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UCC
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An Assessment of the Oral Health Status and Dental Treatment Needs of Oncology Patients Receiving Bone Modifying Agents

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For the degree of

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2024

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Terms and Abbreviations

AAOMS	**American Association of Oral and Maxillofacial Surgeons**
AAP	American Association of Periodontology
Abbreviation	Term
ASCO	American Society of Clinical Oncology
BMD	Bone Mineral Density
BMI	Body Mass Index
BMP	Bone Morphogenic Protein
BPE	Basic Periodontal Examination
CREC	Clinical Research Ethics Committee
CT	Computed Tomography
CTIBL	Cancer Treatment-Induced Bone Loss
CUDSH	Cork University Dental School and Hospital
CUH	Cork university Hospital
DMFT	Decayed, Missing, Filled Teeth
EBM	Evidence Based Medicine
EFP	European Federation of Periodontology
EGF	Epidermal Growth Factor
FDG-PET	18-Fluoro-Deoxyglucose positron Emission Tomography
FGF	Fibroblast Growth Factor
GDP	General Dental Practitioner
GMP	General Medical Practitioner
HBO	Hyperbaric Oxygen
HCW	Health Care Worker
HSE	Health Service Executive
IGF	Insulin-like Growth Factor
IgG2	Immunoglobulin G2
IV	Intravenous
MCSF	Macrophage Colony-Stimulating Factor
MHC	Major Histocompatibility Complex
MMP	Matrix Metalloproteases
MRI	Magnetic Resonance Imaging
MRONJ	Medication-related Osteonecrosis of the Jaw
MUH	Mercy University Hospital
NCCP	National Cancer Control Programme
NIH	National Institutes of Health
NSCLC	Non-Small Cell Lung Cancer
ORN	Osteoradionecrosis
PBM	Photo biomodulation
PI	Plaque Index
PPD	Periodontal Probing Depth
PRGF	Platelet Rich in Growth Factors
PRP	Platelet-Rich Plasma

PTH	Parathyroid Hormone
RUNX	Runt-Related Transcription Factors
SC	Subcutaneous
SIC	Significant Caries Index
SD	Standard Deviation
SIVUH	South Infirmary Victoria University Hospital
SRE	Skeletal-related Event
TGF-beta	Transforming Growth Factor
TKI	Tyrokinase Inhibitor
TRAP	Tartrate Resistant Acid Phosphatase
VEGF	Vascular Endothelial Growth Factor
WNT	Wingless and Int-1

Abstract

Aims

To assess the oral health status and dental care treatment needs of oncology patients receiving bone modifying agents (BMAs). Additionally, to explore barriers to dental care for this cohort of patients.

Materials and Methods

This was a mixed methods study conducted in 2 phases. In Phase 1, patients were recruited from the oncology clinics in the Cork University Hospital (CUH), South Infirmary Victoria University Hospital (SIVUH) and Mercy University Hospital (MUH). The oral health status and dental care needs were assessed using the Decayed, Missing and Filled teeth (DMFT) index, periodontal staging and grading classification (AAP) and their dental care requirements. Dental treatment was then completed to stabilise the oral health prior to commencing a BMA. Multivariate analysis was conducted to identify certain characteristics which may highlight added risk factors for dental disease and dental treatment needs. Phase 2 included focus group discussions with general dental practitioners alongside a focus group and qualitative interviews with patients to explore their opinions of the oncodental interface. Ethical approval was granted for a prospective, observational study by the Clinical Research Ethics Committee, University College Cork.

Results

In Phase 1, a total of 150 patients were assessed prior to a BMA. 70% (n=105) were female and 30% (n=45) were male, with a mean age of 61.5 years (SD 11.75 years). Breast cancer was the most common cancer amongst females (n=95) and prostate cancer amongst males (n=22). 94% (n=142) were planned for intravenous (IV) zoledronic acid and 6% (n=8) were planned for subcutaneous (SC) denosumab. 37 patients were current smokers (24.7%), and 23 patients were ex-smokers (15.3%). 65 patients (43.3%) did not have a general dental practitioner (GDP) at the time of presentation and 76 patients (50%) had a dental presenting complaint, where dental neglect (n=53, 35.3%) and functional issues (n=35, 23.3%) were the most common presenting complaints.

The mean DMFT was 17.68 (SD 7.85) and 145 (97%) had periodontal disease. 20% (n=30) wore a denture, 9% (n=3) did not adequately fit and 16% (n=5) had clinical evidence of substandard denture hygiene. 86 restorations were placed and 188 teeth were extracted over the course of treatments. 121 teeth (64.4%) were extracted due to periodontal disease and 67 (35.6%) teeth were extracted due to dental decay. 82 teeth (95%) were restored due to primary decay and 6 teeth (5%) were restored due to secondary decay. 8 patients (5%) required an intraoral biopsy and dysplasia was reported in 2 patients. 7 patients (5%) required a new denture and 147 patients (98%) achieved dental fitness prior to BMA treatment. Multivariate analysis revealed a significant result for a periodontal extraction and increasing age, which increased by 21.2% every 10 years (p=0.0239). Patients who did not have a GDP were twice as likely to require dental restorations (OR=2.122) and required 67.5% more restorations.

Patients that attended on an irregular (every 2-4 years) were 2.5 times and rare (5 years or more) basis were 3.4 times as likely to require an extraction compared to frequent attenders (OR=2.5 and OR=3.407), respectively. A current smoker was 3.4 times as likely to require an extraction, particularly due to periodontal disease ($p<0.001$).

In Phase 2, 10 patients and 20 dentists were included in qualitative interviews. Data was collected until data saturation was achieved. Data were then transcribed and analysed using thematic analysis. Multiple themes emerged amongst dentists, including the difficulties of treatment planning for oncology patients planned for or receiving BMA, lack of guidance criteria to assist treatment planning, poor knowledge of medication-related osteonecrosis of the jaw (MRONJ) amongst general medical practitioners (GMPs), and management of these patients in the emergency setting. Patients expressed concerns about the additional burden of dental care, their lack of knowledge of MRONJ prior to their dental assessment, and the reassurance of a multidisciplinary co-ordinated dental service.

Conclusion

Our study highlights the vulnerability of this cohort of patients due to their dental care treatment needs. Dental disease is an integral factor for MRONJ, which must be addressed as a component of their overall oncology treatment plan.

Declaration

This is to certify that the work I am submitting is my own and has not been submitted for another degree, either at University College Cork or elsewhere. All external references and sources are clearly acknowledged and identified within the contents. I have read and understood the regulations of University College Cork concerning plagiarism and intellectual property.

Multivariate analysis was completed with assistance from Mr Michael Cronin (UCC) and figures 7, 12 and 13 were completed with assistance from Mr Charlie Ruxton (UCC).



Harriet Byrne

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Chapter 1

Introduction

1.1 Introduction

Bone modifying agents (BMAs) are an integral component of cancer care (Anderson *et al.*, 2018a; R. Coleman *et al.*, 2020). Their utilisation is paramount to the management of skeletal related events (SLEs) in metastatic disease (Coleman, 2006; Coleman *et al.*, 2020). They are also used to treat hypercalcemia of malignancy, cancer treatment induced bone loss (CTIBL) and reduce the risk of recurrence in specific cohort of cancer patients, most notably early-stage breast cancer (Hellstein *et al.*, 2011; Van Poznak *et al.*, 2017; Marx, 2021; Ruggiero *et al.*, 2022a). BMA therapy improves quality of life and survival for patients and helps reduce the burden of healthcare expenditure (Tella et al., 2018). Recent data extrapolated from the American Cancer Society 2022, National Program of Cancer Registries and the North American Association of Central Cancer Registries; reported 1,918,030 new cancer cases and 609,360 cancer-related deaths in 2022 (Siegel *et al.*, 2022). Similar trajectories are seen across Europe with rising trends of new cancers cases reaching 2.7 million in 2022 and cancer deaths at 1.3 million (*European Cancer Information System*, 2023). Cancer cases in Europe increased by 2.4% from 2020 to 2022 (excluding non-melanoma skin cancers), and cancer-related deaths increased by 2.3% from 2020 to 2022 (*European Cancer Information System*, 2023). Breast cancer was the most common cancer diagnosis in 2022 (13.8%), followed by colorectal (13%), prostate cancer (12.1%) and lung cancer (11.6%) (*European Cancer Information System*, 2023). Bone metastases are common in 3 of the 4 most prevalent cancers in Europe, with bone metastases noted in 65-90% of prostate cancers, 65-75% of breast cancers and 17-64% of lung cancers (Sousa and Clézardin, 2018; D'Oronzo *et al.*, 2019). Bone metastases are noted in 70-95% of multiple myeloma cases (Anderson *et*

al., 2018b; D'Oronzo *et al.*, 2019). Although, the incidence of bone metastases is difficult to truly ascertain, we know that incidence increases with age and bone is the most common site of metastatic deposit (Macedo *et al.*, 2017).

The integral relationship of bone and metastatic deposits in these cancers is based on a bidirectional relationship between cancer cells, bone microenvironment and the specific propensity of primary tumour cell genetic changes with bone affinity, noted in prostate, lung, breast, thyroid and renal cancers (Rubens, 1998; Ryan *et al.*, 2022). Bone metastases are predominantly distributed to the axial skeleton (Rubens, 1998). Data has suggested the vertebral-venous plexus flow from tumours of lung, breast and prostate alongside cellular biological characteristics (Rubens, 1998). Pain, pathological fracture, spinal-cord compression, hypercalcemia, and bone marrow suppression (impaired haematopoiesis and leucoerythroblastic anaemia) result from this process (Rubens, 1998). Metastatic disease is a significant cause of morbidity in cancer patients (Bădilă *et al.*, 2021). Consequently, BMA therapy will remain a prominent regime in oncology care (Coleman *et al.*, 2020).

Unfortunately, BMA treatment subjects patients to the risk of developing medication-related osteonecrosis of the jaw (MRONJ). MRONJ was first diagnosed 21 years ago (Marx, 2003). The prevalence of MRONJ in the metastatic cohort ranges from 0 – 12% (Ruggiero *et al.*, 2014) while prevalence rates in patients with metastatic bone disease specifically on zoledronic acid therapy varies from 0.186% to 14.4% (Marx, 2003; Coleman *et al.*, 2014; Ruggiero *et al.*, 2014; Raje *et al.*, 2018; Ruggiero *et al.*, 2022a; AlRowis *et al.*, 2022a). RANK-ligand (RANKL) inhibitors have been used as

alternatives to bisphosphonates and the prevalence for MRONJ ranges between 0.7% - 6.7% following subcutaneous denosumab (Ruggiero *et al.*, 2009; Coleman *et al.*, 2020; AlRowis *et al.*, 2022a). A recent systematic review by Schwech et al. (2022), reported an 11.4%-50% incidence of MRONJ post tooth extraction in oncology patients receiving a BMA (Schwech et al., 2022). This data highlights the heterogenous nature of results presented in the literature.

Treatment modalities have included a spectrum of conservative, medical and surgical management to treat MRONJ (Yarom *et al.*, 2019; Sim *et al.*, 2020; Ruggiero *et al.*, 2022b). Guidance has helped clinicians to navigate treatment regimens based on the stage of MRONJ, patient and dental risk factors, and BMA regime however standardisation of predictable treatment protocols remains heterogenous (Owosho *et al.*, 2018; Otto, Schnödt, *et al.*, 2021; AlRowis *et al.*, 2022a; Byrne *et al.*, 2024). Emerging high quality evidence was published recently within a randomised, multicentre trial for variable dosing regimens of intravenous (IV) zoledronic acid (Himelstein *et al.*, 2017). This study noted a 50% reduction in MRONJ (n=18 versus n=9) following introduction of a standardised pre-BMA dental clearance routine alongside dental preventative measures. This was noted in the trial arm alongside a decreased frequency of zoledronic acid which cannot be disregarded as a source of reduction in MRONJ (Himelstein *et al.*, 2017). Given the nature of the mode of action and half-life of bisphosphonates, this data is promising to demonstrate the valuable nature of dental treatment prior to BMA treatment and preventative dental input for these oncology patient. Albeit, MRONJ is a relatively rare condition in the oncology patient, the burden of MRONJ and its deleterious effects on a patient's quality of

survival, must not be under appreciated. Dental care is a modifiable factor within an oncology patient's treatment plan.

Ireland has yet to define a structured pathway for patients prior to or receiving a BMA. Our National Oral Health Policy published in 2019, "*Smile agus Sláinte",* cognitively illustrates the future oral health intent with our health care system however this vulnerable oncology population have not been recognised (Department of Health, 2019). McAuliffe et al. (2022) concretely defined the wavering support for marginalised populations within our health system and concludes that policy development remains the instigator for future provision (McAuliffe *et al.,* 2022). The National Cancer Strategy (2017-2026), published by the National Cancer Control Programme (NCCP) in Ireland, has included recognition for regular oral cancer screenings with a dentist and the inclusion of pre-radiation dental assessments prior to head and neck radiation, similar to *Smile agus Sláinte* (*National Cancer Strategy 2017 - 2026*, 2017; Department of Health, 2019). Oral health provision and future plans appear to be deficient for this subgroup of oncology patients receiving a BMA.

Our study aims to define the oral health status of this subgroup of oncology patients, their dental care treatment needs and barriers to accessing dental care via a mixed methods approach (cross sectional study, providing dental care as a duty of care) within the Cork University Dental School and Hospital (CUDSH). The literature review delves into areas of oral health, MRONJ, and this oncology cohort requiring a BMA to comprehensively assess the relevant data. Our results and discussion

highlight topics of interest surrounding the aim of study and highlights themes for future development.

1.2 Conference presentations, prizes and publications

Conference presentations

1. Irish Society of Medical Oncology (ISMO), January 2023.

"No MRONJ, No Problem?" - Oral presentation.

2. Irish Association of Oral Surgery (IAOS), March 2023.

"The dental oncology complication that wouldn't go away" – Poster presentation.

3. Irish Head and Neck Society Annual Meeting, May 2023.

"The dental oncology complication that wouldn't go away" – Poster presentation.

4. European Society of Medical Oncology (ESMO), Madrid October 2023.

"The impact of a dental oncology clinic for patients prescribed bone modifying agents in a cancer centre" – Poster presentation.

Prizes

ISMO Bursary Award, January 2023 – 1st prize Oral Presentation

IAOS Bursary Award, March 2023 – 1st prize Case-based Poster Presentation.

Publications

Byrne H, Weadick C, Ní Ríordáin R, Barry C, O' Reilly S. The dental oncology complication that wouldn't go away. Archives of Breast Cancer. 2023;10(3):306-13.

DOI: 10.32768/abc.2023103306-313.

Byrne H, O' Reilly S, Weadick C, Brady P, Ní Ríordáin R. How we manage medication-related osteonecrosis of the jaw. European Journal of Medical Research. 2024;29(402). DOI: 10.1186/s40001-024-01912-6.

Chapter 2

Literature Review

2.1 Medication-related Osteonecrosis of the Jaw

2.1.1 Definition

MRONJ is defined as exposed bone, or non-healing bone in the mandible or maxilla that has persisted for more than eight weeks in a patient who has received a systemic drug known to cause osteonecrosis of the jaw and has not received a local tumoricidal dose of radiation to the jaws nor has metastatic disease in the jaws (Hellstein *et al.*, 2011; Marx, 2021; Ruggiero *et al.*, 2022a). Initially, this presentation was related to bisphosphonate therapy however the remit of osteonecrosis of the jaw implicating agents has extended to include multiple bone modifying agents such as RANK ligand inhibitors (denosumab), tyrosine kinase inhibitors (sunitinib), direct vascular endothelial growth factor inhibitors (bevacizumab) and interleukin-6 inhibitor (tocilizumab) (Coleman and McCloskey, 2011a; Miksad *et al.*, 2011; Bramati *et al.*, 2015; Fliefel *et al.*, 2015a). Drug-induced osteonecrosis of the jaw (DIONJ) encapsulates the spectrum of bone modifying agents which potentially induce osteonecrosis of the jaws and places precedent on the outcome rather than the variable pharmacological interactions in bone (Marx, 2021; Ruggiero *et al.*, 2022a). Bone modifying agents are used across a wide range of disciplines including oncology, endocrinology, nephrology, orthopaedics and haematology (Marx, 2021; Ruggiero *et al.*, 2022a; Byrne *et al.*, 2023). Due to the heightened propensity for adjuvant therapies in oncological treatment regimes, MRONJ is a rising complication in cancer patients and the spectrum of causative medications are growing (Miksad *et al.*, 2011; Coleman *et al.*, 2020). These medications warrant a risk-benefit consideration depending on the nature of disease, the therapeutic margin and the potential morbidity. The case-based assessment of individuals at risk is paramount to the context of MRONJ.

MRONJ criteria has developed since its initial definition in the literature by Marx in 2003 (Marx, 2003). The evolution of definitions have progressed throughout the years; bisphosphonate-related osteonecrosis of the jaw (BRONJ, 2007) (Ruggiero et al., 2006), antiresorptive – related osteonecrosis of the jaw (ARONJ, 2011) (Hellstein *et al.*, 2011) , medication-related osteonecrosis of the jaw (MRONJ, 2014) (Ruggiero *et al.*, 2014) and drug-induced osteonecrosis of the jaw (DIONJ, 2022) (Marx, 2021). The AAOMS have released position papers relating to MRONJ in 2007 (Ruggiero, et al., 2006), 2009 (Ruggiero *et al.*, 2009), 2014 (Ruggiero *et al.*, 2014) and most recently in 2022 (Ruggiero *et al.*, 2022a). These position papers aimed to conceptualise the risks of MRONJ development, evidence for treatment decision-making, guidance in the clinical setting, promote preventative and appropriate treatment strategies and support the diagnosing clinician in cases of suspect MRONJ (Ruggiero *et al.*, 2022a).

2.1.2 Indication

Bisphosphonate therapy is indicated for the prevention of skeletal-related events in osteolytic disorders or in patient with bony metastases (pathological fractures, spinal cord compression, palliative radiotherapy for bone pain or orthopaedic surgery) and malignant hypercalcaemia (Van Poznak *et al.*, 2017; Eisen *et al.*, 2022a). They are pyrophosphate analogues that reduce bone resorption by interfering with osteoclast recruitment, differentiation, and promoting osteoclast apoptosis. Bisphosphonates play a vital role in oncology for patients with bony metastases, skeletal complications and bone pain (Hillner *et al.*, 2000; Gnant and Hadji, 2010; Gnant *et al.*, 2015; Van Poznak *et al.*, 2017). Bisphosphonates improve quality of life in advanced-cancer involving the skeleton or preventing skeletal-related events (Caminha *et al.*, 2020; Ruggiero *et al.*, 2022a). Bisphosphonates are associated with lower rates of recurrence

in early stage breast cancer patients according to a meta-analysis from Early Breast Cancer Trialist Collaborative Group (Heeke et al., 2018). Osteoclast activation is the primary mechanism for both bone mineral density loss during cancer treatment and osteolytic metastases (Heeke et al., 2018). There are multiple treatment induced therapies in breast cancer that reduce bone mineral density (BMD); in premenopausal breast cancer patients treated with chemotherapy, 3-6% of BMD is lost in the first 12 months (Heeke, Nunes and Lynce, 2018).

Denosumab, a human monoclonal immunoglobulin G2 (IgG2) antibody disrupts the RANK Ligand /RANK /Osteoprotegrin system and consequentially is used to inhibit bone resorption in osteoporosis, and solid metastatic tumours of breast, prostate and to a lesser extent multiple myeloma (Gnant *et al.*, 2015; Aljohani *et al.*, 2018; Diel *et al.*, 2020; Jiang *et al.*, 2021; Jung *et al.*, 2022). Bone is composed of osteoblasts which secret the matrix osteoid. Osteocytes subsequentially are entrapped in the mineral matrix for their 180 day lifespan. Osteoprotegrin, which competes and inhibits RANKL-induced natural cell death via activation of osteoclasts, is disrupted by Denosumab. Denosumab has the ability to disrupt multiple stages of osteoclast maturation; including differentiation of the committed osteoclast precursor and differentiation of the multinucleated osteoclast. This mechanism is favourable and effective at reducing the risk of skeletal events in this cohort however very active bone regeneration regions in the alveolus and femur can subsequently develop osteonecrosis (Peddi *et al.*, 2013; Marx, 2021).

Antiangiogenic and antineoplastic medications have also been implicated in the development of MRONJ. Bevacizumab, sunitinib, aflibercept, dasatinib and everolimus are examples of oncological therapies used in the treatment for breast, renal cell carcinoma, metastatic colorectal cancer, chronic myelogenous leukaemia and renal cell tumours, respectively. They inhibit cancer neoangiogenesis cycles, helping to slow cancer progression. Their association with MRONJ in the literature is growing (Teoh *et al.*, 2021).

The cost effectiveness of BMA therapy in cancer care is undisputed and reduces both patient and healthcare burdens (Tella et a., 2018). We understand from the literature that SREs incur increased health care costs and demands on health care resources (Decroisette *et al.*, 2011). Reducing SREs via BMA therapy was first introduced by the American Society of Clinical Oncology (ASCO) in 2000 for breast cancer patients (Mokbel, 2000; Eisen *et al.*, 2022a). Cost effectiveness data reported using Markov model estimates reported the overall cost of bisphosphonate therapy to prevent a SRE was £250 and £1500 per event for breast cancer and multiple myeloma, respectively (Ross *et al.*, 2004). The reduction in SREs is also coupled by a delay in the time to the potential first SRE however overall survival is not effected (Ross *et al.*, 2004). These savings were also noted across a multinational analyses of BMA treatment in the advanced-stage renal cell carcinoma patients, where bisphosphonate therapy following cost of the treatment incurred a €1358, €1223 and €719 per SRE in France, Germany and the United Kingdom, respectively (Botteman *et al.*, 2011). Even within subgroups of cancer patients, the cost of managing SREs is a significant burden on healthcare systems (Decroisette *et al.*, 2011). A multicentre data from France reported the monthly cost for lung cancer patients with bone metastatic disease increased

significantly from the patient with asymptomatic disease (€190), symptomatic disease (€374) and in patients with SRE (€4672) (Decroisette *et al.*, 2011). Bone modifying therapy can reduce healthcare costs alongside help to improve overall health and quality of survival for patients with bone metastases.

Bone metastases result in significant morbidity for cancer patients. Their influence on quality of survival can have deleterious effects, adding to the complexity of their care (Miksad *et al.*, 2011). The treatment rationale for bisphosphonates early into the oncological journey aims to reduce complications associated with low bone mineral density or progressive bone loss fractures (Coleman *et al.*, 2020).

