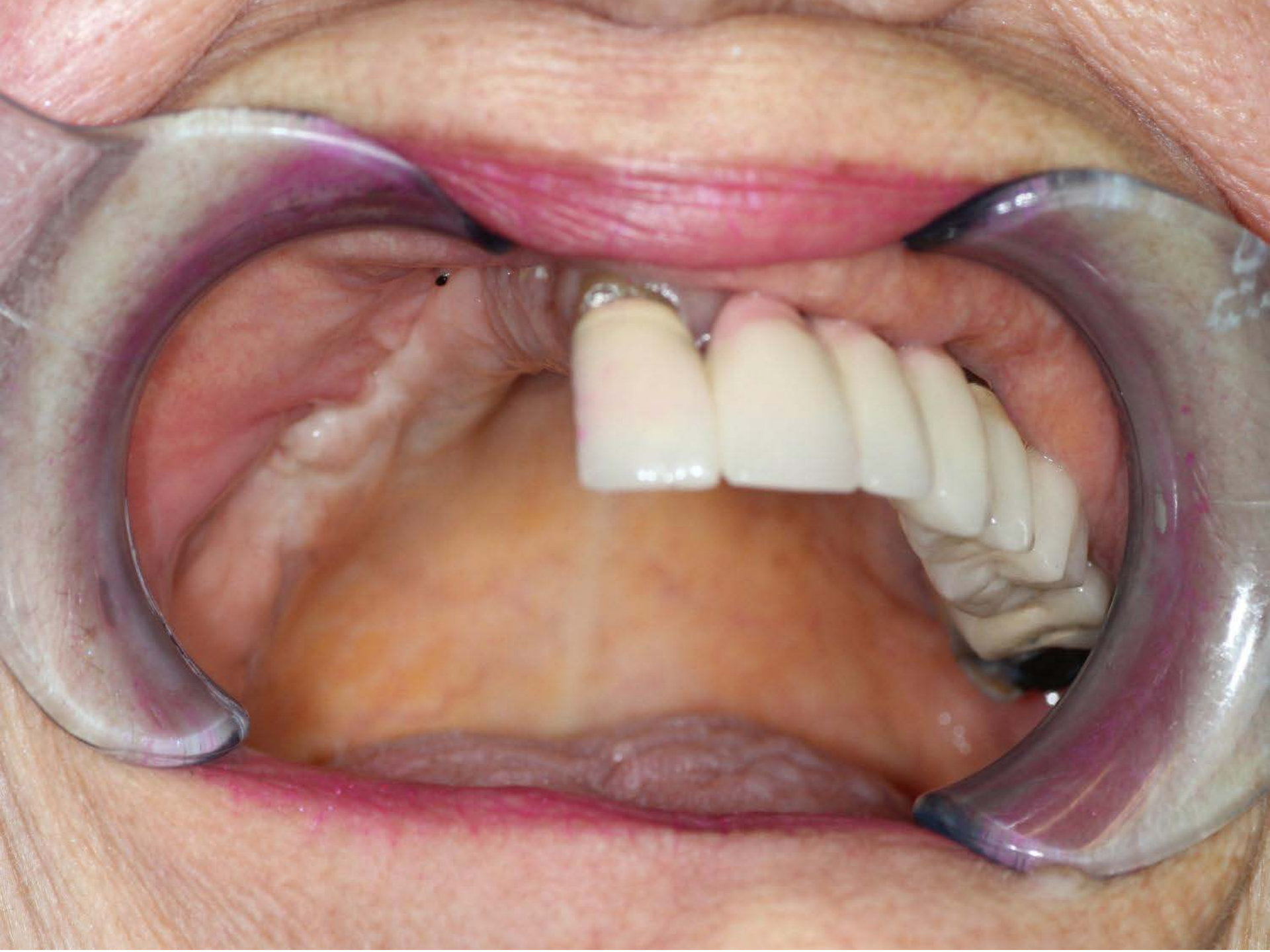


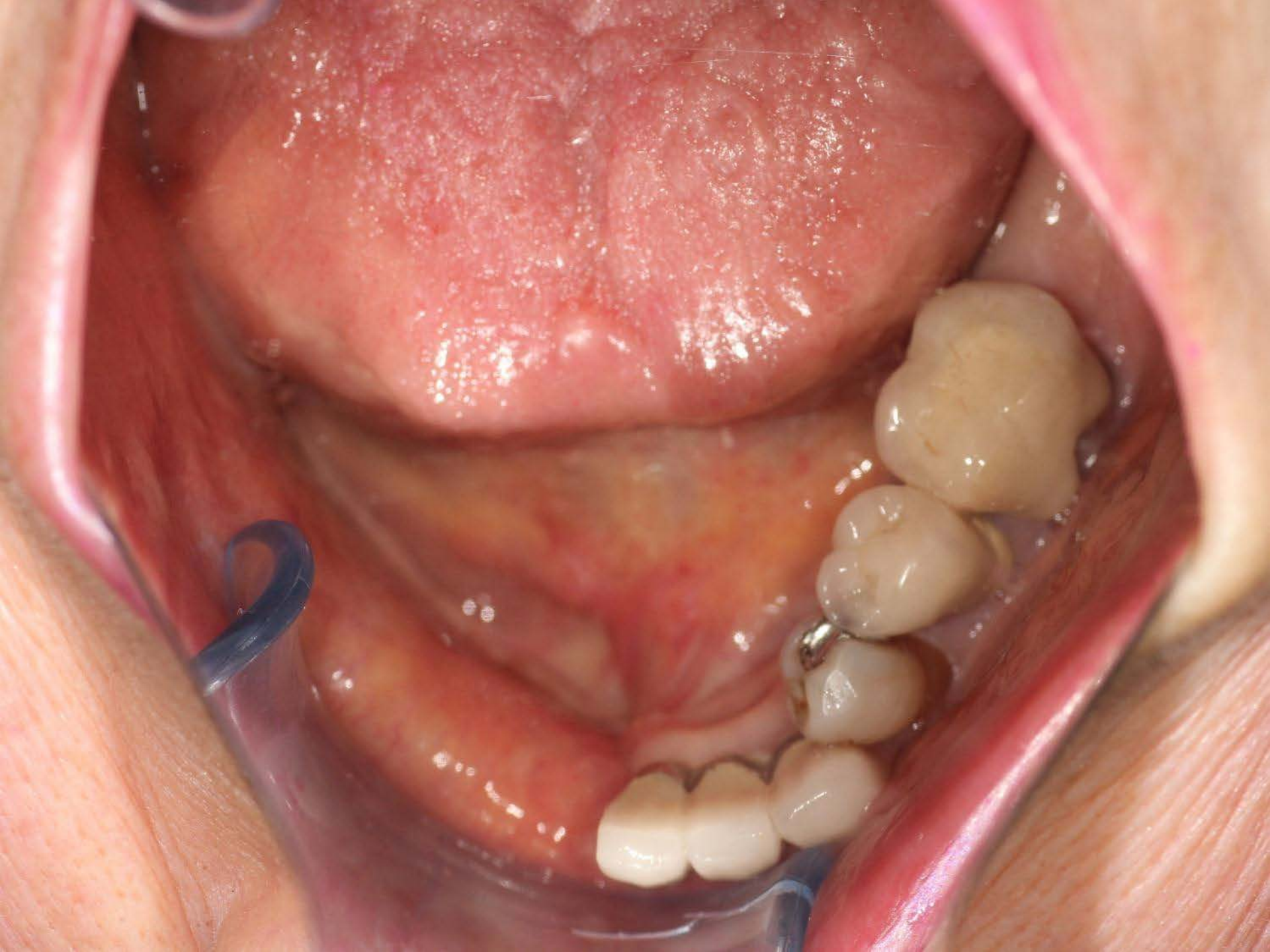












Outcome Analysis OF 200 IV BIONJ Cases

1. **Died from their cancer**
   36/200 (18.0%)
2. **Required a resection**
   62/200 (31.0%)
3. **Pain free living with exposed bone**
   102/200 (51.0%)

Note!

Uncontrolled cancer is life threatening. DIONJ is painful and impacts quality of life.

If the BP or Denosumab remains a therapeutic advantage, continue it.

We will manage the DIONJ.

Conclusions

1. DIONJ is a real entity caused by bisphosphonates and denosumab etc.
2. Pretreatment dental/omfs care can reduce the incidence of DIONJ
3. If possible dose adjustment can reduce the incidence of DIONJ
4. Many DIONJ cases can be managed without aggressive surgery
5. Surgery can resolve DIONJ in selected

Goals Of This Presentation

1. DIONJ is a real entity
2. We are on your side
3. We are on the patient's side
4. Review prevention and treatment protocol

Only the Dead Have Seen The Last Of War

- Plato Circa 360 B.C.
- General Douglas MacArthur 1945 A.D.

Only The Naïve Would Think We Have Seen The Last Of ONJ

Robert E. Marx, 2016 A.D.


The End
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