2.1.3 Epidemiology

The scope of this review will include literature relevant to the oncology cohort. Their risk of MRONJ is variable depending on the potency of the BMA, the duration of treatment, the form of administration, the dosing regime and its intended use for either metastatic or non-metastatic disease (Ruggiero *et al.*, 2022a). These variables influence the epidemiological data across the oncology cohort.

There are higher numbers of MRONJ cases reported in patients with malignancies compared to those with multiple myeloma, however the antiresorptive / antiangiogenic treatment was not standardised in these studies (Coleman and McCloskey, 2011a). The prevalence rates in patients with metastatic bone disease on zoledronic acid

therapy also vary from 1.5 – 6% (Ruggiero *et al.*, 2022a) while the prevalence of MRONJ following subcutaneous denosumab ranged between 0.7% - 6.6% (Ruggiero *et al.*, 2009; Coleman *et al.*, 2020; AlRowis *et al.*, 2022a). Following a meta-analysis by Srivastava et al. (2021), they concluded that there was a higher prevalence of MRONJ associated with dual therapy compared to a single antiresorptive/antiangiogenic therapy. Bisphosphonate therapy had a 5% pooled weighted prevalence and denosumab had a 4% pooled weighted prevalence for the development of MRONJ. Combination therapy with bisphosphonate-denosumab therapy increased compared to monotherapy to 13% (Srivastava *et al.*, 2021).

MRONJ is a relatively new condition first documented by Marx in 2003 (Marx, 2003) which dictates shortcomings on long term data. Deficiencies in under-reporting, drug surveillance, limitation of studies and short term studies restrict accurate epidemiological reporting of MRONJ. Early data is confined to bisphosphonate use however the literature has quickly develop a database for MRONJ experiences worldwide (Filleul et al., 2010; Mhaskar *et al.*, 2012).

2.1.4 Bone Physiology

2.1.4.1 Normal bone remodelling

Bone is structurally comprised of cortical and cancellous bone. The composition of bone varies in different sites in the skeleton and the bone marrow is the primary site of haematopoiesis (Clarke, 2008; Mallorie and Shine, 2022). Modelling is an adaptive

process to loading where bone can change shape, mass or geometry. Remodelling is a life-long continual process for renewal and repair. The balance between resorption and formation is vital to maintain bone mass and systemic mineral homeostasis. It is a tightly controlled and regulated process. Bone contains cells of mineral and matrix origin. Osteoid type one collagen forms the tensile strength and lamellar collagenous layers (Clarke, 2008; Mallorie and Shine, 2022).

The four bone cells include osteoblasts, osteoclasts, osteocytes and bone lining cells. Bone-producing osteoblasts originate from mesenchymal stem cells (Marx, 2021). They secrete the type 1 collagen network and regulate mineralisation. They can differentiate into a bone lining cell, an osteocyte or undergo apoptosis. Bone-resorbing osteoclasts are multinucleated cells, originating from the macrophage lineage (Al-Bari and Al Mamun, 2020; Mallorie and Shine, 2022). They have an innate ability to resorb bone using matric metalloproteases (MMPs) and cathepsin K. Osteocytes make up the predominant bone cell (90%). They are located in the lacunae of the bone matrix and play a pivotal role in intracellular communication and mechanosensory feedback; influencing osteoblast and osteoclast activity (Clarke, 2008). Bone lining cells are quiescent osteoblasts that are lined along bone surfaces and not undergoing active remodelling. They have an oestrogen-related role in bone homeostasis (Siddiqui and Partridge, 2016).

Bone remodelling takes place in cycles of approximately 200 days and involves seven sequential steps including quiescence, activation, resorption, reversal, formation, mineralisation and termination highlighted in figure 1 (Marx, 2021). Multiple

systemic hormones control this process including calcitonin, oestrogen, parathyroid hormones and vitamin D3, each which influence osteoclastic activity. Growth factors (IGFs, TGF-beta, FGFs, EGF, WNTs and BMPs) influence and help regulate remodelling (Siddiqui and Partridge, 2016).

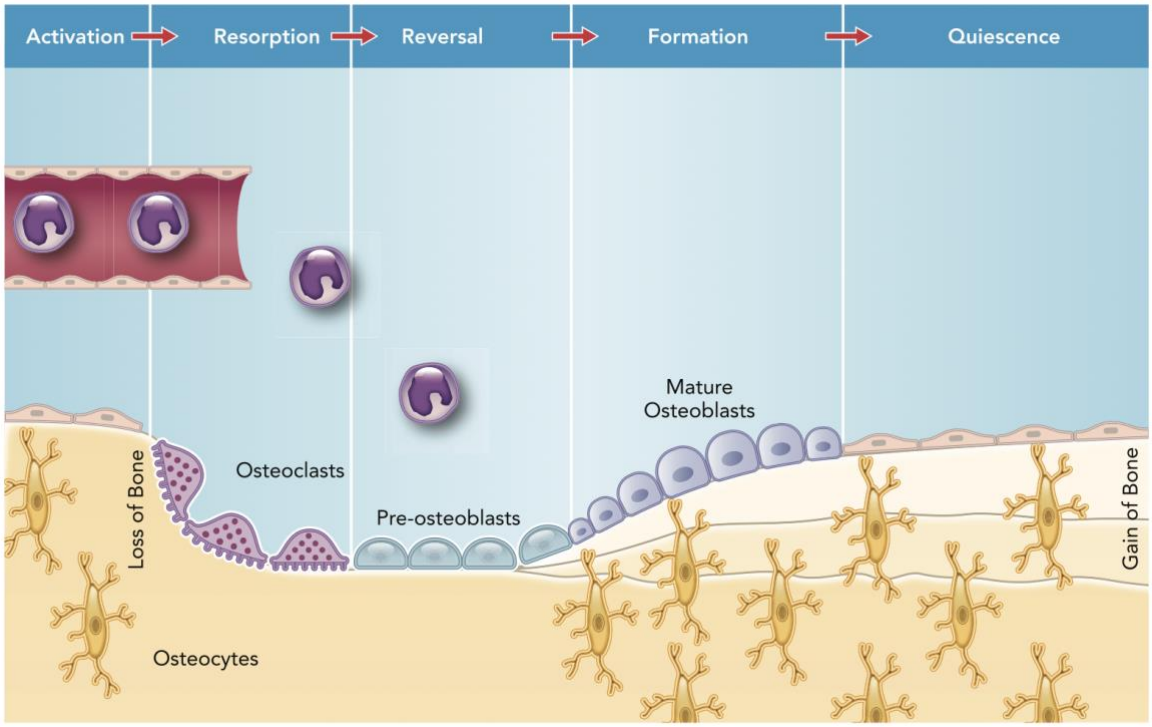


Figure 1 Physiological Bone Remodelling Sequential Phases

Remodelling signals are initially detected which corresponds to resorption by osteoclasts. In the resorption phase, osteocytes initiate osteoblasts or by direct endocrine recruitment to stimulate osteoclast precursor cells to the region. The level of osteoclast stimulation will regulate osteoclast activity and time. Reversal phase follows resorption and osteoclasts disappear. Osteoblastic cells proceed with bone formation. Termination of bone remodelling includes terminal differentiation of osteoblasts. The resting bone surface environment maintains its status until the cycle

is initiated again as shown in figure 2 and 3 (Siddiqui and Partridge, 2016; Marx et al., 2021) .

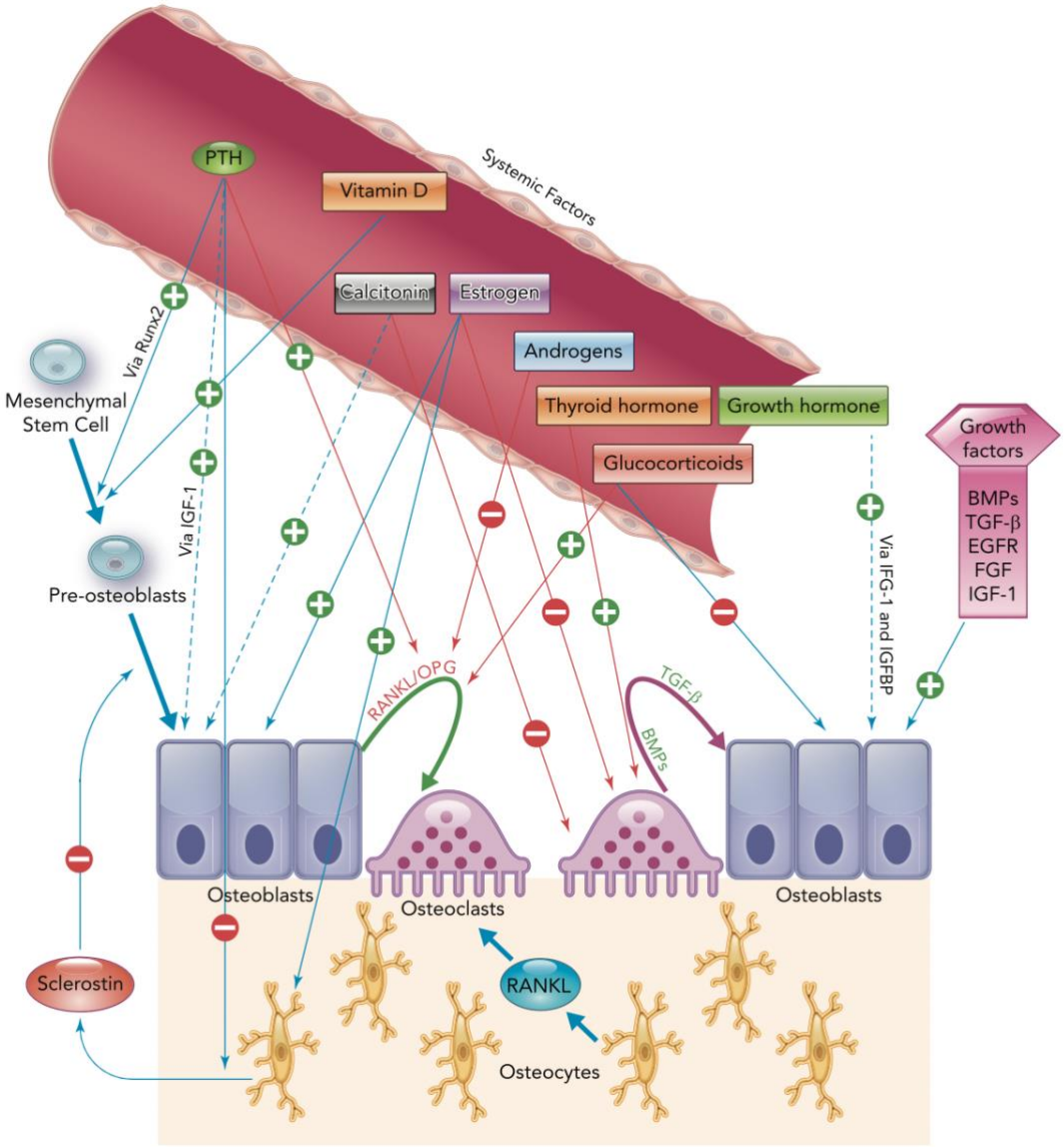


Figure 2 Physiological Bone Remodelling Sequential Phases

Parathyroid hormone (PTH) induces RUNX expression on osteoblasts which increases the quantity and longevity of osteoblasts. IFG-1 is also controlled by the parathyroid

hormone promotes maturation of osteoblasts. PTH induces RANK-L and macrophage colony-stimulating factor (MCSF) from mature osteoblasts and promotes the development of osteoclasts. Vitamin D3 ($1,25(OH)_2D_3$) stimulates osteoblastogenesis via recruitment of mesenchymal stem cells. Calcitonin inhibits osteoclast activity and promotes osteoblast proliferation. Oestrogen also inhibits osteoclasts via osteoclast apoptosis. Androgens can indirectly inhibit resorption by modulating the RANK/RANK-Ligand/OPG system. Growth factors and BMPs also influence bone remodelling (Siddiqui and Partridge, 2016; Marx, 2021).

Bone resorption starts the process by activation of osteoclasts. The progression to bone formation continues by stimulated osteoblasts. The transition phase which occurs between the resorption and formation processes, and osteoclasts disappear. Systemic signals can also initiate the remodelling cycle such as PTH as a result of hypocalcaemia or microtrauma. Osteocytes associated with microtrauma undergo apoptosis and signal osteoclast recruitment.

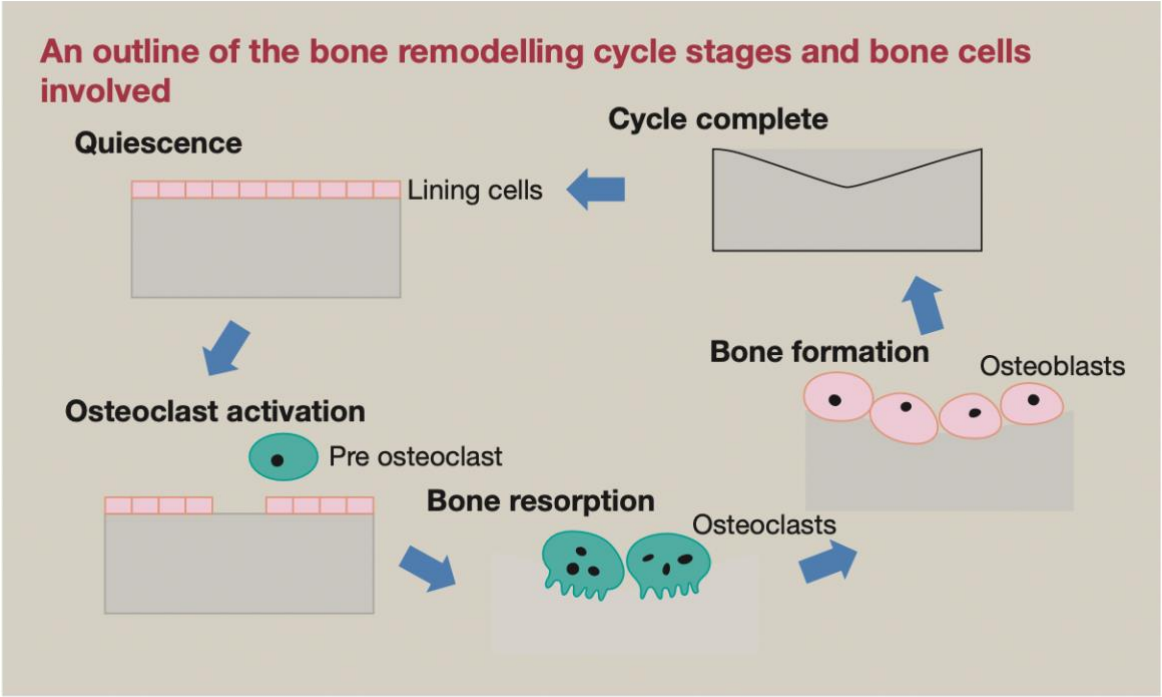


Figure 3 Outline of the Bone Remodelling Cycle and the Bone Cells Involved in Each Element of the Process

M-CSF and RANK-Ligand are two pivotal factors in osteoclast stimulation. Bone mass remains constant and bone formation-resorption cycles maintain the bone mass (Al-Bari and Al Mamun, 2020). The key signalling pathways involved in the coupling of resorption – formation cycles are RANK/RANKL/ OPG systems coupled and Wnt signalling. RANK is a receptor on osteoclasts and pre-osteoclasts. Activation of RANK stimulates osteoclast differentiation and activity. RANKL is secreted by osteoblasts and is the main paracrine factor in bone remodelling. OPG operates as a counterpart to RANKL, that can reduces osteoclast differentiation. These systems are controlled by hormones and cytokines including IL-1, cortisol, oestrogen and prostaglandin E2 as shown in figure 4 and 5 (Ming et al., 2020; Tobeiha *et al.*, 2020; Marx, 2021).

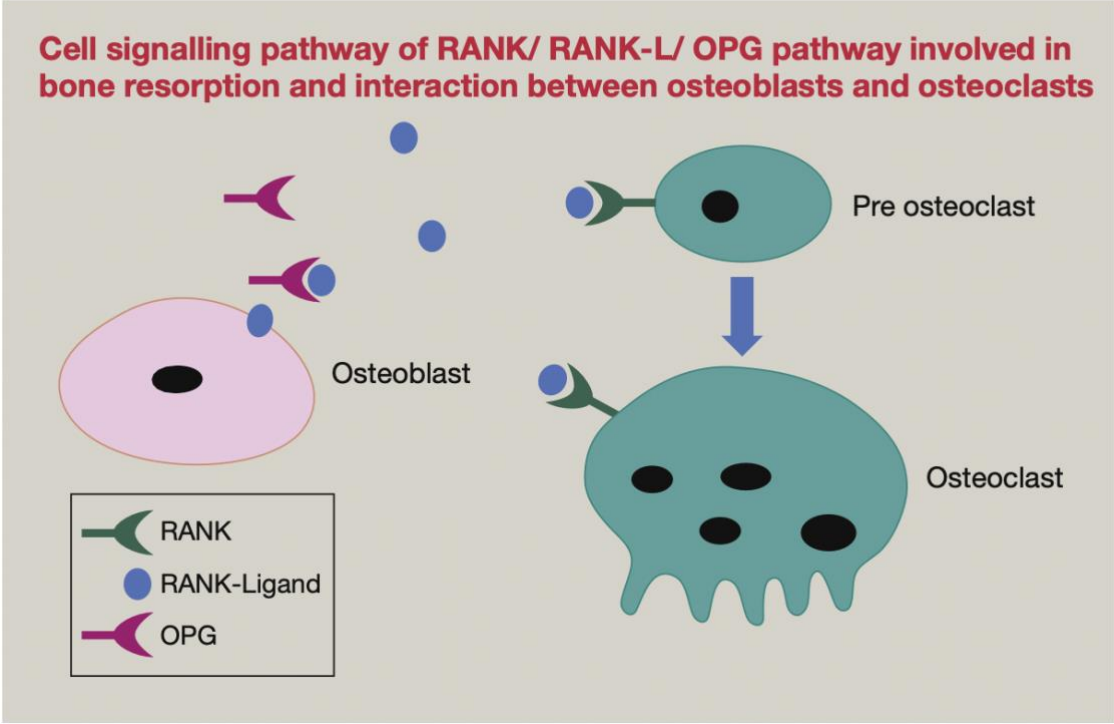


Figure 4 Interactions Between the RANK/RANKL/ OPG Pathways in the Activation of Osteoclasts

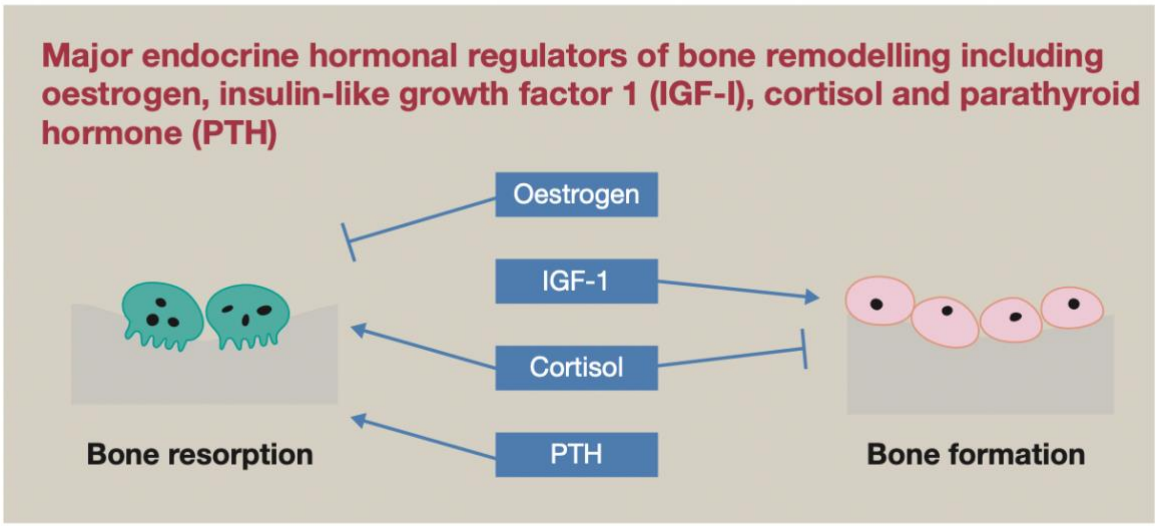


Figure 5 Control of Hormones to Promote and Inhibit Bone Resorption and Formation

2.4.1.2 Bone regulation by osteoclasts

Osteoclasts are derived from the monocyte/macrophage lineage which stems from osteoclasts precursors and originally the haemopoietic stem cell. This differentiation occurs in the presence of two essential factors; RANKL and M-CSF. These two factors are expressed on osteoblasts and control osteoclasts differentiation and function. M-CSF is imperative for pre-osteoclast growth and survival. M-CSF also induces RANK to RANKL and other RANK/NF-k beta pathway elements in osteoclastogenesis. Intracellular RANK signalling by its communication with RANKL causes recruitment and activation of TRAF6 leading to the downstream cascade for osteoclast differentiation. The negative feedback controller to suppress osteoclast differentiation is OPG, which is expressed on osteoblasts. OPG inhibits osteoclast maturation, and bone resorption via RANK/RANKL/OPG systems (Al-Bari and Al Mamun, 2020; Tobeiha *et al.*, 2020).

2.4.1.3 BMA interactions with bone

2.4.1.3.1 Antiresorptive (bisphosphonates)

Few cancers have the inherent ability to directly resorb bone due to lack of internal enzymatic machinery. Cancer cells normally recruit osteoclasts due to their stimulation of RANKL or a RANKL-like proteins (Bouganim *et al.*, 2011; Marx, 2021). Zolendronate is the most common drug currently used to prevent bone metastases or hypercalcaemia of malignancy. It is two to five times more potent that the original drug pamidronate, making IV zoledronate 4mg/month high risk of

MRONJ development (Coleman and McCloskey, 2011a; Coleman *et al.*, 2020). Bisphosphonates act by irreversibly binding and inhibiting the enzyme farnesyl synthase. As a cancer cell stimulates osteoclasts and begins to resorb bone which has been exposed to a bisphosphonate, following ingestion, it subsequentially kills the osteoclasts within 24 hours and ceases the resorption process (Luckman *et al.*, 1998; Russell, 2007). This anti-osteoclastic mechanism reduces resorption and reduces the risk of cancer-directed resorption and fracture. Calcium also remains in the bone during this process. This same process prevents constant remodelling at the alveolus, and consequentially leads to MRONJ (Luckman *et al.*, 1998; Russell, 2007; Marx, 2021). The risk of MRONJ becomes significant after four doses of zoledronate or eight doses of pamidronate (Marx, 2021).

2.4.1.3.2 Biological antiresorptive (denosumab)

Denosumab is a direct RANKL inhibitor and consequentially has anti-osteoclastic properties (Lacey *et al.*, 2012). It disrupts the development of preosteoclasts which reduces formation of viable osteoclasts. The direct cancer signalling pathway for bone resorption is not affected however cancer cells have the ability to stimulate fewer osteoclasts (Gnant *et al.*, 2015; 2019). Due to denosumab's inhibitory effect on preosteoclasts, the risk of MRONJ development is significant after one dose as seen in figures 6 (Marx, 2021). This selective binding of the RANKL inhibits osteoclast formation and activity, resulting in decreased bone resorption and increase bone density. Irreversible binding is not the case with denosumab compared to

bisphosphonates. Denosumab was originally introduced in 2010 and its risk of MRONJ in cancer patients is comparable to Zoledronate (Aljohani *et al.*, 2018).

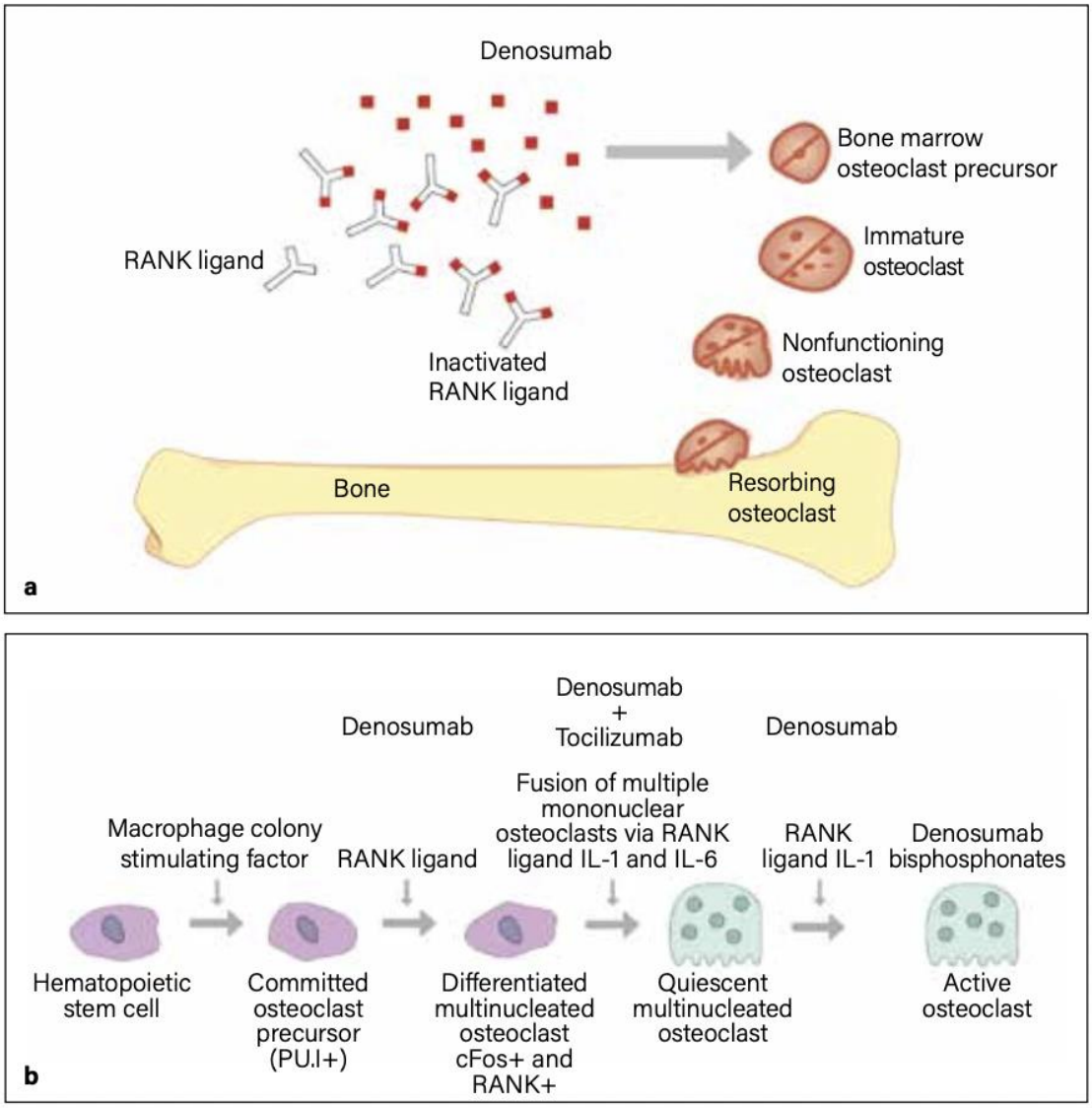


Figure 6 Mechanism of Action of Denosumab, Selective Inhibition at Multiple Stages of the Osteoclast Development

2.4.1.3.3 Antiangiogenics

Antiangiogenics are a antineoplastic medications that target a cancer's innate angiogenic properties. They impair the formation of new blood vessels, or a process known as angiogenesis. Neo-angiogenesis is an essential process for the growth of tumours and the development of metastasis in some solid tumours. Anti-Vascular Endothelial Growth Factor Inhibitors (Anti-VEGF) and Anti-Tyrosine Kinase Inhibitors (Anti-TKIs) are implicated in the development of MRONJ. Their precise aetiopathogenesis is unknown however they alter angiogenesis, indirectly impacting bone regeneration, repair and increases the susceptibility to superinfection (Pimolbutr, et al., 2018; Guirguis *et al.*, 2023). Bevacizumab and sunitinib are further examples that have been implicated in the development of MRONJ. Their role as adjunct medications as part of chemotherapy protocols, influence tumour angiogenesis however cancer mutations can develop alternative angiogenesis stimuli. Bevacizumab is used in lung cancer for both metastatic and non-metastatic disease. It is a direct potent inhibitor of VEGF which inhibits blood supply to the tumour. It also reduces blood supply to the alveolus inducing a local medication-related / avascular necrosis and inhibits macrophage chemotaxis and osteoblast differentiation (Aldridge *et al.*, 2005). Sunitinib also directly inhibits multiple growth factors including VEGF, osteoclasts differentiation and monocytes/macrophages which alters local immune response (Pazianas, 2011). The accumulative dose exacerbates a localised necrosis, particularly if used in combination therapy. Further reports of MRONJ associated with antiangiogenics include Dasatinib (Abel Mahedi Mohamed et al., 2018), Erlotinib (Abel Mahedi Mohamed et al., 2018), Imatinib (Abel Mahedi Mohamed et al., 2018),

Axitinib (Patel *et al.*, 2017), Sorafenib (Garuti *et al.*, 2016), Cabozantinib (Marino *et al.*, 2015) and Afibercept (Zarringhalam et al., 2017).

2.4.1.3.4 Biological immunomodulators

Humanised monoclonal antibodies are used to reduce inflammatory processes in systemic disease such as Crohn's disease, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis and psoriatic arthritis (Patel *et al.*, 2015; Milosavljević *et al.*, 2022). They are also indicated in the treatment of selective cancers (von Moos *et al.*, 2019). Their emergence in the development of MRONJ has been sparsely cited in recent literature associated with infliximab (anti-TNF alpha) (Favia *et al.*, 2017), tocilizumab (anti- IL-6) (Sakkas *et al.*, 2021), adalimumab (anti-TNF alpha) (Preidl *et al.*, 2014) and rituximab (anti-CD20) (Allegra *et al.*, 2014; Keribin *et al.*, 2017). Currently, there is no definitive mechanism to demonstrate their contribution to the development MRONJ. However, anti-TNF alpha medications can inhibit bone remodelling via RANKL pathways, apoptosis via monocyte activation, and local immunosuppression (von Moos *et al.*, 2019). In rare instances, tocilizumab an interleukin-6 (IL-6) inhibitor is used to treat rheumatoid arthritis, giant cell arteritis and some juvenile polyarthritis conditions. Il-6 inhibits affect osteoclast development and reported risk factor for MRONJ (Genovese *et al.*, 2008; Kaneko, 2013).

Currently, there is a lack of definitive aetiopathogenic mechanisms confirming their direct contribution to MRONJ, however it would be prudent to treat this cohort with preventative protocols given their close affinity to antiangiogenics in oncological protocols.

2.4.1.3.5 Adjunctive therapies

Long-term systemic corticosteroid therapy reduces inflammation but also heightens the risk of avascular necrosis, reducing blood supply to bone. When corticosteroids are used in combination with an antiresorptive, it can increase the risk of MRONJ development (Milosavljević *et al.*, 2022). Methotrexate is also used in the treatment of inflammatory and autoimmune diseases alongside a number of solid tumours and haematological malignancies (Aletaha and Smolen, 2018). Methotrexate is cytotoxic to T and B cells, inhibiting the release of IL-1, TNF alpha and other cytokines. It has been cited in the literature as a monotherapy causative for the development of MRONJ (Henien *et al.*, 2017; Milosavljević *et al.*, 2022). Mammalian target of paramycin (MTOR) inhibitors (Everolimus and Temsirolimus) are used to prevent transplant rejection, and at higher doses in late stage breast cancer, renal cancers, select neuroendocrine cancers and leukaemia. They have been described in cases of MRONJ in conjunction with bisphosphonates or other antiangiogenics however they have now been noted as a monotherapy risk factor for MRONJ (Yamamoto *et al.*, 2017).

2.1.5 Pathophysiology

The pathophysiology of MRONJ remains uncertain. Multimodal drug classifications are clinically, radiographically and histologically indicative of MRONJ, however further investigative therapies are advancing our understanding towards a definitive aetiological process (AlRowis *et al.*, 2022a). The alveolar bone is a highly active bone, capable of remodelling at a greater pace than bones elsewhere. Site specific jaw involvement has been attributed to bone remodelling inhibition, inflammation or infection, angiogenesis inhibition, innate or acquired immune dysfunction, alongside genetic predisposition (Granate-Marques *et al.*, 2019; Ruggiero *et al.*, 2022a). It is likely the pathogenesis is multifactorial. MRONJ is associated with microcirculatory dysfunction, direct toxicity to osteoblasts and osteoclasts, infection, immunosuppression and dysregulation of TGF-β production. The typical histological picture of osteonecrosis includes marrow fibrosis, hypovascularisation, and bacterial colonisation with inflammation (Granate-Marques *et al.*, 2019; Ruggiero *et al.*, 2022a).

The main theory for MRONJ pathogenesis is associated with interrupted bone remodelling due to impaired osteoclast function (Marx, 2021). Bisphosphonates have a direct effect on osteoclast formation, maturation, and function. The accepted mechanism of action is to prevent osteoclast differentiation and migration (Yuan *et al.*, 2020). Bisphosphonates also affect angiogenesis and neovascularisation in bone (Delfrate *et al.*, 2022). Over ossification of bone can occur due to suppression of the bone turnover and reduced osteocyte function which is impacts the bone's regular

homeostasis. Ischemic necrosis can occur due to an increased metabolic demand that is unmet (Yuan *et al.*, 2020). Cancer patient dosing regimens heighten the risk of MRONJ development (Coleman and McCloskey, 2011b). Denosumab has been observed to suppress bone remodelling to a greater extent by directly affecting bone microarchitecture, with increased bone mineral density and microarchitectural changes in cortical bone seen on micro-CT in postmenopausal women with osteoporosis (Yuan *et al.*, 2020).

Vascular alterations play a role in MRONJ (Allen and Burr, 2009). Zoledronic acid and dexamethasone have been proven to inhibit angiogenesis in rat models where impaired vascularity was noted after the precipitation of MRONJ (Tamari *et al.*, 2019). Osteonecrosis is typically defined as an avascular necrosis, due to osteocyte death after following reduced blood flow (Ruggiero *et al.*, 2022a). VEGF-A is one of the most potent pro-angiogenic factors involved in wound healing. During angiogenesis, endothelial cell proliferation is required to form new vessels, and VEGF-A promotes proliferation and migration of vascular endothelial cells. VEGF-A reduction is often observed in patients with MRONJ (King, Tanna and Patel, 2019). The incidence of MRONJ is lower in patients receiving antiangiogenics compared to an antiresorptives (Ruggiero *et al.*, 2022a). Soft tissue healing relies on epithelial and fibroblast function, immune response, and adequate vascularity (Tamari *et al.*, 2019; Zhang *et al.*, 2021).

Inflammation and infection, specifically the role of proinflammatory cytokines in MRONJ has been documented but also the removal of inflammatory nidus in

periodontal disease, has shown to regress progression and prevent disease (Ruggiero *et al.*, 2022a). Superinfection of bacterial colonies and clinical signs contribute to disease severity from stage 1 to stage 2 (Ruggiero *et al.*, 2014). Reducing biofilms and infection have been described as treatment goals, particularly in the oncological patient where surgery and resection may not be suitable (Thumbigere-Math *et al.*, 2014). Dental inflammatory and infective processes are implicated in initiating processes of MRONJ which has been documented prior to extraction of teeth (Otto *et al.*, 2015). Severe dental disease and infection coupled with osteoclast inhibition are predominant initiators of MRONJ (Aghaloo *et al.*, 2014; Katsarelis *et al.*, 2015; Hadaya *et al.*, 2018; Bolette *et al.*, 2019; Otto, Aljohani, *et al.*, 2021; Soutome *et al.*, 2021).

Innate acquired immune dysfunction is seen in patients with medical comorbidities such as diabetes mellitus, rheumatoid arthritis, or immunocompromised statuses, who are at a higher risk of MRONJ development. The oncology cohort with primary or metastatic bone malignancies have compromised immune systems (Kabilova *et al.*, 2014). These adjunctive therapies which alter the immune system have been attributed to higher risks of MRONJ, such as chemotherapy, corticosteroids, and disease-modifying antirheumatic drugs (Ruggiero *et al.*, 2022a).

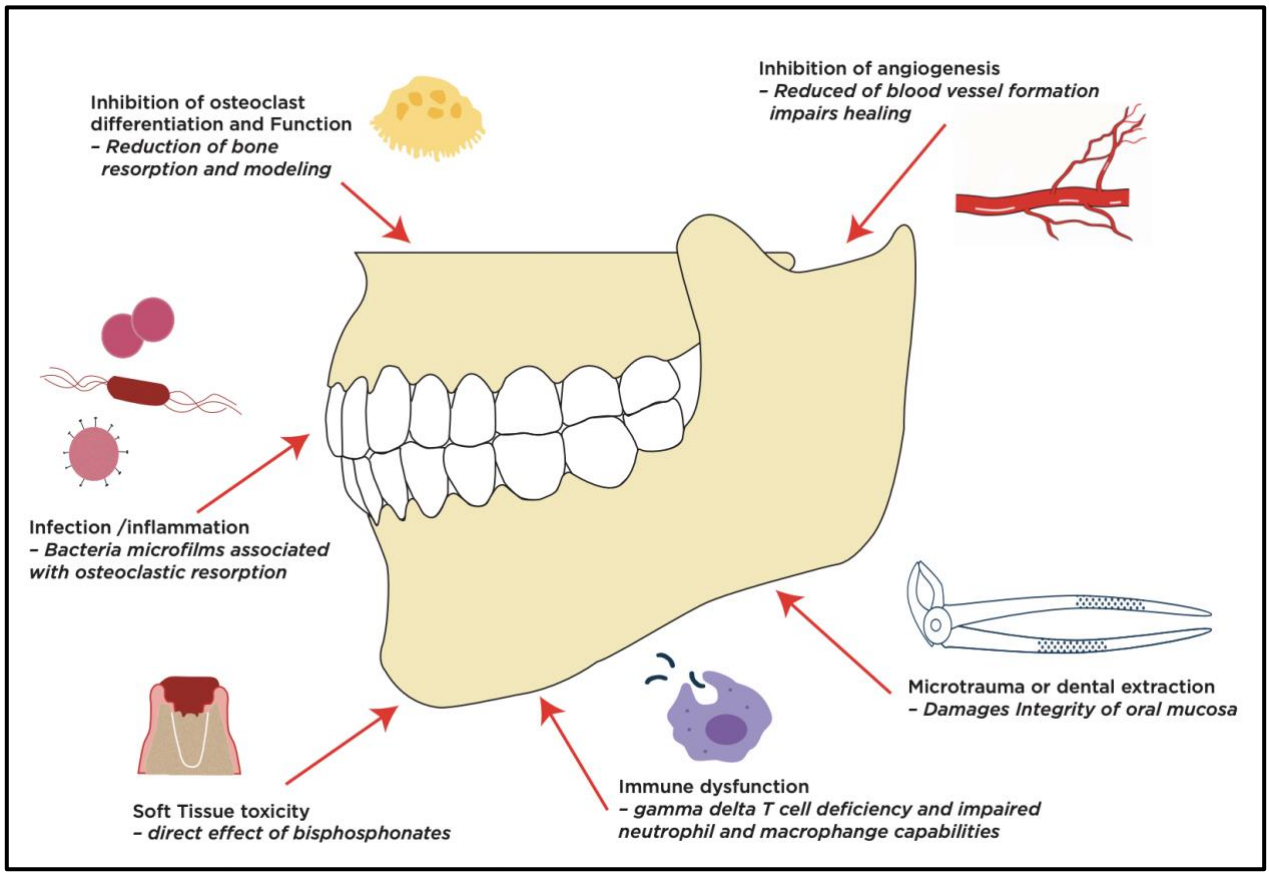


Figure 7 Multifactorial Nature of MRONJ Pathophysiology

2.1.6 Risk factors

The only true risk for MRONJ development is history of a bone modifying agent which has the potential to alter bone homeostasis (Marx, 2021). The relative risk of MRONJ can vary depending on the type of bone modulating agent, the route of administration, the duration of treatment, the potency of the drug, mechanism of action and sequential or dual therapy treatment regimes (Khan *et al.*, 2015, 2017; Beth-Tasdogan *et al.*, 2022a; Ruggiero *et al.*, 2022a).

The route of administration can change the propensity for MRONJ development (Ruggiero *et al.*, 2022a). 83.2% of MRONJ cases were reported following intravenous forms of bisphosphonates compared to the oral counterpart, demonstrating the higher potency of intravenous forms of bisphosphonate therapies (Fliefel *et al.*, 2015a). Oral bisphosphonates are poorly absorbed from the digestive tract. Intravenous therapies have a higher and quicker risk of MRONJ related to bone loading, which is 140 times faster than the oral alternative (Lowry, 2009). Denosumab alternatively is always administered subcutaneously however potency varies according to dosing regimen (60 vs 120mg for the osteoporotic versus the cancer patient). Denosumab consequentially is administered every 6 months (osteoporosis) or monthly (oncology) depending on nature of disease. There are higher numbers of MRONJ cases reported in patients with malignancies compared to those with multiple myeloma (Hillner *et al.*, 2000; Burkiewicz et al., 2009; Van Poznak *et al.*, 2017).

The type of BMA can change the relative risk of MRONJ development. Bisphosphonates act by inhibiting the cytoplasmic enzyme farnesyl synthetase(von Moos *et al.*, 2019; Marx, 2021). Mature osteoclasts are exposed to a high concentration of bisphosphonate in bone and toxicity is related to the half-life and continuous accumulation due to its irreversible binding to bone. Indirectly, bisphosphonates inhibit osteoblast differentiation (AlRowis *et al.*, 2022a). This is noted in the reduction of osteoclast cytokines that inhibit bone regeneration (Shibahara, 2019). Denosumab in contrast targets multiple stages of the osteoclast development; due to its inhibition of RANKL. Denosumab carries a similar risk of MRONJ development in cancer patients to zoledronate however the specific drug half-life in bisphosphonates includes significant periods (11.2 years) compared to

denosumab (approximately 26 days) (King, Tanna and Patel, 2019; Jiang *et al.*, 2021; Jung *et al.*, 2022). Antineoplastic medications such as bevacizumab have a markedly lower half-life, however their therapy can often be complicated with the addition of an adjuvant bisphosphonate (Teoh *et al.*, 2021).

The potency of the BMA can influence MRONJ development (Marx, 2021). Etidronate has a relative potency of 1, compared to ibandronate of 1,000 and alendronate as 5,000 (Marx, 2021). Even within drug classifications such as bisphosphonates there are variable factors such as potency that can influence MRONJ development. Haematological and oncological patients receiving IV zoledronic acid are a vulnerable cohort at risk of developing MRONJ due to its relative potency. Administration of pamidronate and clodronate appear to have lessened risks of developing MRONJ however this is in the absence of randomised trials (Vahtsevanos *et al.*, 2009; Anastasilakis *et al.*, 2022). The latter are usually used in myeloma patients. The intensity of drug therapy can vary which contributes to these findings. Dosing regimen, frequency, and the nature of underlying bony pathology dictate the treatment rationale accordingly. Denosumab used in the cancer setting is at least equivalent to IV zoledronate (Jiang *et al.*, 2021).

Table 1 Summary of Medications Implicated in the Development of MRONJ.

Medication	Mode of Action	Route of Administration	Level of Evidence
Bone Modifying Agents			
Zoledronic acid	Inhibits osteoclast proliferation	IV	Prospective cohort study
Clodronate	Inhibits osteoclast proliferation	PO	Multicentre retrospective cohort
Denosumab	Anti-RANK-L	SC	Retrospective cohort
Cytotoxic agents			
Methotrexate	Folate antagonist	PO/IV	Systematic review
5-fluorouracil /Irinotecan	Nucleotide analog / Inhibitor of topoisomerase I	IV	Case report
Paclitaxel	Cytoskeletal disruptor	IV	Case report
Azacytidine	Anti-DNA methyltransferase	SC	Case report
Immunotherapy			
Ipilimumab	Anti-CTLA-4	IV	Case report
Pembrolizumab	Anti-PD-1	IV	Case report
Nivolumab	Anti-PD-1	IV	Case report
Targeted Agents			
Sunitinib	Anti-TKI	PO	Systematic review
Infliximab	Anti-TNFα	IV	Case series
Bevacizumab	Anti-VEGF	IV	Case report
Rituximab	Anti-CD20	IV	Case report
Everolimus	mTOR inhibitor	PO	Case report
Imatinib	TKI	PO	Case report

Genetic susceptibility by major histocompatibility complex (MHC) class 2 polymorphism may necessitate the development of MRONJ in the susceptible patient (Sandro Pereira da Silva *et al.*, 2019). The 2022 AAOMS position paper made reference to genetic susceptibility related to single nucleotide polymorphisms in genes linked with bone formation (Ruggiero *et al.*, 2022a). Specifically, there has been an association made with the sirtuin1 (SIRT1) gene, a bone remodelling regulator which may be protective to MRONJ. Overall, the genetic causation factor is weak and there is a multidimensional explanation regarding genetic, and environmental factors (Ruggiero *et al.*, 2014; Sandro Pereira da Silva *et al.*, 2019). Bone homeostasis imbalances due to disease processes such as hypocalcaemia, hyperparathyroidism, osteomalacia and bone mineralisation disorders have been suggested to precipitate MRONJ development however study cohort are small with further research required (Bedogni *et al.*, 2012).

Accumulative doses of zoledronic acid and pamidronate have demonstrated dose-risk response in cancer therapy regimes (Hoff *et al.*, 2008; Vahtsevanos *et al.*, 2009). Mean time for development included 1.8 years following administration of zoledronic acid and 2.8 years for pamidronate (Palaska et al., 2009)21/08/2024 14:24:00. Concurrent antiangiogenic therapies in this cohort using sunitinib or bevacizumab can increase the risk of MRONJ development alongside the antiresorptive therapy (Fusco *et al.*, 2015). Bone is a common site for metastatic deposits in breast, prostate, lung, thyroid and renal cancers (Coleman and McCloskey, 2011a; Coleman *et al.*, 2020). Currently 70% of patients with advanced prostate or breast cancer and up to 40% of patients with advanced solid tours will develop bone metastases (Coleman and McCloskey, 2011a; Coleman *et al.*, 2020). The risk of MRONJ is <5% (range 0-18%) in the

oncology patient compared to <0.05% in the osteoporotic patient (Ruggiero *et al.*, 2022a).

Duration of BMA therapy plays a vital role in risk stratification (Ruggiero *et al.*, 2022a). The risk of MRONJ in the cancer patient is 0.8% in year 1, 1.8% in year 2, 1.8% in year 3 (Henry *et al.*, 2014). Specifically for zoledronate the risk was 1.6 – 4% at 2 years and 3.8-18% after 2 years (Clemons *et al.*, 2021).

2.1.7 Initiating factors

After the administration of a bone modifying agent, other associated factors heighten the likelihood of developing MRONJ.

2.1.7.1 Dental

The oral cavity is an environment that harbours copious amounts of bacteria that can colonise exposed bone (Ali and Sumita, 2022). The oral mucosa is constantly under repair from micro and macro trauma. Occasionally ill-fitting prostheses can contribute to mucosal wear and expose the functionally compromised bone in these patients (Ali and Sumita, 2022). Pre-existing inflammatory processes such as periodontal disease and periapical infections are known contributory factors for the development and progression of MRONJ (Srivastava *et al.*, 2021). Dental extractions were noted as an initiating factor, ranging from 45% to 82%, however these are crude figures for non-specific extraction techniques and surgical difficulty (Otto *et al.*, 2015; Bolette *et al.*,

2019; Soutome *et al.*, 2021; Ruggiero *et al.*, 2022a). The risk of MRONJ development following an extraction in the cancer patient ranges from 1.6 – 14.8% however the literature varies significantly on this topic (Scoletta *et al.*, 2013; Srivastava *et al.*, 2021; Ruggiero *et al.*, 2022a). Dental infections in cancer patients have shown to increase the risk of MRONJ, with a periapical infection compared to extraction of non-infected teeth alone. The presence of periapical infection alone increases the risk of MRONJ (Soutome *et al.*, 2021). Dental implants and periodontal surgery are also associated as contributory factors for MRONJ in 5% of cases for both entities (Marx, 2021). Microtrauma in the oral cavity attributed to a denture, occlusion or a region of mucosa exposed to repeated functional trauma have heightened risks namely due to the particularly high rate of bone turnover required at the surface. The posterior lingual mandible in particular and bony exostoses such as a torus are two common sites of initiation. Mucosal thinning and oral biota superinfection optimise the vulnerable sites (Marx, 2021; Ali and Sumita, 2022). Trauma such as a dental procedure or ill-fitting prosthesis, challenging this compromised cycle of bony repair can result in localised necrosis. The oral microbiota superinfect the necrotic bone and whether their superinfection is a result or a cause of MRONJ has not been confirmed (Ali and Sumita, 2022).

2.1.7.2 Medical

The literature has attributed specific contributory factors to the development of MRONJ related the host's systemic factors (Sacco *et al.*, 2021). Uncontrolled diabetes, smoking, concurrent corticosteroids, chemotherapy, immunosuppression and

peripheral vasculopathy enhance the potential development of MRONJ however heterogeneity and poorly controlled studies have proven challenging to conclude. Chemotherapy and corticosteroid use are the two major contributions to potentiate MRONJ (Khan *et al.*, 2017; Yarom *et al.*, 2019; Ruggiero *et al.*, 2022a).

2.1.8 Classification

Marx (2003) was the first to report the incidence of a bony necrosis related to antiresorptive therapies in patients without radiation to the head or neck or metastases in thirty-six cases associated with zoledronate and pamidronate (Marx, 2003). The American Association of Oral and Maxillofacial Surgeons (AAOMS) documented inclusion and exclusion criteria for accurate diagnosis and disease management (Ruggiero *et al.*, 2022a). The classification of MRONJ has evolved with many authors devising classifications systems based on clinical presentation of associated necrotic bone, pain, radiological markers such as extent, osteoblastic activity, and involvement on neighbouring structures (Yarom *et al.*, 2019; Ruggiero *et al.*, 2022a).

The initial classification devised by Ruggiero et al. (2006) structured classification based on asymptomatic, symptomatic and extensively involved necrotic bone. Ruggiero et al. (2009) revised the classification with introduction of the non-exposed bone with non-specific symptoms and radiographic evidence attributed to MRONJ (Ruggiero, Fantasia and Carlson, 2006; Ruggiero *et al.*, 2009). Mc Mahon et al. (2007), Bedogni et al. (2012) and Yoneda et al. (2017) all require radiographic findings to calibrate classification (McMahon *et al.*, 2007; Bedogni *et al.*, 2012;

Yoneda *et al.*, 2017). There are numerous other classifications of MRONJ, all of which signify the extent of exposed bone, and associated signs and symptoms. The following classifications are modifications of the AAOMS Ruggiero et al. (2009) and modified (2014) staging system which remains the most common MRONJ classifications (Yoneda *et al.*, 2010; Patel *et al.*, 2012). There was no change made to the staging system in the 2022 AAOMS position paper addition, which reiterated the importance of Stage 0 and the radiographic variability that can occur with MRONJ prior to bone exposure (Ruggiero *et al.*, 2022a). A stage 0 patient must be a patient at risk, with clinical symptoms, and radiographic changes suggestive of MRONJ. No bone exposure is noted. The progression of patients from stage 0 to stage 1 occurs in 50% of the cohort and its recognition is imperative in the management of the patient.

AAOMS staging system is included for definition and widespread use globally (Ruggiero *et al.*, 2022a).

Stage 0 - Also known as the non-exposed variant, presents without any clinical features of necrotic bone, however non-specific clinical symptoms and other features are associated. Radiographic changes present (alveolar bone loss, changes in trabecular pattern, regions of osteosclerosis, thickening of lamina dura).

Stage 1 - Presents with asymptomatic necrotic bone exposure, without any evidence of infection. Radiographic changes may be like stage 0 and is localised to the alveolus.

Stage 2 – Patients are symptomatic with necrotic bone exposure and infection, alongside features such as pain and erythema. Suppurative discharge may or may not be present. Bone loss is localised to the alveolus.

Stage 3 – Presents with infected necrotic bone exposure alongside one or more of the following: bone necrosis extending past alveolar bone which can lead to any already be exhibiting symptoms such as pathological fracture, fistula (extra oral and or intraoral), oro-nasal or antral communication and osteolysis capable of extending to sinus or mandibular floor.

Patient medical history, clinical assessment, and radiographic analyses performed in tandem leads to the diagnosis of MRONJ (Ruggiero *et al.*, 2022a).

2.1.9 Clinical manifestations

Patient's clinical manifestations vary depending on the stage and advanced nature of the MRONJ. Typically there is an area of exposed bone however this is not always the case (Ruggiero *et al.*, 2022a). Common clinical manifestations include pain, swelling, purulence, mobile teeth, fistula (intra or extraoral), pathological fracture, sensory changes and deformity. Mucosal breakdown and exposure of bone can be misleading and radiographic analyses aid true size definition. The cyclical nature of superinfection and purulence is prominent with pain and swelling (Filleul et al., 2010). These symptoms may be associated with a lack of exposed bone which should not hinder a diagnosis and appropriate management (Fedele *et al.*, 2010). These findings are

verified after exclusion of odontogenic causes or other known bone disorders (Ruggiero *et al.*, 2022a). Extension of the osteonecrosis into the mandible or maxilla can result in large necrotic regions of bone with sensory deficit to the maxillary or mandibular trigeminal nerve branches, pathological fracture, and oroantral communication.

2.1.10 Imaging

Chronic bone infections are becoming ever more prevalent (General (US), 2004; Wu *et al.*, 2021). Chronic purulent osteomyelitis, osteoradionecrosis, diffuse sclerosing osteomyelitis alongside MRONJ all encompass a chronicity that affects quality of life (Wu *et al.*, 2021). Their diagnosis is paramount to aid adequate planning and treatment. However, with increasing severity, their typical clinical presentation and histopathological picture tend to lack clarity. Their diagnosis can be challenging and illness persists (Fleisher *et al.*, 2016). Plain radiographic imaging of the jaws include orthopantomogram or intraoral periapical radiographs which are the first point of imaging in an area suspect of MRONJ. Classical radiographic characteristics include areas of osteolysis, disruption in the normal trabecular bone pattern, irregularity or involucrum separating the lingual cortex in one or more areas of the mandible, a disruption in the floor of the maxillary sinus/opacification of the maxillary sinus and osteolysis extending to the inferior border of the mandible or a pathologic fracture (Wortmann *et al.*, 2020; Marx, 2021).

Radiographic analysis for MRONJ includes plain radiographs such as panoramic x-ray, alongside computed tomography (CT), magnetic resonance imaging (MRI) and bone scintigraphy. 18-fluoro-deoxyglucose positron emission tomography (FDG-PET) has been implicated in the accurate diagnosis of MRONJ due to its uptake in inflammatory cells (Kitagawa *et al.*, 2019). FDG-PET enables non-invasive detection and demonstration of an accurate extent of bone involvement. MRONJ uptake of 18F-FDG was elevated in comparison to other forms of osteomyelitis and that the range of inflammation was not limited to the marrow rather that the inflammatory cells were active through the hard and soft tissues. The activity of MRONJ may often be difficult to assess (Kitagawa *et al.*, 2019). Characteristic findings may be implicated and represented accurately using nuclear medicine scanning. FDG-PET could be used to evaluate MRONJ activity (Kitagawa *et al.*, 2019).

MRONJ staging radiographically has been questioned with conventional radiograph deemed inappropriate to accurately demarcate the extent of the MRONJ. Being metabolic in nature, correct assessment of the maxillofacial bones using bone seeking radiopharmaceuticals can identify osteoblast activity in areas of regenerative vascularity or inflammation. FDG-PET allows identification of enhanced glucidic metabolism related to either regenerative or infected processes. Lower spatial resolution is characteristic of nuclear medicine imaging compared to CT, normal bone metabolism can be diagnosed exclusive to MRONJ, currently defining necrotic bone. 18-fluorodeoxyglucode (FDG) PET/CT has a theoretical lower radiation dose and higher resolution than bone scintigraphy. The accurate delineation of healthy metabolic bone is paramount for diagnosis, treatment planning and follow-up (Kitagawa *et al.*, 2019).

Conventional imaging with periapical or panoramic radiography, CT, and MRI exhibits little or no change in bony architecture in the early stages of MRONJ and detects lesions only after structural changes have taken place. The orthopaedic literature reports greater accuracy and sensitivity of FDG PET with CT for detecting musculoskeletal infections compared to MRI, due to the increased glucose uptake by activated macrophages and neutrophils of inflammatory reactions seen with bone scintigraphy (Fleisher *et al.*, 2016). Refractory MRONJ is difficult to assess and unreliable on conventional image analysis (Kitagawa *et al.*, 2019).

2.1.11 Histological and immunohistochemical analysis

Bone biopsies have been used with increasing frequency for the diagnosis of metabolic bone disease and for research purposes. An appropriate sample size is a major determinant for the accurate qualitative and quantitative histological analysis of the bone disease (Park *et al.*, 2009). Histological observations on specimens must be obtained to assess new bony activity or monitor proliferation. New bone formation after hypobaric oxygen (HBO) has been noted at the arrest line between the affected and healthy bone, indicative of mini-modelling and osteoblast activity (Yuan *et al.*, 2020).

Histomorphometric analysis of human bone in the maxillofacial region has been assessed on a microscopic level for calvarial bone grafts to the atrophied maxilla. New

bone formation was examined in these specimens after histological identification of both osteoid and osteocytes. Bone volume and quality may be examined to assess bone structure and density (Park *et al.*, 2009). Micro-CT scanning of bone samples to assess microstructure, architecture, and density have proven valuable however crushing artefacts on retrieval can cause morphometric damages structurally. Diameters of greater than 5mm are recommended. Shrinkage during processing can also lead to distortion of specimens. Micro-CT has been used as a surrogate for histological analysis of the structure of bone samples. Micro-CT has been advocated instead of histomorphometry in the analysis of quantitative bone diagnosis.This form of analysis permits a non-destructive examination of bone specimens before pathological analysis and skips preparation steps such as decalcification, cutting, and shrinkage distortion (Park *et al.*, 2009). Staining with haematoxylin and eosin to assess for signs of infection and cellular make-up, RANKL and OPG for bone remodelling activity, tartrate-resistant acid phosphatase (TRAP) for osteoclast activation, toluidine blue for bony architecture can be used. This involves incubation of antibodies and staining thereafter (Wortmann *et al.*, 2020).

2.1.12 Prevention

Preventative, pre-therapeutic dental regimes play a significant role in reducing the likelihood of MRONJ development (Vandone *et al.*, 2012a; Bramati *et al.*, 2015; Bledsaw *et al.*, 2023a). Bramati et al (2015) demonstrated a decreased incidence of MRONJ following a dental preventative programme from 11 to 7% (Bramati *et al.*,

2015). Not only was MRONJ incidence reduced, the requirement for less invasive surgeries were warranted compared to the population without a pre-therapy preventative dental programme. Dental examinations, identification of risk factors, proactive management of dental disease prior and during bone modulating agent therapy, less invasive dental procedures under antibiotic therapy if required and a strict maintenance regime are important dental elements of this oncology cohort (Vandone *et al.*, 2012b). A randomised control trial on the impact of preventative dental treatment strategies and 3-monthly dental reviews following BMA administration were associated with a 2.59 reduced risk reduction for MRONJ (Mücke *et al.*, 2016). Patient education, cohesive dental regimes, smoking cessation, diabetes optimisation and liaison with the dental team prior to starting a BMA optimises dental outcomes (Bramati *et al.*, 2015; Ruggiero *et al.*, 2022a; Bledsaw *et al.*, 2023a). No preventative strategy eliminates risk, however reduction of risk can be influenced. Establishing multidisciplinary communication and engagement at this point will help optimise overall health for the patient (Campisi *et al.*, 2020a; Bledsaw *et al.*, 2023a). The cancer diagnosis can also have an influence on the development of MRONJ, however the literature is not unanimous on this extrapolation (Ripamonti *et al.*, 2009; Mauceri *et al.*, 2023a).

Most recent documents to guide MRONJ preventative regimes include the Cochrane Oral Health, 2022 (3rd version) (Beth-Tasdogan *et al.*, 2022a), American Association of Oral and Maxillofacial Surgeons, 2022 (4th version) (Ruggiero *et al.*, 2022a) and the Italian Society of Maxillofacial Surgery / Italian Society of Oral Pathology and Medicine, 2023 (3rd version) (Bedogni *et al.*, 2023) define time lines for review

regimes (3monthly) (Beth-Tasdogan *et al.*, 2022a), risk stratification (Ruggiero *et al.*, 2022a), advocate the use of antibiotic therapy and primary closure following an extraction (Beth-Tasdogan *et al.*, 2022b; Bedogni *et al.*, 2023) and do not recommend the placement of implants in high risk oncology patients following BMA therapy (Ruggiero *et al.*, 2022a; Bedogni *et al.*, 2023). Maintenance of pre-existing implants remains an important aspect of dental care in this cohort (Ruggiero *et al.*, 2022b; Bedogni *et al.*, 2023) Another cornerstone document in the prevention and management of MRONJ is the Multinational Association for Supportive Care in Cancer / International Society of Oral Oncology / American Society of Clinical Oncology (MASCC/ISOO/ ASCO) Clinical Practice Guidance, 2019 (1st version) (Yarom *et al.*, 2019). This document was produced by an expert panel of oncologist based on 10 randomised control trials. It reinforces the necessity of multidisciplinary co-ordination of care between specialities, does not advocate the use of drug holidays, guides MRONJ risk stratification and could not conclude on the role of prophylactic antibiotic therapy with dental extractions.

There are three main preventative strategies employed by Marx (2021) to combat the development of MRONJ prior to the administration of a BMA. These include patients prior to therapy, during therapy and after exposure of bone (Marx, 2021). For patients prior to removal of non-restorable or hopeless periodontally involved teeth, elimination of any periodontal inflammation or periodontitis, commencement of a stringent hygiene protocol for the patient to maintain a high standard of oral care, occlusal adjustment / parafunctional protection and caries control (Campisi *et al.*, 2020a; Mauceri *et al.*, 2022). Timely dental care screenings and appropriate dental

care prior to therapy will reduce risk of MRONJ and inform patients of the ongoing risk of MRONJ development (Ruggiero *et al.*, 2022a). After patients have been exposed to BMAs a number of core dental principles are paramount to reduce risk of MRONJ development. Avoiding elective surgeries that may initiate MRONJ, caries control both therapeutically using fluoride and conventional restorations, maintaining professional oral hygiene regimes, splint mobile teeth, and maintain occlusal balance (Marx, 2021; Mauceri *et al.*, 2022).

Patients presenting with exposed bone attributed to MRONJ require meticulous management and patient compliance. Debridement of sharp regions of bone which traumatise adjacent tissues will benefit comfort and reduce diet restrictions; however repeated cycles of local debridement can be counterproductive for the overall process. Treatment should encompass a strict regime of oral hygiene, using 0.12% chlorhexidine three times daily and adjuvant antibiotics (amoxicillin 500mg TID / doxycycline 100mg once daily) if infection is present. More potent antibiotic regimes can be prescribed including metronidazole. Correspondence with the oncologist is imperative for multidisciplinary interactions to ensure optimal patient care. Maintenance follow-up every three months is suitable and sooner if required (Yarom *et al.*, 2019; Beth-Tasdogan *et al.*, 2022a).

Drug holidays have yet to be proven as definitively effective strategies to prevent MRONJ, their benefit has been reported but lacks definition and clarity (Ottesen et al., 2020; Aboalela *et al.*, 2022; Ottesen *et al.*, 2022). The length of drug holiday is specific

to each medication (Russell, 2007; Ottesen *et al.*, 2022). The foundation of a drug holiday is despite the 11.2-year half-life of oral bisphosphonates, the bone marrow stem cells and osteoclast precursors can regenerate to sufficient numbers to remodel and renew bone in the healing process. However, an effective drug holiday is not achievable in cancer patients taking an antiresorptive for skeletal related events due to more rapid and gradual bone depletion of bone marrow osteoclast precursor cells and potency of the therapy (Russell, 2007; Marx, 2021). Drug holidays for osteoporotic patients may be utilised under the prescribing physician's responsibility however this preventative strategy is ineffective in the cancer patient. A double-blinded, multicentre, clinical randomised control trial by Black et al. (2006) demonstrated no fracture risk difference in osteoporosis patients who had stopped their alendronate (placebo) compared to the continuing cohort after 5 years. This is attributed to bisphosphonate's high affinity to bone and half-life (Black *et al.*, 2006). No bone turnover biomarker is currently warranted in the monitoring and detection of MRONJ. Beta-C-terminal telopeptide (CTX), VEGF activity, endocrine function and PTH levels have yet to be proven as reliable indicators in this field (Ruggiero *et al.*, 2022a).

2.1.13 Treatment

There is no definitive cure for MRONJ. Risk identification and stratification are imperative to reduce the potential for MRONJ development. The goal of treatment is curative therapy and optimise quality of life. Patient care flow pathways and guidance have been developed via interdisciplinary collaboration however the risk of MRONJ development is never irradicated (Yarom *et al.*, 2019; Ruggiero *et al.*, 2022a). Patient

information and active engagement in preventative dental strategies have proven beneficial at reducing the risk of MRONJ. Anatomical variation intraorally such as tori and mylohyoid ridge susceptibility, ill-fitting prostheses, poor oral hygiene and periodontal health, unrestorable teeth with the presence of apical infection must be adequately addressed prior to commencing therapy (Thumbigere-Math *et al.*, 2014; Yarom *et al.*, 2019; Ali and Sumita, 2022). After therapy has commenced, invasive dental procedures such as bone grafting, and implant placement are contraindicated in certain groups of patients such as myelomas treated on bisphosphonates (Ruggiero *et al.*, 2022a).

Non-operative and operative treatment strategies are available, both where indicated appropriately have successful outcomes.

2.1.13.1 Non-operative management

Non-operative treatment strategies have an important role in the management of MRONJ and are valuable as adjunct management strategies to operative treatments. Non-operative strategies can be utilised in all stages of MRONJ (Yarom *et al.*, 2019; Ruggiero *et al.*, 2022a). Patient education, analgesia, and control of infection are key non-operative strategies to allow for sequestration of necrotic bone (Hadaya *et al.*, 2018). Difficulty lies in the decision based on risk – benefit analyses for each individual patient. Aspects such as wound care post operatively, superinfection, disease spread, oral function and quality of life each require consideration prior to intervention (Ruggiero *et al.*, 2022a).

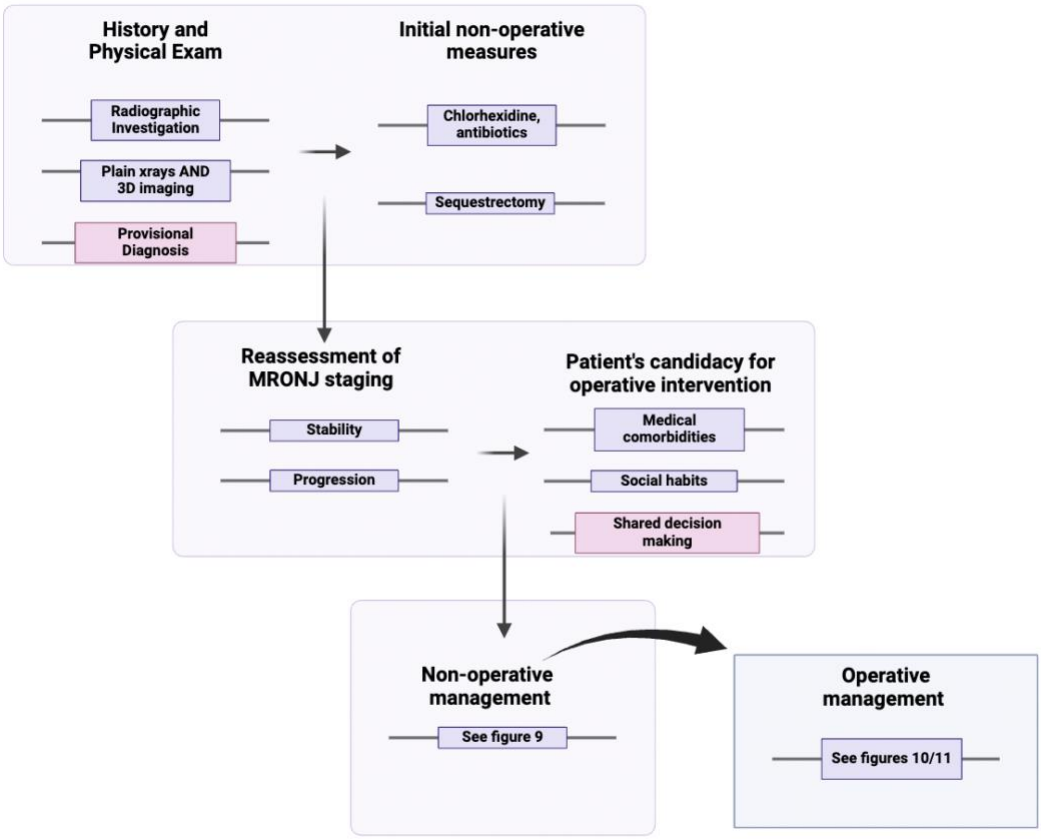


Figure 8 MRONJ Initial Assessment

Ruggiero et al. (2014) devised a treatment strategy based on staging and symptoms (Ruggiero *et al.*, 2014) Antibacterial mouth wash, patient education and regular reviews are basic regimes for conservative treatments. This can progress to pain control, systemic antibiotics and debridement to relieve soft tissue trauma (non-responding stage 2). Surgical debridement and resection are held for to palliate patients or in cases of severe infection (Ruggiero *et al.*, 2014).

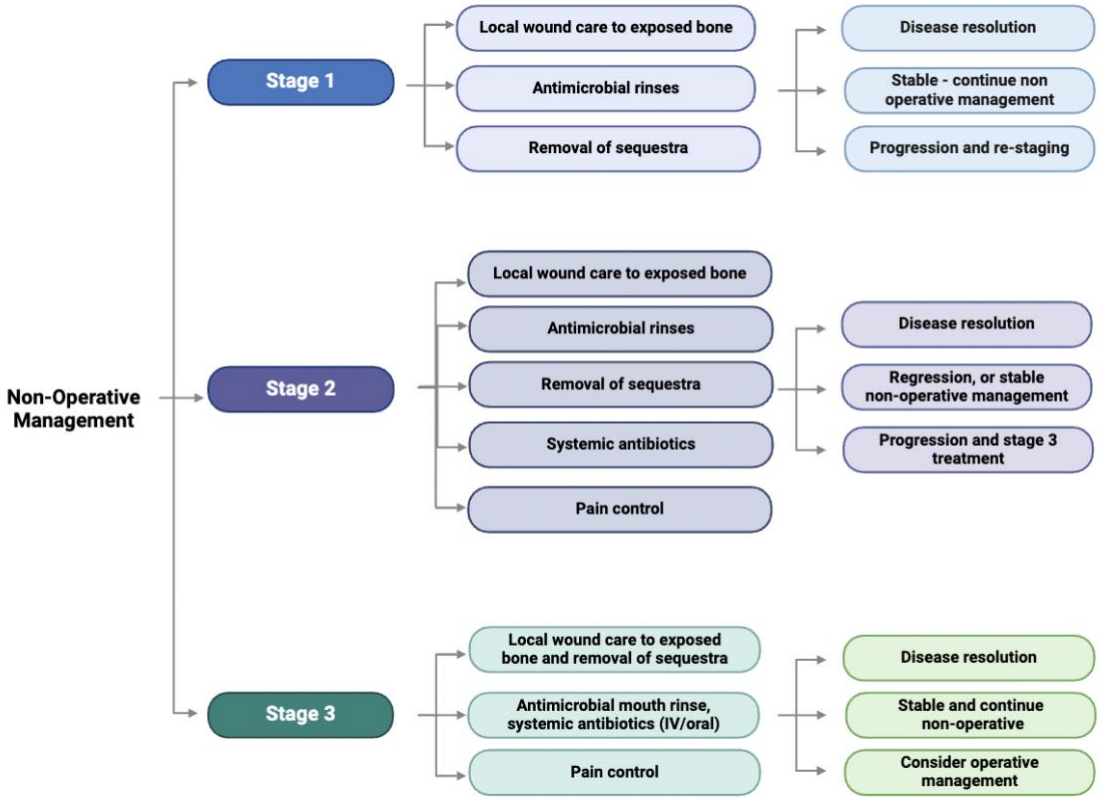


Figure 9 Non-operative Management Strategies

Non-surgical management aims to optimise stability and halt progression. Chlorhexidine mouth wash, local antiseptic measures, analgesics, antibiotics, sequestrectomy have all been routinely used in the management of MRONJ (Heifetz-Li *et al.*, 2019; Varoni *et al.*, 2021). Broad-spectrum antibiotics (amoxicillin, metronidazole, clavulanic acid and doxycycline) are first line therapies and second line adjuncts have been used (erythromycin and ciprofloxacin). The role of antibiotics relates directly prominent micro-organisms that reside in the biofilm, Actinomyces species (Petrovic *et al.*, 2019; Varoni *et al.*, 2021). Systemic indicators of infection require adjunctive antibiotics and some cases intravenous therapies may be required. Bacterial load can influence the disease progression however balancing recurrent antibiotic exposure, resistance and optimising local antiseptic regimes can be difficult

to obtain. The oncological cohort also have additive complications which may manifest intraorally such as candidiasis infection, hyposalivation, mucositis and graft versus host disease (Raber-Durlacher, Elad and Barasch, 2010; Al-Ansari *et al.*, 2015). Alternative therapies such as systemic recombinant human parathyroid replacement therapy (teriparatide), hyperbaric oxygen, low intensity laser, medical ozone therapy and PENTE regime (pentoxifylline, tocopherol) have demonstrated some degree of efficacy but not confirmative to definitively stop progression (Govaerts *et al.*, 2020). Medical management of MRONJ has proven difficult to predict effective therapeutic responses and studies are largely based on expert opinion in low quality evidence trials. The variation in patient and therapy driven factors can be difficult to standardise.

There is conflicting evidence to include teriparatide (PT) and pentoxifylline, tocopherol (PENTE) regimes in the management of MRONJ (V. Patel *et al.*, 2016; Cavalcante and Tomasetti, 2020; Ruggiero *et al.*, 2022a). Data from a double-blinded, randomised control trial on the efficacy of teriparatide in the management of MRONJ reported higher MRONJ resolution rates in the treatment arm compared the placebo at 52 weeks (Sim *et al.*, 2020). Sim et al. (2020) noted a 45.4% resolution of MRONJ (radiographic and clinical improvement) compared to 33% resolution in the placebo group over 12 months (Sim *et al.*, 2020). The side effects profile was balanced between groups, demonstrating short term use of teriparatide is both efficacious and safe for the management of MRONJ (Sim *et al.*, 2020). The incidence of osteosarcoma increased in rats with the administration of teriparatide hormone, this dose-dependency was seen in observed toxicology studies in rats only (Krege *et al.*, 2022). Low dosing regimens prior and post-surgical intervention can offer superior outcomes in the adjunct setting to accompany surgical intervention (Morishita *et al.*, 2020; Shim

et al., 2022). A recent systematic review concluded following multivariate analysis that teriparatide treatment has a 1.218 times more likely complete resolution of MRONJ stage 1 compared to MRONJ stage 3 with teriparatide treatment (Ferreira *et al.*, 2022).

Current treatment regimens of MRONJ are often limited to compromised by the lack of high quality data which provokes consensus driven management of MRONJ compared to evidence-based treatment modalities. Pentoxifylline, tocopherol and occasional clondronate have been originally reported for its benefits in the management of osteoradionecrosis (Kanatas *et al.*, 2024). Data was limited to three observational studies and two abstracts for the use of pentoxifylline and tocopherol in the medical management of MRONJ, which all yielded promising results (Heifetz-Li *et al.*, 2019).

Bio-stimulation methods such as hyperbaric oxygen, low-intensity laser, and medical ozone therapy, offer no definitive evidence to support cure or cessation of progression (Freiberger *et al.*, 2007; Moretti *et al.*, 2011; Agrillo *et al.*, 2012; Khan *et al.*, 2015; V. Patel *et al.*, 2016; McGowan et al., 2018; Sacco *et al.*, 2021). Recombinant human bone morphogenic protein-2 is a transforming growth factor beta. Its use has been in the treatment of MRONJ however further research is implicated to define its efficacy and safety in this cohort (Chen et al., 2004; Min *et al.*, 2020). Photobiomodulation (PBM) therapy has evoked interest in the treatment of acute oral mucositis following radiation therapy in head and neck oncology patients. The role of PBM remains under examination, their recommendation of LED / low level laser therapy was

recommended (Robijns *et al.,* 2022). Inflammatory suppression signalling and low level laser therapy have also shown promising results in vitro studies for gingival wound healing and subsequent bone regeneration following tooth extraction in zoledronate treated specimens (Zheng *et al.*, 2023). PBM has been incorporated into MRONJ treatment regimens, proving beneficial alongside surgical and antibiotic therapy (Nica *et al.*, 2021).

Sole medical management cases have been based on case reports and small clinical trials to optimise the potential synergistic effects of multiple medical management strategies in MRONJ in the maxilla where complex surgical intervention was contraindicated in oncology patients (Epstein *et al.*, 2023). A multimodality care algorithm was proposed including chlorhexidine with exposed bone, antibiotics when clinically required, PBM delivered by medical and patient at home LED-based PBM device, teriparatide (20micrograms per day for 2 months), and pentoxifylline and tocopherol (Epstein *et al.*, 2023).

The literature has begun to challenge the boundaries of medical management, and its role in the management of MRONJ is advancing. Despite the advances of medical management, surgical (operative) management remains a cornerstone in the treatment of MRONJ (Freiberger *et al.*, 2007; Harper and Fung, 2007; Cheung and Seeman, 2010; Agrillo *et al.*, 2012; Ruggiero, 2013).

2.1.13.2 Operative management

Surgical management has been extensively researched (Wutzl *et al.*, 2012). Surgical management was initially employed to palliate MRONJ which was unresponsive to medical management. Surgical management has been introduced earlier in the treatment cycle such as superficial debridement, sequestrectomy, and alveoloplasty with necrotic bone removal and primary mucosal closure. Primary intentional healing, under tensionless mucosal flap conditions, is imperative to stimulate angiogenesis and basal lamina signalling pathways (Campisi *et al.*, 2011; Fliefel *et al.*, 2015a, 2015b; Otto *et al.*, 2015). The AAOMS (2022) have promoted the avenue of resective surgery to restore function and slowing progression as highlighted in figure 10 and 11 for the mandible and maxilla, respectively (Ruggiero *et al.*, 2022a). The Joint Committee of the Italian Societies of Maxillofacial Surgery and of Pathology and Medicine have proposed a treatment classification using adjunctive imaging to dictate surgical extent and boundaries (Campisi *et al.*, 2011). CT-based surgical planning has a beneficial role to play in the surgical management of MRONJ (Otto *et al.*, 2021).

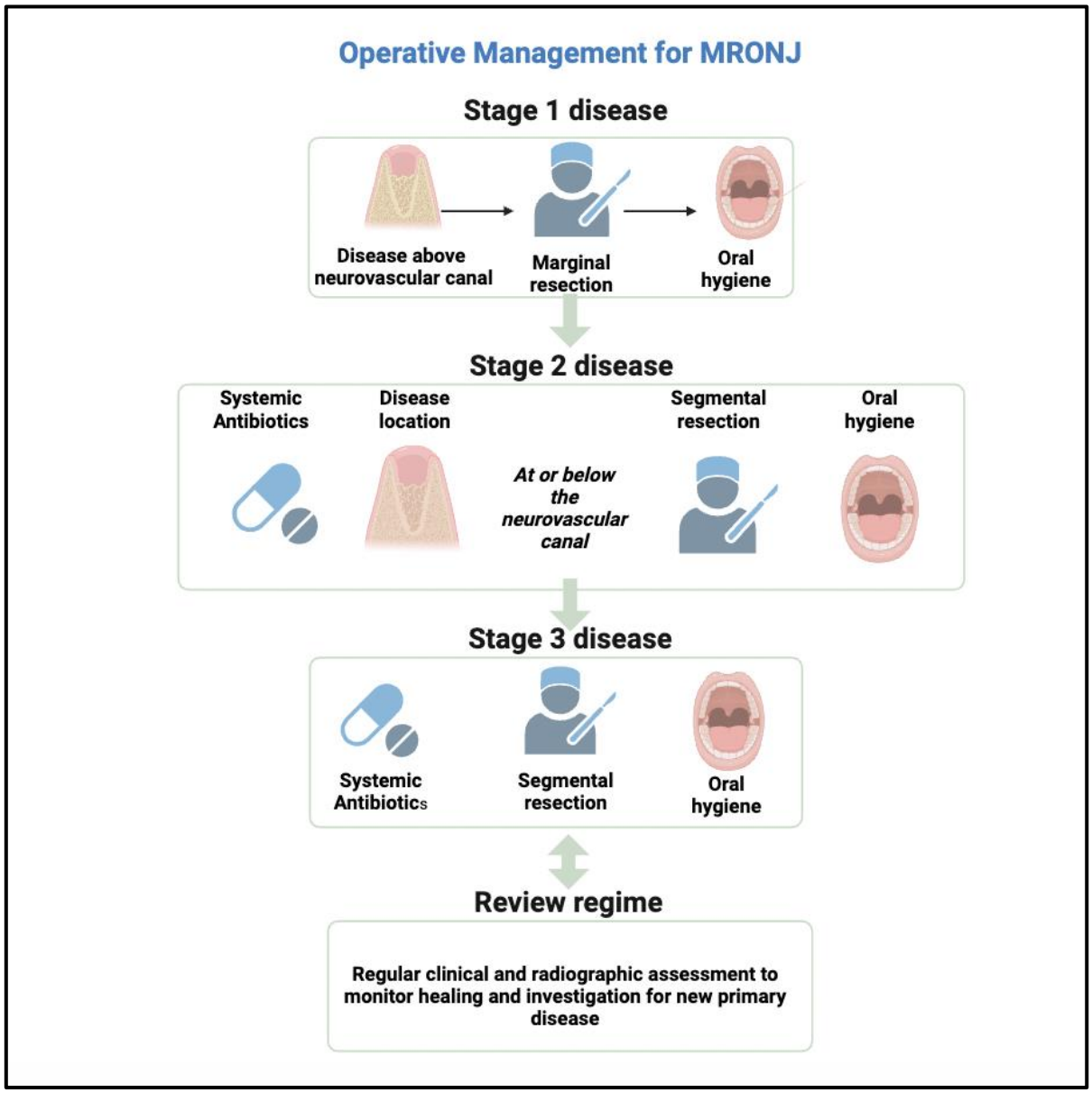


Figure 10 Operative Management for the Mandible

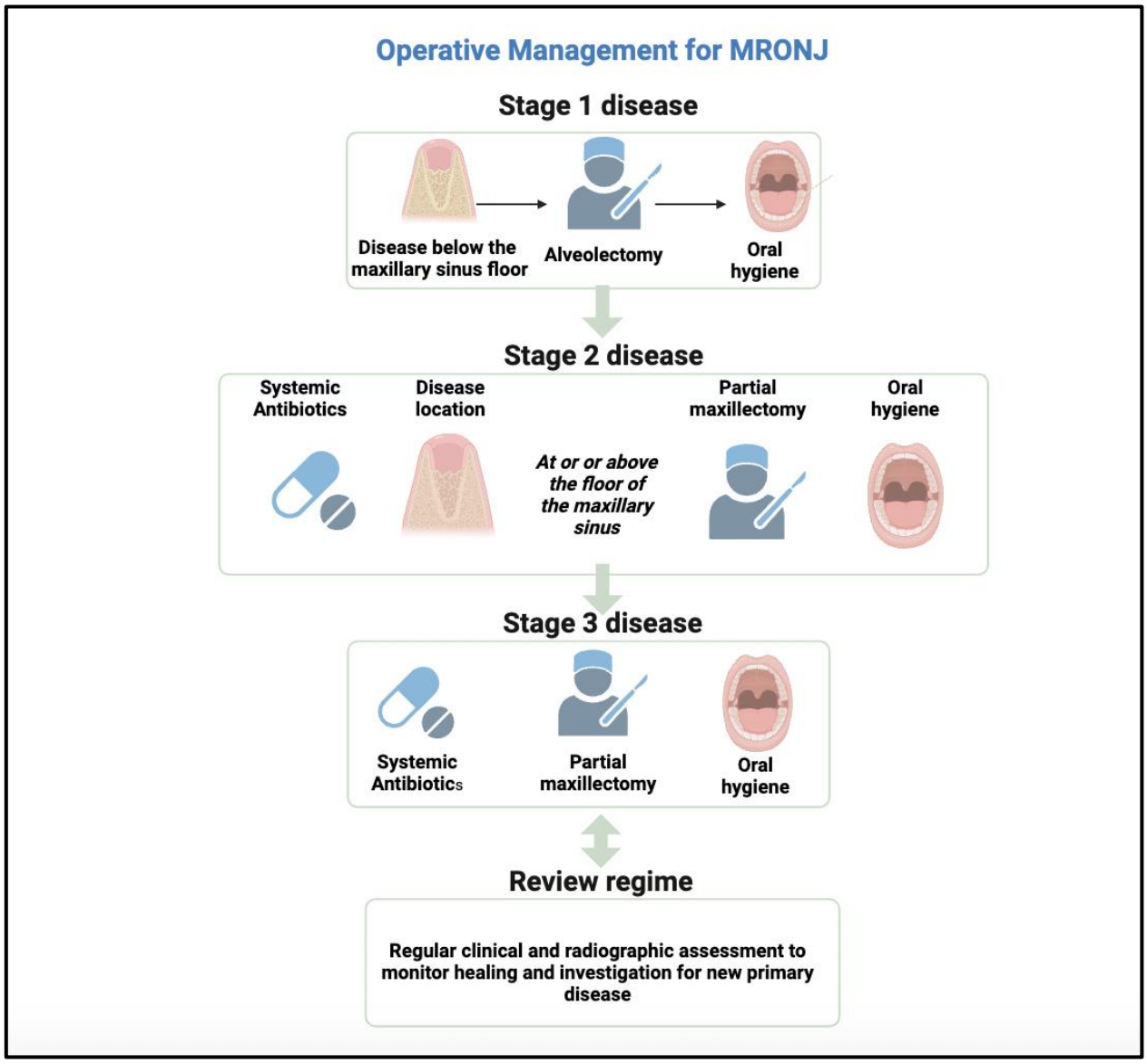


Figure 11 Operative Management for the Maxilla

Surgical management of MRONJ presents difficult challenges concerning exposed bone management, superinfection, disease progression, oral function, and quality of life (Ruggiero *et al.*, 2022a). Radical decortication, submarginal bone resection, rim mandibulectomy, local resection and free tissue transfer flaps are progressively being utilised for advanced stage surgical procedures for MRONJ. Replacement of tissue with biocompatible scaffolds and osteogenic potentiator cells such as buccal fat pad, autogenous platelet-rich plasma, autogenous platelet-rich growth factors, and

restoration of form and function using free tissue transfer flaps may be utilised (Khan *et al.*, 2015).

Marcianò et al. (2020) reported on a ten-year retrospective, single-centre study on surgical outcomes for MRONJ. A surgical decision tree was devised based on their findings of 128 MRONJ surgeries, in both curative and palliative cases, to guide the hard and soft tissue management of local MRONJ sites (Marcianò *et al.*, 2020). They advocated the use of piezoelectric devices in saucerisation and additional osteoplasty measures in more aggressive alveolar-block resections to eliminate residual bone asperity. Free tissue transfer flaps with microvascular reconstruction have been used to address large defects in stage 3 patients and case studies have reported promising success rates of 96% (Sacco *et al.*, 2018). Fibula free flaps have been favoured in these oncology patients due to low incidence of primary bone malignancy or metastatic bone disease (Qaisi and Montague, 2017). Soft tissue management in deficient cases may require advancement of mucoperiosteal flaps, mylohyoid flaps or pedicled buccal fat pad flaps to ensure primary closure and provide additional protection to wound dehiscence. The literature has not advocated the use of locally derived growth factors such as Platelet Rich in Growth Factors (PRGF) and Platelet-Rich Plasma (PRP) in the effective management of MORNJ (Marcianò *et al.*, 2020). Surgical intervention plays a role in the management of MRONJ, with successful and more predictable results obtained in earlier stages of MRONJ (stages 1 and 2) (Wilde *et al.*, 2011). Surgical intervention can be associated with a deterioration in a patient's clinical status following surgery (Lopes *et al.*, 2015). Case selection and appreciation of exacerbation factors are an important consideration prior to surgical intervention.

Surgical management of MRONJ for all stages have reported successful outcomes. Stage 2 and 3 defects can be controlled with segmental or marginal resections of the mandible or partial maxillectomy (Wilde *et al.*, 2011). Margins beyond the necrotic bone are required into vital bone.

Cohesive care for the management of MRONJ and incorporation of specialities including medical oncology, general dental practitioners, dental specialist, maxillofacial surgery and dental auxiliaries will ensure optimal patient care for patients at risk or experiencing MRONJ (Campisi *et al.*, 2011; Vandone *et al.*, 2012a, 2012a; Yarom *et al.*, 2019).

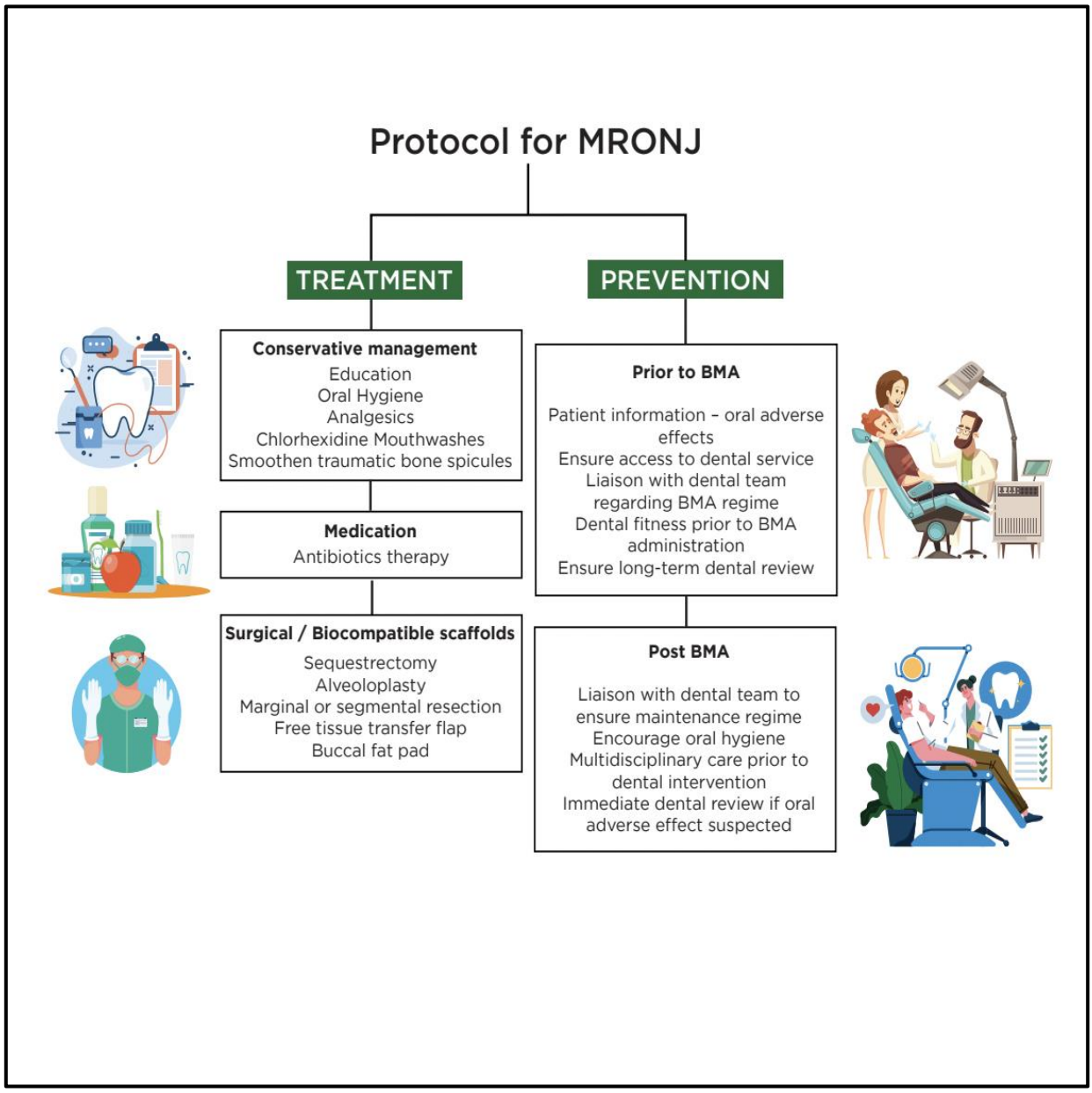


Figure 12 Management Protocol for Patients at Risk or Undergoing Treatment of MRONJ

2.1.14 MRONJ guidance

Evidence based medicine (EBM) and clinical guidelines provide a platform for clinical decision-making and treatment plans. EBM relies upon accurate data and high-quality literature to define standards of treatment for patients. Devising a specific clinical question forms the basis of the process, and provide reliable advise for clinicians and patients. Data in the literature must be appraised on its value and reliability. Levels of evidence help provide a stratified system to demarcate tiers of research, which can be translated into clinical practice. The literature is rich with data regarding the management of MRONJ however limitations must be accepted prior to engagement with MRONJ clinical guidelines concerning the level of evidence used to produce the guidance. The literature relies on twenty one years of data since first reporting of MRONJ, which is predominantly based of level 2-5 data including well-designed cohort studies, systematic reviews and cohort studies (Sacco *et al.*, 2021). In a recent review of the literature, 25 systematic reviews were available for MRONJ regarding interventional and non-interventional studies of case series, and retrospective cohort studies (Sacco *et al.*, 2021). This review of the literature highlighted the low-quality evidence surrounding MRONJ.

The prevention of MRONJ is documented worldwide from an array of both medical, oncological and dental organisations. The first clinical guidance for MRONJ was published in 2005 by the American Academy of Oral Medicine to promote preventative and management strategies of MRONJ (Pickett, 2006). Since then, organisations such as the Scottish Dental Clinical Effectiveness Programme (SDCEP),

Cochrane Oral Health (Beth-Tasdogan *et al.*, 2022a), MASCC/ISOO/ASCO Clinical Practical Guidance (Yarom *et al.*, 2019), American Association of Oral and Maxillofacial Surgeons (AAOMS) (Ruggiero *et al.*, 2022a), Italian Societies of Maxillofacial Surgery and Oral Pathology and Medicine / Italian Allied Committee on ONJ (SICMF / SIPMO) (Campisi *et al.*, 2020a; Bedogni *et al.*, 2023), Royal College of Physicians London (*Medication-related osteonecrosis of the jaw: guidance for the oncology multidisciplinary team*, 2019) and Workshop of European task force on medication-related osteonecrosis of the jaw (Schiodt *et al.*, 2019) have published documentation in the literature to guide the management of MRONJ. The table below (see table 2) summarises their strategies and guidance regarding MRONJ.

Table 2 Summary of Key Points in Current Dental and Oncology Guidance for the Prevention and Management of MRONJ.

	SDCEP	**Cochrane Oral Health**	**MASCC/ ISOO/ ASCO**	**AAOMS**	**SICMF / SIPMO**	**Workshop of European Taskforce on MRONJ**	**Royal College of Physicians**
Year of Publication	2017	2022	2019	2022	2023	2019	2019
Funding endorsement	Scottish Dental Clinical Effectiveness Programme	National Health and Medical Research Council	Multinational Association of Supportive Care in Cancer / International Society of Oral Oncology / American Society of Clinical Oncology	American Association of Oral and Maxillofacial Surgeons	National Dental Council Register of Italy / Interuniversity Consortium for Bio-Oncology	Amgen	Clinical Standards Committee of the Faculty of Dental Surgery (RCS) / UK Chemotherapy Board

	SDCEP	Cochrane Oral Health	MASCC/ ISOO/ ASCO	AAOMS	SICMF / SIPMO	Workshop of European Taskforce on MRONJ	Royal College of Physicians
Version	2nd versions	3rd version	1st version	4th version	3rd version	1st version	1st version
Prior publication	2011	2016, 2017	N/A	2007, 2009, 2014	2013, 2020	N/A	N/A
Speciality	Dental	Dental	Oncology	Dental	Dental / oncology	Dental	Oncology
Principle Author	Macluskey and Sammut et al.	Beth-Tasdogen et al.			Bedogni et al.		
	Guid-ance develop ment	Guid-ance develop ment	Expert panel	Expert panel	Expert opinion – Italian Expert panel position paper	Expert panel	Pre-existing guidance and expert panel
Objective	Defini-tion Risk identific ation Manage-ment of at risk patients.	Prevent-ion Interven -tion Surgical manage ment Combin ation manage -ment	Best practices in the prevention and manage-ment of MRONJ.	Risk estimate for MRONJ. Guidance for diagnosis , prevent-ion and manage-ment strategies .	Definitio n Epidem-iology Clinical features Staging System	Definition Staging Risk Factors Manage-ment	Pre and peri BMA dental guidance Dental pathways Communi-cation aids
Level of evidence	1b	1b (5 RCTs - preventi on) (8 RCTs – treat-ment)	1b – 3b (10 RCTS of 135 publicat-ions)	1b – 3b	2a – 3b	2a – 3b	

Prevention	**SDCEP**	**Cochrane Oral Health**	**MASCC/ ISOO/ ASCO**	**AAOMS**	**SICMF / SIPMO**	**Workshop of European Taskforce on MRONJ**	**Royal College of Physicians**
Recommendations	Risk stratification importance. Personalised preventtative dental strategies prior and ongoing throughout BMA therapy. Cumulative dose, dual therapy (AR and AA) and 4 years or greater of BMA therapy – careful consideration into high risk category. Untreated periapical infection contributory and over looked as a common initiating factor of MRONJ. Avoidance of dental implants in high-	3 monthly-dental reviews, Antibiotics prior to extraction and primary wound closure following extraction reduce the risk of MRONJ in advance-stage cancer patients (low evidence).	Co-ordination of care with multidisciplinary teams. Address modifying factors. Elective dentoalveolar surgery should be avoided in oncologic dose or specialist opinion to over-rule with individual assessment. Comprehensive communication between dental and oncology specialities. Inability to draw confirmative conclusion regarding prophylactic antibiotic therapy. Exacerbation factors with immune-suppressive therapy. Drug-holiday does not have justified benefit for temporary discontinuation versus	Definition and staging system as per AAOMS 2014. Epidemiology grouped by indication for treatment. Local and systemic contributory factors. Completion of oral surgical procedures prior to BMA administration. Use of pre and post operative antibiotics, primary closure of extraction sockets and oral hygiene regime, smoking cessation and diabetes optimisation for MRONJ prevention. Importance of multidisci	Communi-cation, and counseling prior to BMA therapy. Physician involvement for adherence to oral care. 4-monthly dental recall regime. Route of administer-ration "downsized" as a high risk factor for MRONJ. Important role of periapical infection in the initiation of MRONJ. Giant Cell Tumours of Bone on Denosumab - high risk category due to dosing regimen. Risk assessment for implant placement is contraindicated in	Dental infection major risk factor for MRONJ. Risk stratification of patients important factor – intraven-ous regimen carefully considered not always implicated in high risk category.	Metastatic (0-12%) and adjuvant (0.06-0.7%) prevalence of MRONJ development post BMA. Duration and dosing intensity influences relative risk. Dental alert cards and primary dental setting (prior to adjuvant treatment) and specialist dental treatment (in metastatic treatment setting). Invasive dental procedure 4 weeks prior to BMA with fluoride containing prevent-ative regime in place. Emergency administration for cases with hypercalcaemia – dental treatment promptly after stabilisation. During BMA treatment, dental reviews at least every 6

	risk regimes. Patient risk assess-ment algorith m develop-ment. Manage ment of modifi-able factors. Drug holiday not recomm-ended.		potential for skeletal-related events.	plinary care. Optimisat-ion of oral health and eradicatio n of periapical and periodon-tal inflamma-tion / infection. High risk implant place-ment strongly ill-advised. Early and delayed implant failure and peri-implant-itis (>12 months) MRONJ consequ-ences.	high risk oncology cohort. Lack of evidence for a prophy-lactic drug holiday.		months for both adjuvant and metastatic groups. No guidance for dental implants in adjuvant setting, contraind-icated in metastatic cohort.
Predis-position	Previous antire-sorptive history consider ations / dual therapy AR/AA therapy consider ations.	Dento-alveolar surgery (most preva-lent)		Periapical and periodont al inflamma tion / infection.			Dental extraction (52-68%), periapical infection.
Treatment	**SDCEP**	**Cochra ne Oral Health**	**MASCC/ ISOO/ ASCO**	**AAOMS**	**SICMF / SIPMO**	**Workshop of European Taskforce on MRONJ**	**Royal College of Physicians**
Recommen dations	Antibioti cs prophyla xis not warrante d.	No differen ce between auto-fluoresc ence +/- tetracyc	Mucosal closure monitored every 6-8 weeks and oncology correspond nce on	Non-operative managem ent has a role in every stage of MRONJ.	Non-invasive diagnos-tic approach to confirm MRONJ case with	Adheres to AAOMS 2022 staging and clinical manifestatio ns protocol. Reflection of accurate MRONJ	Prompt referral to a specialist with symptoms or suggestive symptoms of MRONJ.

		line fluorescence guided and conventional surgery (cure rates). Poor quality evidence to claim or refute the use of growth factors, autologous platelet concentrate, platelet-rich fibrin, and bone morphogenic protein 2.	healing status. Insufficient evidence to support drug-holidays. Staging system AAOMS (2014) advocated. Conservative, non-surgical management first option of treatment and refractory MRONJ with aggressive surgical intervention. Non-conclusive evidence regarding the role of surgical intervention – no difference between less aggressive surgical than aggressive surgical treatment. Antibiotic therapy and promotion of sequestration in conjunctional conservative surgery to avoid surgical resection. Advocates AAOMS (2022)	Non-operative therapies algorithmas stage dependent, operative management of mandibular and maxillary disease surgical management.	CT images. Clinical and radiographic input prior to definitive diagnosis. Surgical risk reduction protocol for tooth extraction, alveolectomy and tension-less closure. Surgical management is the basis for MRONJ resolution. Surgical extent and complexity determined by radiographic extent. Introduction of a stage-related surgical algorithm.	extent should include clinical and radiographic analyses to align with appropri-ate treatment band. Consideration for surgical input at all stages of MRONJ to "cure" – mucosal coverage and resolution of symptoms.	

			manage-ment strategy				
	SDCEP	**Cochrane Oral Health**	**MASCC/ ISOO/ ASCO**	**AAOMS**	**SICMF / SIPMO**	**Workshop of European Taskforce on MRONJ**	**Royal College of Physicians**

Dental and oncology specialities have formalised efforts to devise guidance for BMA prescribers and the dental community. Ireland currently makes reference to the SDCEP (2017) and The Cochrane Oral Health Report on MRONJ (2020) however deficiencies lie within the interdisciplinary guidance for all patients prescribed BMAs e.g. incorporation into oncology guidance for the management of patients on BMAs and their liaison with the dental committee. To date, Ireland does not possess a multidisciplinary service for oncology patients receiving BMAs. Furthermore, the majority of guidance is led by the dental community where the BMA prescriber may not integrate dental care into the overall oncology regime. BMA prescription was introduced and the development of MRONJ following the release of current Irish oral health policies. Over reliance on patients to actively seek dental care and navigate aspect of their cancer care should be alleviated.

The guidance documents above focus on a variety of aspects of MRONJ including definition, classification, preventative measures and pathways and treatment of MRONJ. The Cochrane Oral Health report on MRONJ (2020) contains the highest level of evidence (13 randomised control trials) and encourages the increased frequency of dental reviews to 3 monthly dental reviews in the oncology cohort, the

use of antibiotics with MRONJ treatment regimes, alveolectomy and extraction site closure as a preventative role and defines the poor quality evidence associated with the use of growth factors, platelet derived concentrates and the use of autofluorescence-guided surgical procedures in the management of MRONJ (Beth-Tasdogan *et al.*, 2022b). The SDCEP (2017) concentrates on risk identification, stratification of patients with regard to appropriate management, algorithms to categorize patient risk factors and management of modifiable factors. A third important European document, the Italian position paper (SICMF / SIPMO) tackles some important clinical, radiographic and surgical questions. They address the importance of extent of effected bone, the role of pre-existing periapical infections, advised the position of implant placement in different BMA-receiving cohorts, propose the importance of CT-guided treatment plans and an associated surgical algorithm (Bedogni *et al.*, 2023). The American-based guidance (AAOMS, 2022), **(**MASCC/ISOO/ ASCO, 2019) have co-ordinated comprehensive accounts of staging, pathophysiology, prevention and management particularly regarding the surgical component of MRONJ management (Yarom *et al.*, 2019; Ruggiero *et al.*, 2022a). Both American publications encourage the importance of multidisciplinary communication and team work with oncology patients on BMA therapy. The AAOMS (2022) 4th version, solidifies methods of risk management, identification, and the pathophysiological understanding of MRONJ. It has progressed since its first publication in 2007, and defined many of the cornerstones of diagnosis, prevention and management of MRONJ worldwide (Ruggiero, 2007; Ruggiero *et al.*, 2022a).

Dental and oncology guidance has formed a platform for individual units to create their pathway between dental and oncology services. However, the role of the general dentist in their management must not be overlooked.

2.2 Bone modifying agents in oncology

BMAs have provided essential and supportive roles in oncology to treat hypercalcemia, bone metastases and skeletal related events. Their efficacy is undisputed particularly with solid tumours and in multiple myeloma (Van Poznak *et al.*, 2017; Campagnaro *et al.*, 2018; Leng and Lentzsch, 2018). Treatment induced bone loss and adjuvant treatment for early stage cancer is also an important element of treatment. All post-menopausal patients irrespective of tumour sensitivity with primary breast cancer will have adjuvant therapy considered to prevent recurrence (Eisen *et al.*, 2022b). There are a number of categories of oncology patients where BMA therapy is planned namely bone metastases and multiple myeloma, early stage breast cancer in post-menopausal women, and treatment induced bone loss.

2.2.1 Metastatic bone disease and multiple myeloma

Metastatic bone disease is common in prostate (85%), breast (70%), lung (40%), kidney (40%) and in multiple myeloma (95%) (Coleman, 2006). These patients are at risk of predominantly axial SREs such as pathological fractures, surgery to bone, radiotherapy to bone, spinal cord compression and hypercalcaemia. Bone pain and

structural damage to bone impacts quality of life for these patients (Coleman *et al.*, 2020). Breast cancer patients have the highest incidence of SREs, most notable in the first year following diagnoses in advanced stage breast cancer (Coleman, 2006; Jensen *et al.*, 2011). In the first year following diagnosis, 172.5 patients per 1,000 experienced a SRE. Early stage breast cancer, localised and regional spread were 3.3 and 12.9 per 1,000 in their first year, respectively. Bisphosphonates are effective at reducing the rate and median time of SREs, noted by significantly reducing the median time from 7 months to 13.1 months in a clinical trial by Hortobagyi et al. (Hortobagyi *et al.*, 2017). Bisphosphonates reduce the risk of bone metastases, and disease-free survival in post-menopausal women with breast cancer compared to placebo noted from a recent Cochrane Review (O'Carrigan *et al.*, 2017).

Antiresorptive therapy is also a valuable treatment in advanced stage prostate cancer by reducing the number of skeletal related events and disease progression. Bone pain was not significantly reduced with bisphosphonate therapy and unwanted effects such as renal impairment and nausea are common side effects related to bisphosphonate therapy and this was noted in another Cochrane Database Systemic Review for Bisphosphonates in Advanced Stage Prostate Cancer (Macherey *et al.*, 2017).

Metastatic lung cancer to bone is associated with significant reduced morbidity, which is an important consideration particularly as 30-40% of non-small cell lung cancer (NSCLC) develop bone metastases (Coleman, 2001). Malignant cells possess a potential to increase bone resorption, including the secretion of IL-1, IL-6, RANKL, parathyroid hormone-related protein and macrophage inflammatory protein 1-alhpa

(Roodman, 2001). Lung cancer bone metastases are predominantly osteolytic, predisposing a patient to SREs and consequential deleterious effects on morbidity (Marinis *et al.*, 2009). Retrospective analyses of NSCLC patients revealed bone metastases in 30.4% of the cohort and 50% experienced a SRE (Tsuya *et al.*, 2007). Aside from the high morbidity rates in NSCLC, survival rates have improved from 20% to 29% mainly due to advances in chemotherapy regimens (NSCLC Meta-Analyses Collaborative Group, 2008). Bone metastases are associated with a poor overall survival in patients with NSCLC which was worsened with SRE on initial presentation. Denosumab reduces SRE incidence and is associated with increased survival times (26.6 months versus 20.1 months) (Ko *et al.*, 2022). As a consequence, prompt treatment with BMAs is advocated in NSCLC which significantly improves quality of life and impacts survival rates (Rosen *et al.*, 2003; Kohno *et al.*, 2005; Ko *et al.*, 2022). There is no current international guidelines for the use of bisphosphonates in NSCLC however expert panel published by Rosen et al. (2003) advocated the use of 4mg IV zoledronic acid every 3 - 4 weeks and shown to significantly reduce SREs by 31% over 21months (Rosen *et al.*, 2003). Duration of therapy remains unclear (Marinis *et al.*, 2009).

Patients with multiple myeloma most commonly present with bone pain due to vertebral fractures which is often recalcitrant to antineoplastic therapies. Diffuse osteoporosis is also present in patients with multiple myeloma, which heightens their requirement for antiresorptive therapy (Coleman *et al.*, 2020). Bisphosphonates contain antitumour activity in patients with multiple myeloma by inhibition of the mevalonate pathway, protein prenylation and block in S-phase. The American Society of Clinical Oncology (ASCO) who revised their 2007 guidance in 2017 advocated that

lytic lesions on radiograph in multiple myeloma dictate treatment including pamidronate 90mg (IV) or zoledronic acid 4mg (IV) every 3-4 weeks (Anderson *et al.*, 2018b). In the absence of lytic disease with associated osteopenia (solitary plasmacytoma or smouldering), IV pamidronate or zoledronic acid is recommended in conjunction with radiation therapy, analgesics and surgical intervention, depending on the case demands (Anderson *et al.*, 2018b). Treatment of osteoporosis will be addressed with antiresorptive therapy in these patients too. Treatment is routinely continued for 2 years unless relapse with new-onset SREs. Bisphosphonates remain the mainstay of treatment in multiple myeloma (Pozzi and Raje, 2011). The duration, intensity and cumulative dose places multiple myeloma patients at high risk of MRONJ development, as MRONJ risk increases with the duration of treatment (Ruggiero *et al.*, 2022a). Questions are valid comparing the length of treatment with a BMA (duration and cumulative dose) compared to observation time and patient survival is not fully understood (Bedogni *et al.*, 2023). Long duration of treatment and increasing survival rates necessitates the increased risk in metastatic cancer groups (breast, prostate and multiple myeloma) compared to lung cancer and the shorter duration of antiresorptive treatment (Hata *et al.*, 2022).

Due to the intensity of antiresorptive treatment in metastatic bone disease and multiple myeloma, this cohort is categorised as a high risk of MRONJ development (Ruggiero *et al.*, 2022a; Bedogni *et al.*, 2023).

2.2.2 Early stage breast cancer in post-menopausal women

Breast cancer is most common in women, and 0.5-1% of cases occur in men. There is 2.1 million cases each year worldwide of breast cancer and over half of those cases have no specific risk factors other than sex and age according to the World Health Organisation (2019) (Gnant and Hadji, 2010; *Breast Cancer - Statistics*, 2012). Irrespective of improvements in cancer therapy, 11,500 female deaths in the UK are breast cancer-related each year (*Facts and statistics, 2021*). Over the past 20 years, significant advances have been noted in breast cancer, in particular early breast cancer anticancer therapies. Trials such as the ZO-FAST, AZURE and ABCSG-12 documented the efficacy of adjuvant bisphosphonates in early breast cancer, reducing bone metastases and increasing survival in post-menopausal women (Coleman *et al.*, 2013, 2014; Gnant *et al.*, 2015). The Early Breast Cancer Trialist Collaborative Group reported the efficacy of bisphosphonates in reducing breast cancer recurrence, distance recurrence, bone recurrence, and mortality in post-menopausal breast cancer patients (including pre-menopausal on ovarian suppression) (Early Breast Cancer Trialists' Collaborative Group (EBCTCG), 2015). Denosumab has shown less convincing and inconsistent data in the field of early breast cancer and reduction in recurrence (Coleman *et al.*, 2020). Although no consensus has been standardised, 4mg IV zoledronic acid every 6 months for 3-5 years is routinely administered for these patients (Coleman *et al.*, 2020). The cumulative dose of IV zoledronic acid is less than that in the metastatic setting, however considerable risk remains regarding the risk of MRONJ development in this cohort; and patients are placed in a high risk category (Ruggiero *et al.*, 2022a).

2.2.3 Cancer treatment-induced bone loss (CTIBL)

Early stage breast cancer patients are at risk of cancer treatment-induced bone loss due to the resorptive effects of adjuvant endocrine treatments for hormone receptor-positive breast cancer (Kearns, 2023). Tamoxifen and aromatase inhibitors can affect bone and increase bone loss, which is also related to the specific pharmacology and menopausal state of the patient. Aromatase inhibitors increase bone turnover and cause oestrogen depletion. Bone loss is more marked in pre-menopausal women with ovarian suppression (Reid *et al.*, 2008). Bisphosphonate therapy has been shown to be effective to reduce the extent of CTIBL and regimes of IV 4mg zoledronic acid 6 monthly for 5 years or risedronate 35mg/weekly for 24 months are routinely prescribed (Van Poznak *et al.*, 2010; Coleman *et al.*, 2013). The first case series was published in 2023 of breast cancer patients on BMAs for CTIBL (Mauceri *et al.*, 2023a). Fifteen females were included in the series, and 53.3% of MRONJ cases were related to denosumab therapy. 66.7% had local risk factors for MRONJ development and 40% of the patients had tooth extractions related to periodontal disease. This is the first case series to highlight MORNJ as a consequence of CTIBL (Mauceri *et al.*, 2023a). The curative setting has seen an increase in breast cancer survivals and the number of patients on antiresorptive therapy due to cancer treatment (Gnant and Hadji, 2010).

2.3 Assessment of the oral health status and treatment need

2.3.1 Role of the dentist

Oral health is the condition of the mouth, and teeth which enables individuals to perform essential functions such as eating, breathing and speaking and encompasses psychosocial dimensions such as self-confidence, well-being, and the ability to socialise and work without pain, discomfort and embarrassment (*WHO*, 2019a). Oral diseases compromise oral health which is the most common non-communicable disease worldwide (*WHO*, 2019a). Oral health is a significant, progressive burden worldwide, most notable in low to middle income countries, which displays disproportionate tendencies in vulnerable cohorts of society (*WHO*, 2019a).

Assessment of oral health is based on both qualitative and quantitative parameters, in which a predictive value allows at-risk group identification. The concept of oral health in cancer survivorship is understudied (Taichman et al., 2013). Given the prevalence of oral complications seen in cancer care (30-35%), for annual cancer patients (400,000) in the US, the National Institutes of Health (NIH) Development Consensus Conference on the Oral Complications of Cancer Therapies have strongly advised dental assessments for oncology patients prior to cancer therapy (Hong *et al.*, 2010; Taichman et al., 2013). Chemotherapy regimens, radiation therapy and immunotherapy increase the risk of acute odontogenic and opportunistic infections (Hong *et al.*, 2010; Watson *et al.*, 2020). Dental screening examinations have proven effective at reducing oral complications in the oncology setting (Hong *et al.*, 2010;

Watson *et al.*, 2020). Oral complications predominantly fall under three classifications of cancer treatment (i) antineoplastic chemotherapy and haemopoietic stem cell transplantation, (ii) head and neck radiation therapy, and (iii) antiresorptive and antiangiogenic therapy (Hong *et al.*, 2010).

Patient, cancer and treatment specific factors influence the propensity for oral complications. A study assessed the oral health statis of acute myeloid leukaemia patients following a dental screening assessment. Dental disease was present in 59% of the patients, including dental decay, tooth mobility, dental pain, signs of an odontogenic infection, failing restorations and periodontal disease (Watson *et al.*, 2020). Dental disease was more prevalent in patients who did not seek regular dental care and screening reduced the potential for acute odontogenic infections, 0.68% in the screened group compared to 4.21% in the unscreened group at induction of chemotherapy (Watson *et al.*, 2020).

A recent report of the oral health status in oncology patients with MRONJ reported poor oral health statuses, and specifically a correlation was between higher MRONJ clinical staging and high DMFTI scores. Infection was noted as the precipitating factor in 79/80 patients (Caldas, 2021). The management of the at risk patients has seen little development to standardise the oncodental approach or to sustain communication for service needs and development. Primary and secondary prevention of MRONJ require cohesive service provision and interdisciplinary relations. Di Fede et al. (2018) published on the at risk patient (oncology and non-oncology cohorts) and the necessity for a multidisciplinary approach prior and during BMA therapy (Di Fede, 2018).

Data is sparse regarding the oral health status and dental treatment needs of patients prior to or during BMA therapy. This gap in knowledge is substantial and information in this field is an essential prerequisite for the prescription of a BMA and optimisation of patient outcomes.

2.3.2 Oral health status of patients at risk of MRONJ

Dental care is a subsidiary of oncology care for patients with both early and late-stage cancer on BMA regimes. The guidance documents above (see table 2) highlight the role of general dental practitioners (GDPs) in the management of patients at risk of MRONJ. The table below (see table 3) summarises valuable input lead by the GDP. Dental auxiliary teams such as hygienist also are an invaluable asset to a dental team. This has been clearly highlighted in Italy as an important aspect of routine dental care and maintenance for these patients (Mauceri *et al.*, 2022). There are barriers to dental care and cohesive onco-dental care must not be under-appreciated. Lack of correspondence between care providers, inadequate training of professionals and financial restraints were documented as barriers to streamlined onco-dental services in the US (Dang *et al.*, 2022; Bledsaw *et al.*, 2023a).

Table 3 Preventative Recommendations and Interventions Summarised from International MRONJ Guidance

Stage of treatment	**Role**	**Guidance**
Prior to BMA administration	Elimination of periapical infection / source of infection (Katsarelis *et al.*, 2015; Bolette *et al.*, 2019; Otto, Aljohani, *et al.*, 2021; Beth-Tasdogan *et al.*, 2022c).	Cochrane, AAOMS, SDCEP, MASCC/ISOO/ASCO, SICMF /SIPMO
	Management of periodontal health (Thumbigere-Math *et al.*, 2014; Kwoen *et al.*, 2023).	SDCEP, SICMF/SIPMO, AAOMS
	Restoration of viable teeth (Di Fede *et al.*, 2018; Campisi *et al.*, 2020b; Bledsaw *et al.*, 2023a).	SDCEP, SICMF/SIPMO, AAOMS
	Atraumatic removable prosthesis (Ali and Sumita, 2022).	SDCEP, Cochrane, AAOMS, MASCC/ISOO/ASCO, SICMF/SIPMO
	Preventative fluoride and oral hygiene regime (Di Fede *et al.*, 2018; Campisi *et al.*, 2020b; Mauceri *et al.*, 2022).	SDCEP, SICMF/SIPMO, AAOMS
	MRONJ education and counselling (Di Fede *et al.*, 2018; Campisi *et al.*, 2020b; Bledsaw *et al.*, 2023a)	SDCEP, AAOMS,
	Address modifying factors (smoking, diet advice) (Campisi *et al.*, 2020b; Mauceri *et al.*, 2022).	SDCEP, Cochrane, AAOMS, MASCC/ISOO/ASCO, SICMF/SIPMO
Following BMA exposure	Restoration of viable teeth (Di Fede *et al.*, 2018; Campisi *et al.*, 2020b; Bledsaw *et al.*, 2023a).	SDCEP, Cochrane, AAOMS
	Management of periodontal health (Thumbigere-Math *et al.*, 2014; Kwoen *et al.*, 2023).	SDCEP, Cochrane, AAOMS, MASCC/ISOO/ASCO, SICMF/SIPMO
	Denture maintenance (Ali and Sumita, 2022).	AAOMS, SDCEP
	Fluoride therapy (Mauceri *et al.*, 2022)	SDCEP, Cochrane, AAOMS, SICMF/SIPMO
	Oral hygiene (Di Fede *et al.*, 2018; AlRowis *et al.*, 2022a; Bacci *et al.*, 2022a; Mauceri *et al.*, 2022).	SDCEP, Cochrane, AAOMS, SICMF/SIPMO
	MRONJ screening	SICMF/SIPMO
	Appropriate referral when suspected	SDCEP, Cochrane, AAOMS,

GDPs play a pivotal role in the prevention and recognition of MRONJ (Mauceri *et al.*, 2022). Prevention of MRONJ has shown to be a valuable strategy by reducing morbidity for the oncology cohort during and after cancer treatment. Preventative strategies begin with patient counselling and education. The literature has reported the poor knowledge of oral consequences of MRONJ with only 54.72% of patients understood the necessity for a dental examination prior to therapy (Al Abdullateef and Alhareky, 2020). Guidance has attempted to bridge the knowledge gap between health care professionals, nursing staff, dental community and oncology supportive services however awareness of dental services in oncology BMA prescription remains suboptimal (Sturrock *et al.*, 2019; Al Abdullateef and Alhareky, 2020; Patil *et al.*, 2020). The lack of knowledge amongst GDPs is also prevalent despite guidance and efforts to inform patients and BMA prescribers about the potential of MRONJ development (Patil *et al.*, 2020). In a recent multi-centre study, 61.5% of GDPS had no knowledge of risk factors of MRONJ and 61.% were happy to identify clinical indicators of MRONJ (Patil *et al.*, 2020). Recognition of gaps in knowledge is paramount for GDPs prior to assessing and advising this cohort of oncology patients. Patient care is guided by health care professionals and their intent to deliver successful care. BMA prescribers have a duty to understand the potential risks of MRONJ, which was evident in a cross-sectional study where prescriber unawareness of MRONJ included 37.5% of the medical prescribers (El Osta *et al.*, 2015). Patient perceptions of MRONJ concluded that there was a significant impact to quality of life and preventative strategies were lacking. Interprofessional management, perception and knowledge of MRONJ, the associated risk and preventative factors and dental care resources were all highlighted as key deficiencies to patients at risk of MRONJ (Sturrock *et al.*, 2019). The most recent publication from SICMF / SIPMO and SDCEP

guidance place individual emphasis on education and counselling for patients prior to BMA therapy (Bedogni *et al.*, 2023;).

Dental disease is an integral component of MRONJ (Thumbigere-Math *et al.*, 2014; Lorenzo-Pouso *et al.*, 2020; Kwoen *et al.*, 2023). MRONJ development has been associated with increase periodontal disease, in particular severe periodontal disease. A recent systematic review investigated the relationship of periodontal disease and MRONJ development compared to unaffected patients (Lorenzo-Pouso *et al.*, 2020). Subjects with MRONJ were twice as likely to have periodontal disease compared unaffected at risk patients (Lorenzo-Pouso *et al.*, 2020). However, pooled analysis revealed no significant results when the plaque index (PI), periodontal probing depths (PPD) and clinical attachment loss (CAL) were assessed (Lorenzo-Pouso *et al.*, 2020). However, tooth loss in a patient with periodontal disease, has shown to increase the risk of MRONJ and elevate the risk compared to an unaffected at risk patient; hazard ratio increase to 2.5 (Kwoen *et al.*, 2023). There is a lack of evidence to define the direct cause and effect association of periodontal disease and MRONJ development, however the pathophysiology of periodontal disease may render the oral microenvironment susceptible to necrosis alongside antiresorptive agents (Aghaloo *et al.*, 2014; Katsarelis *et al.*, 2015). The local aetiopathogenic model of local trauma (tooth extraction) and low grade inflammatory response in a patient with reduced osteoclastic activity renders a patient susceptible to MRONJ (Allen and Burr, 2009; Lesclous *et al.*, 2009; Gkouveris *et al.*, 2019). Periodontal disease can predispose a patients to tooth loss and induces a state of oral dysbiosis and production inflammatory mediators (Pazianas, 2011; Katsarelis *et al.*, 2015; Kwoen *et al.*, 2023). The maintenance of periodontal health in patients exposed to BMAs must be closely

monitored by GDPs. Measurements of periodontal health vary depending on parameters based on the extent of CAL, PPD, active bleeding of the periodontium and plaque scores with may be used in tandem with radiographs (Dhingra and Vandana, 2020). Diagnostic scores have been used in dentistry to combine and standardise disease activity however operator and index limitations are widespread (Shayeb et al., 2014; Dhingra and Vandana, 2020). Periodontal screening tools have merit as rapid, non-invasive methods to predict progression to in-depth periodontal records and treatment (Verhulst *et al.*, 2019). The literature is rife with periodontal indices however the investigators used a translatable periodontal screening tool (Basic Periodontal Examination), alongside measurement of plaque, radiographic analysis and disease activity using the Staging and Grading system documented by the American Association of Periodontology / European Federation of Periodontology – World Workshop Classification (2017) (Dietrich *et al.*, 2019; Dukka *et al.*, 2022). Periodontal risk assessment tools have good predictive capabilities and utilising models to distinguish disease severity and patient susceptibility (Dietrich *et al.*, 2019). The British Society of Periodontology (BSP) implemented a simplified version of the World Workshop Classification on the staging and grading of periodontal disease for use in clinical practice (Dukka *et al.*, 2022). The authors have classified patients using a periodontal screening (BPE), current disease activity indices (Silness and Loe Plaque index, bleeding score) and the periodontal staging and grading classification alongside radiographic analysis in each case (Löe, 1967; Dietrich *et al.*, 2019; Dukka *et al.*, 2022). These indices and risk assessment tools are translatable to the general dental practitioner, alongside their merits in periodontal disease diagnostics, both for teeth and implants. Dental hygienist play an important role to optimise oral health status in patients at risk of MRONJ and the first position paper was published in 2022 to guide

incorporation of the auxiliary dental team in the management of MRONJ (Mauceri *et al.*, 2022).

Dental decay is the most common, untreated non-communicable disease according to the World Health Organisation (2019). This trend has shown no improvement over the past 30 years and the most recent report in 2022, highlighted the prevalence of untreated dental disease in 3.5 billon people world-wide and in 75% of people living in middle income countries (*WHO,* 2019). Dental decay is a prerequisite to periapical infection if not treated appropriately. The prevalence of dental disease is indicative of future MRONJ, particularly in BMA cohorts with curative intent (Patel *et al.*, 2018; Kizub *et al.*, 2021; Mauceri *et al.*, 2023b). 91% of non-metastatic breast cancer patients survive over 5 years and the 10 year survival is 85% (*Breast Cancer - Statistics*, 2012). Improvement in adjuvant therapies and increasing life expectancy in BMA cohorts, indicates growing populations of patients at risk of MRONJ (Mauceri *et al.*, 2023a). For GDPs, early identification of dental decay, identification of high caries risk patients and incorporation of preventative fluoride programmes can help to treat decay prior to infection. The caries risk assessment tool (American Dental Association) was used in conjunction with the recognised index Decayed, Missing and Filled Teeth (DMFT). The index gives account of both historic and current dental decay and also indicative of a patient's hard tissue oral health status (MORADI *et al.*, 2019).

The role of the GDP is paramount to risk assessment, early identification, prevention and management of dental disease in patients at risk of MRONJ. Dental and oncology

based guidance advocate the interdisciplinary relationship between BMA prescribers, health care professionals, dental communities and patients (Di Fede *et al.*, 2018).

2.3.3 Measurements of oral health

The DMFT index was initially devised by Henry Klein, Carroll E Palmer and Knutson JW in 1938. This index examined all permanent teeth, including 28 teeth only. The WHO altered the index to include wisdom teeth (32 teeth) in 1986. Excluded teeth include primary teeth, unerupted teeth, supernummary teeth and congenital missing teeth. Instruments used are a mirror and dental probe. Dental decay includes a diagnosis of dental caries which is clinically visible and cavitated or non cavitated into dentine. Early hypomineralised patches of enamel are not considered decayed (*WHO, Basic Methods - 5th edition*, 2013). The explorer tip is critical in order to consider tactile differentiation from healthy and decayed tooth structure. Teeth with temporary restorations are considered decayed or a tooth with recurrent caries and a permanent restoration. For missing considerations, teeth that are missing due to decay or carious teeth indicated for extraction. Teeth that are not considered missing include orthodontic extractions, unerupted teeth or lost due to trauma. Filled includes teeth with are stable and filled with a permanent restoration and where no recurrent decay is present. A score is given to one tooth only and one tooth cannot contained two scores for DMFT. The decayed, missing and filled scores must be recorded separately. Multiple restorations in one tooth are counted as one restoration for that tooth. Retained roots are considered as present even if the tooth is decoronated. Unfortunately, the score does not relate to risk of decay, it can be misleading in the

older adult population and overestimates caries experience. Root caries experience is measured using the Katz root caries index (RCI-1979)(Katz, 1980).

Periodontal health can be measured using a vast array of periodontal indices to help measure, and treat periodontal disease. The multifactorial nature of periodontal disease and the use of dichotomous measurements can sometimes exclude relevant information. Periodontal disease represents an inflammatory process which results in destruction of the attachment apparatus, loss of alveolar bone and eventually tooth loss (Socransky and Haffajee, 1997). Periodontal indices have evolved from the simple Russell's index to inclusion of risk factors and genetic susceptibility (Genetic Susceptibility Index) (Dhingra and Vandana, 2020). The Periodontal Screening and Record Index (PSR) which was designed as a screening tool for periodontal disease designed by the American Association of Periodontology (AAP) and American Dental Association (ADA). In 1991, the PSR was modified and endorsed as the accepted periodontal screening tool across America and Canada (Landry and Jean, 2002). The PSR code divides the mouth into sextants, and the greatest score for each sextant is recorded using a 0.5mm diameter ball tip and colour banded at 3.5-5.5mm periodontal probe. Scores range from 0-4 (see table 4). Furcational involvement, mobility, recession and mucogingival issues are highlighted by an asterisk. Treatment needs are correlated to each score and it serves as a uniform method of screening the periodontal health and guidance to the expectant treatment need (Dhingra and Vandana, 2020). Screening tools allow operators to get an over view of the periodontal status of patients however our study aimed to refine the periodontal status beyond a screening tool. The American Association of Periodontology (AAP) and European Federation of Periodontology (EFP) published their joint efforts to reclassify and stage periodontal

disease and peri-implant disease (Tonetti et al.,2018). Stage and classification are used to accurately define an individual's periodontal status and it updates the previous 1999 classification (Armitage, 1999). Staging, which has been adopted by oncology disciplines, has been utilised for periodontal disease which aims to irradicate previous periodontal destruction and serves as a multidimensional diagnostic platform. This staging approach to periodontal disease should unify and allow more accurate communication of a patient's periodontal status both currently and historically. This largely encompasses the severity, extent and complexity of the damage attributed to periodontitis (Tonetti et al., 2018). Grading alternatively aims to estimate future risk of periodontitis progression and response to therapy. Systemic disease, systemic monitoring and co-therapy with medical colleagues is addressed in the grading aspect of this classification. Progression are based on the individual's validated risk factors for periodontitis however there is an element of assumption with this aspect of the classification. Potential and actual evidence of progression can differ however this aspect of the classification informs clinicians and helps to tailor treatment plans (Tonetti et al., 2018). See figures 13 and 14 for AAP/EFP staging and grading parameters (Li *et al.*, 2022).

2.3.4 Service development

The cost effectiveness of dental service inclusion has been sparsely studied in the literature. Cost effectiveness strategies and analyses of claims data reported the impact a dental service can have on an oropharyngeal service, by reducing the cost of treatment and length of days required for treatment compared to reduced dental

support. The dental claims were assessed over a period of 11 years (2008-2019) and multivariate linear regression were used to assess the relationship between primary outcomes and involvement of dentists. Acute oral complications were more expensive ($1,672) when treated without a dentists and average treatment times were 74 days shorter with immediate involvement of a dentist in an oropharyngeal cancer service. Dental decay was the only chronic complications that also benefitted from a dentist incorporated into their service (Choi *et al.*, 2021).

The medical and dental scope of practice unite when oncology treatment results in orofacial problems. Common cancer-related oral health problems include candidiasis, hyposalivation, oral dysesthesia, mucositis, salivary gland hypofunction, aphthous stomatitis and non-specific oral ulceration have been cited in the current MASCC / ISOO reported on oral problems in patients with advanced cancer (Jones *et al.*, 2022). This document fails to address the risk of MRONJ and over-looks the importance of dental-lead involvement of oral complications (Jones *et al.*, 2022). Oral health conditions should be recognised cohesively as an element of overall systemic health.

A key driving factor surrounding dental-oncology care is the availability of resources and an understanding of oncology patient treatment needs. Oral healthcare is isolated from mainstream oncology. Ownness as a result, is placed on patients to ensure access to dental treatment and to ensure their dental needs are met. Reducing the burden of oral care and self-reliance on patients, encourages the incorporation of dental services into oncology care (Bledslaw, 2023). Barriers to dental care in this cohort includes obstacles such as timing restraints prior to a BMA, lack of patient education regarding

oral complications of a BMA, financial restraints and perceived inadequate dentist competence to treat this cohort (Dang, 2022, Taichman, 2015). Interruptions in oncology treatment or delays have the potential to affect overall success of treatment (Dang, 2022). The National Cancer Institute has promoted the development of designated comprehensive cancer care centres for the prevention and management oral complications during cancer treatment (Epstein, 2007). This action plan is not a new phenomenon, published in 2007 for high risk cancer patients. Consideration for service provision, the impact of the oral condition on compromised hosts and the burden of care patients must endure, highlights the importance of a designated, structured, oncodental service.

Optimisation for a cohesive oncodental service can incorporate timely dental needs, sufficient dental expertise, preparation of the patients for dental fitness prior to a BMA and coherent correspondence between GDP and oncology for long term patient care (Dang, 2022). The diagram below depicts a flow chart for patients at risk of MRONJ and the four essential corner stones of consideration for these patients; host related factors, therapy related factors, dental related factors and service provision.

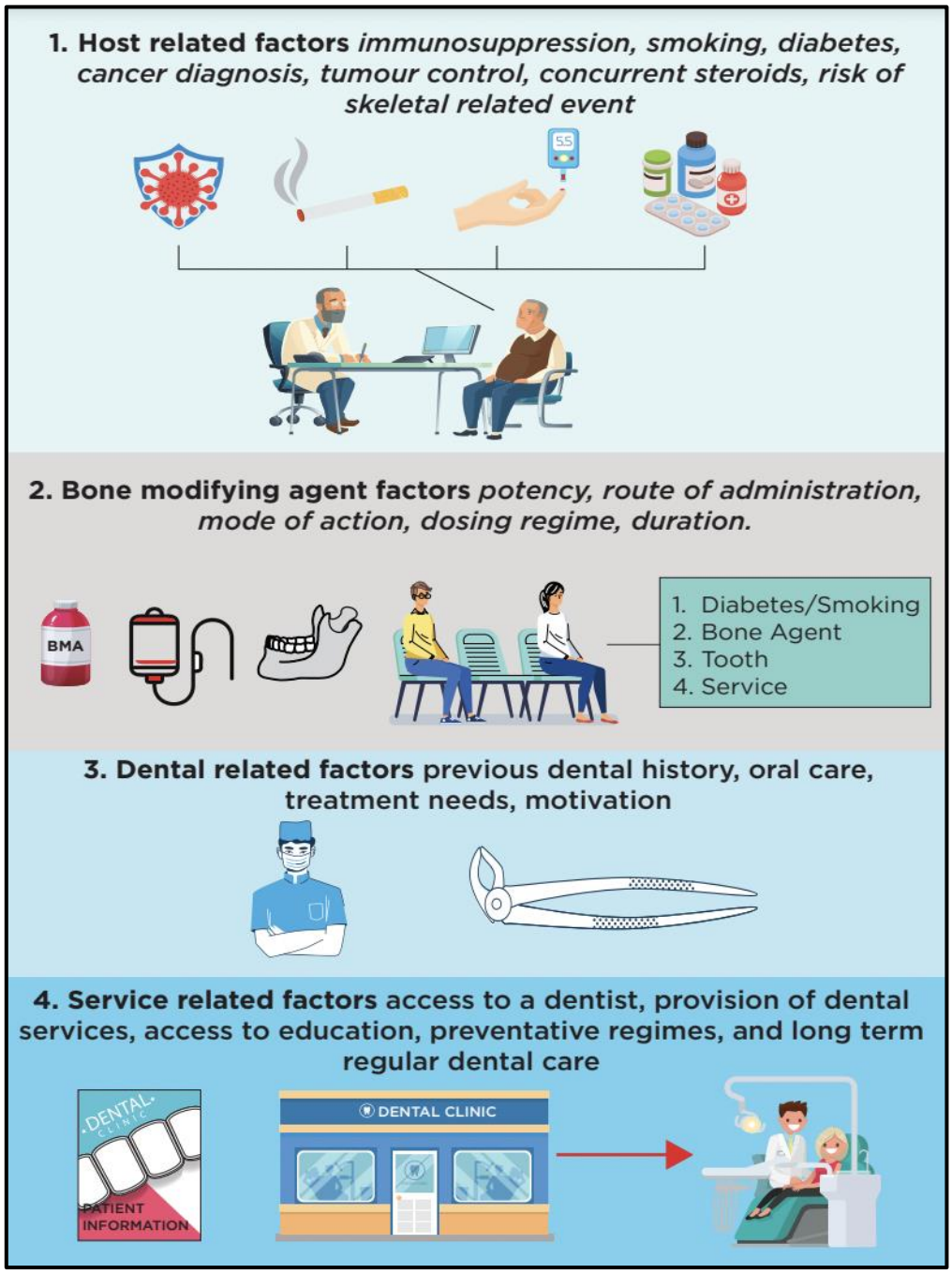


Figure 13 Important Factors Prior to and Following BMA administration

2.4 Summary

To summarise, MRONJ is a relatively new diagnosis first reported 21 years ago (Marx, 2021). The oncology cohort remains the most vulnerable group of patients at risk of developing MRONJ. To date, there is limited availability of high-quality evidence to define accurate, reproducible treatment regimens for MRONJ (Yarom *et al.*, 2019). Dental disease plays an integral role in the development of MRONJ (Campisi *et al.*, 2020c). Dental disease including dental caries is the highest, untreated, non-communicable disease worldwide and is a modifiable aspect of an oncology patient's care (*WHO,* 2019c). We know that dental preventative strategies are effective at reducing the incidence of MRONJ however currently, there is a lack of standardised pathways for patients to access dental services prior to and during BMA treatment (Mücke *et al.*, 2016).

2.5 Gap in Knowledge

The literature review demonstrates a dearth of knowledge available on MRONJ, which is largely based on low quality evidence (Bacci *et al.*, 2022a; Bledsaw *et al.*, 2023a). There are few comprehensive investigations about the oral health status and dental treatment needs of this specific cohort of patients (Bramati *et al.*, 2015; Al Abdullateef and Alhareky, 2020). The literature also highlights poor integration of dental care for patients receiving a BMA in both national and international oral health care policies (McAuliffe *et al.*, 2022). We hope to gain a more accurate insight into the specific oral health status, dental treatment needs and potential barriers to dental care for this group of oncology patients.

2.6 Primary and secondary aims

The primary aim of this study is the assessment of the oral health status and dental care treatment needs of oncology patients prior to administration of a BMA. The secondary aim is to assess and highlight barriers to dental care that arose for this cohort.

Chapter 3

Materials and Methods

3.1 Study overview and design

This study was conducted in two phases; a quantitative clinical phase (phase 1) and a qualitative, interactive phase (phase 2).

Phase 1 includes a prospective study to assess the oral health status and dental treatment needs of oncology patients prior to receiving a BMA (antiresorptive or anti-angiogenic). The BMA treatment was prescribed in conjunction with their oncology treatment plan. Oncology patients were referred to Dr Harriet Byrne via an online referral proforma from oncology services in three Cork-based hospitals: Cork University Hospital (CUH), South Infirmary Victoria University Hospital (SIVUH) and the Mercy University Hospital (MUH). Oncology patients were subsequentially assessed in the Cork University Dental School and Hospital (CUDSH) by a single clinician (Dr Harriet Byrne). One three-hour clinical session was allocated each week for the assessment and treatment of patients. Phase 1 commenced in the CUDSH in March 2022 and data saturation was achieved in February 2024. There was no assessments or treatments in month of July 2022 and 2023. Phase 1 was undertaken for 22 months in total.

Phase 2 includes a qualitative arm in which patients (n=10) and GDPs (n=20) were anonymously interviewed to assess their opinions of BMA therapy and its impact on dental care. The dental participants engaged in focus groups and the oncology patients (n=6) engaged in a focus group and (n=4) were contacted via telephone call to discuss the topics. Topic guides were prepared and approved as a component of the ethics

process (See appendices A and B). Each focus group / interview were conducted in the CUDSH, anonymously recorded and recordings were transcribed for analyses.

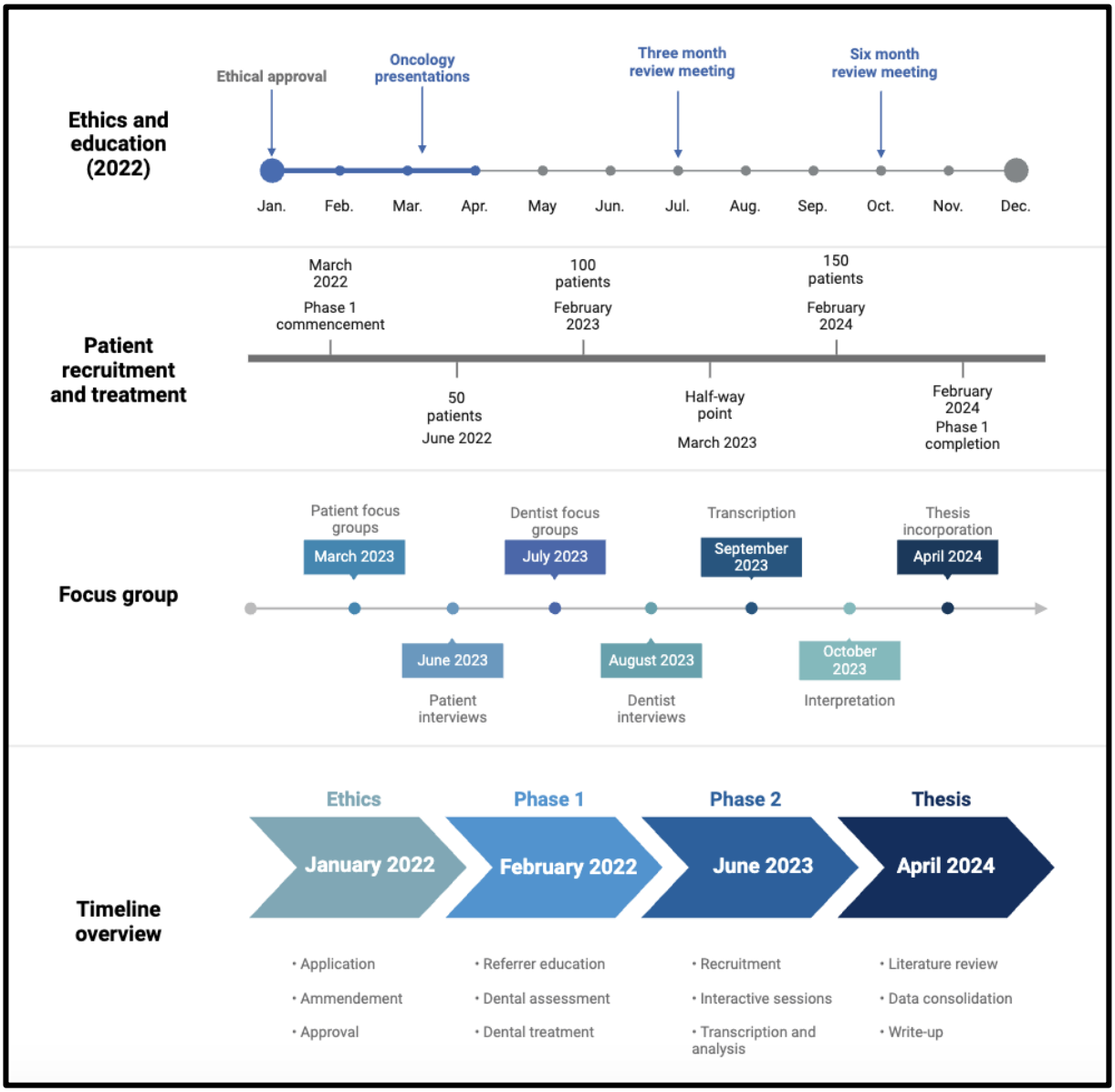


Figure 14 Timeline of Study

3.2 Ethical considerations

The ethical approval application was submitted in December 2021 to the Clinical Research Ethics Committee (CREC), University College Cork (UCC) and received ethical approval in February 2022 under the title "Oral Health Status and Dental Treatment Needs of Oncology Patients Receiving Bone Modifying Agents". The research team included Dr Harriet Byrne (oral surgery speciality registrar), Professor Séamus O' Reilly (consultant medical oncologist) and Professor Richeal Ní Riordáin (consultant in oral medicine). The stakeholders included UCC and Health Service Executive (HSE) and the research project was conducted in the Oral Surgery Department, CUDSH, Wilton, Co Cork. The study was conducted in accordance with the requirements of the WMA Declaration of Helsinki (2008). Written informed consent was obtained from all participants.

3.3 Study participants

The population included oncology patients who were planned for a BMA as a component of their oncology treatment plan. Inclusion criteria included patients from oncology services under the care of consultants in the CUH, SIVUH and the MUH. Their BMA therapy was prescribed for oncology requirements only including bone metastases, bone pain, hypercalcaemia, and preventative of bone metastases in breast cancer patients. All stages of oncology patients were included including stage 1 - 4 (early and late-stage cancer). Their BMA regime was prescribed at oncology dose regimes including intravenous administration of bisphosphonates or subcutaneous RANK-L inhibitors. There was no limit on age.

Exclusion criteria included patients who had previous exposure to a BMA for either non or oncological purposes. Patients were also excluded from the study who did not wish to participate, or who wanted to proceed with treatment from their own general dental practitioner.

3.4 Sampling and recruitment

A customised, designated referral form was developed which was circulated amongst oncology staff members (see appendix C). Interval training and information sessions were arranged with oncology staff (clinical nurse managers, non-consultant hospital doctors, and oncology consultants) prior to commencement of the research project. During this session a power point presentation discussed and guided appropriate handling of referrals and directions about completion of referrals. Oncology staff members were informed about important aspects of the study, and information was provided to members of the oncology teams at these training sessions. Oncology referrals were accepted from CUH, SIVUH and MUH, located in Cork City.

Dental referrals were sent via data protection secured referral pathway using both the HSE and UCC email domains. Patients were contacted via phone call prior to their dental appointment to explain the nature of the study and confirm their interest of involvement. A pre-screening of verbal consent to take part in the research study, medical history, medications, and other specific requirements such as translational services or wheelchair access routes to the dental surgery were arranged.

Patients were appointed to the oral surgery department for their dental appointment. One dental clinic per week (3 hour session) was allocated for the dental assessment and treatments related to the research project. This included the provision of one staff nurse and availability of 1 - 2 dental chairs each week.

3.5 Phase 1 prospective clinical assessment

3.5.1 Consent

Patients were consented for enrolment in the research study (see appendix D). This consent process followed the verbal conversation on the pre-appointment, screening telephone consultation and written consent was obtained on the day of appointment.

The proforma data collection sheet (see appendix E) was used as a template to guide and satisfy data collection criteria. Information was entered and stored in paper charts in accordance CUDSH data protection from (March 2022 – June 2023) and in electronic format, *Salud Platinum Solutions* (July 2023 – February 2024). In addition, anonymised patient details were given a candidate number which was allocated as entry into the research study. Information was additionally stored as anonymous data on an Excel (Microsoft, 2016) data spreadsheet and used for analysis.

3.5.2 Data documentation

Data was stored securely on a Microsoft Office Excel document. Candidates were given a number related to their date of enrolment in numerical order. The data was coded for positives (code 2), negatives (code 1) and categorical variables using numerical codes. Summary data was shared for statistical analysis.

3.5.3 Oral health status

A thorough examination was performed of each patient using a mirror, a probe and artificial lighting in the dental setting.

Firstly, an extra-oral examination was performed, and clinical findings were recorded for the presence or absence, of lymphadenopathy, facial skin pathology, lip pathology, temporomandibular joint pathology, mouth opening, muscles of mastication, maximum mouth opening (interincisal distance), and any other clinical remarks where appropriate.

Secondly, an intra-oral examination was completed by assessing both soft and hard tissue health. The oral cavity soft tissues were visually assessed, and soft tissue pathology was recorded under the relevant surfaces; the buccal and labial mucosae, gingivae, tongue, hard and soft palate, and oropharynx. Soft tissue abnormalities, both

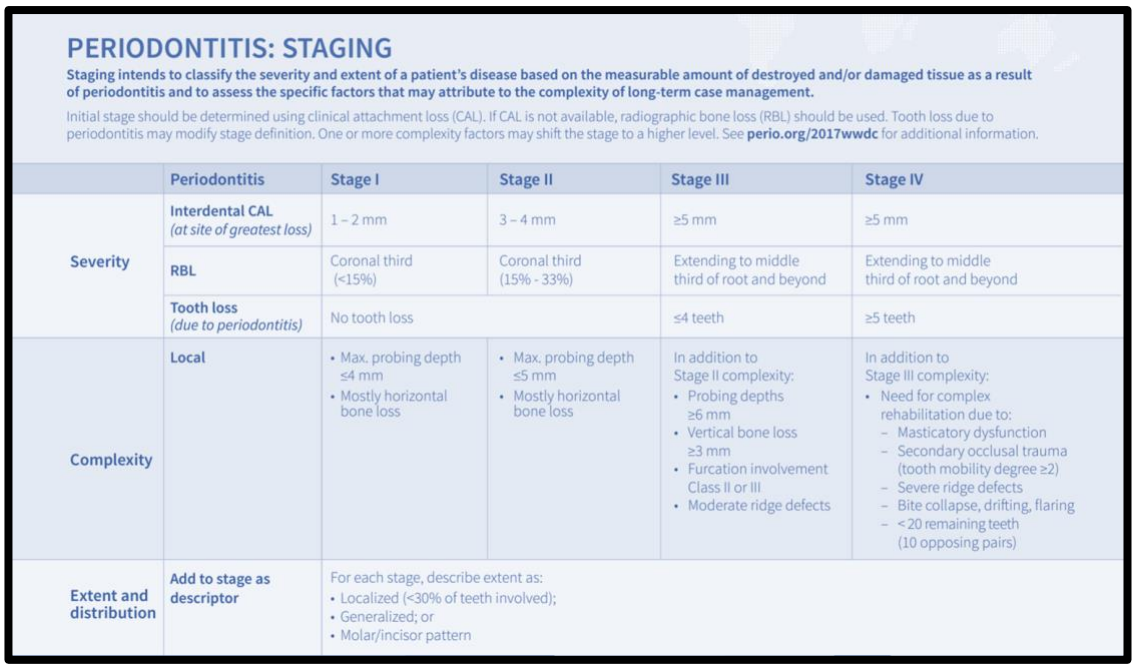
benign and premalignant were recorded. Soft tissue abnormalities which required further soft tissue investigations such as an intraoral biopsy were arranged accordingly.

Gingival health was recorded using the periodontal screening tool, PSR. The periodontal classification is highlighted below in Table 4.

Table 4 Periodontal Screening Record

Code	Description
0	No gingival disease (gingival pockets <3mm)
1	Bleeding on probing (gingival pockets <3mm)
2	Periodontal pocketing <3mm, calculus presence with/out presence of plaque retentive factors
3	Shallow periodontal pocketing 4-5.5mm
4	Deep Periodontal pockets >6mm

A periodontal classification was allocated to each patient using the American Association of Periodontology and European Federation of Periodontology, which was released in 2017 (Dietrich *et al.*, 2019; Dukka *et al.*, 2022).



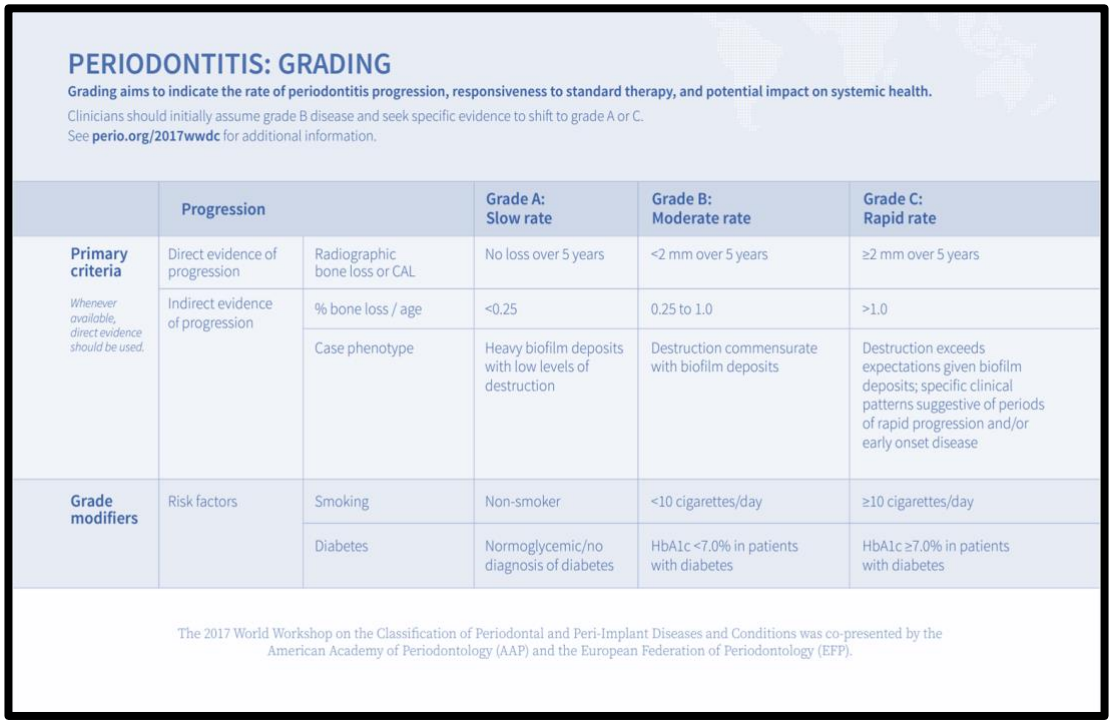
PERIODONTITIS: STAGING

Staging intends to classify the severity and extent of a patient's disease based on the measurable amount of destroyed and/or damaged tissue as a result of periodontitis and to assess the specific factors that may attribute to the complexity of long-term case management.

Initial stage should be determined using clinical attachment loss (CAL). If CAL is not available, radiographic bone loss (RBL) should be used. Tooth loss due to periodontitis may modify stage definition. One or more complexity factors may shift the stage to a higher level. See **perio.org/2017wwdc** for additional information.

	Periodontitis	Stage I	Stage II	Stage III	Stage IV
Severity	Interdental CAL *(at site of greatest loss)*	1 – 2 mm	3 – 4 mm	≥5 mm	≥5 mm
	RBL	Coronal third (<15%)	Coronal third (15% - 33%)	Extending to middle third of root and beyond	Extending to middle third of root and beyond
	Tooth loss *(due to periodontitis)*	No tooth loss		≤4 teeth	≥5 teeth
Complexity	Local	• Max. probing depth ≤4 mm • Mostly horizontal bone loss	• Max. probing depth ≤5 mm • Mostly horizontal bone loss	In addition to Stage II complexity: • Probing depths ≥6 mm • Vertical bone loss ≥3 mm • Furcation involvement Class II or III • Moderate ridge defects	In addition to Stage III complexity: • Need for complex rehabilitation due to: – Masticatory dysfunction – Secondary occlusal trauma (tooth mobility degree ≥2) – Severe ridge defects – Bite collapse, drifting, flaring – < 20 remaining teeth (10 opposing pairs)
Extent and distribution	Add to stage as descriptor	For each stage, describe extent as: • Localized (<30% of teeth involved); • Generalized; or • Molar/incisor pattern			

Figure 15 American Association of Periodontology Periodontitis Staging Classification



PERIODONTITIS: GRADING

Grading aims to indicate the rate of periodontitis progression, responsiveness to standard therapy, and potential impact on systemic health.

Clinicians should initially assume grade B disease and seek specific evidence to shift to grade A or C.
See **perio.org/2017wwdc** for additional information.

	Progression		Grade A: Slow rate	Grade B: Moderate rate	Grade C: Rapid rate
Primary criteria *Whenever available, direct evidence should be used.*	Direct evidence of progression	Radiographic bone loss or CAL	No loss over 5 years	<2 mm over 5 years	≥2 mm over 5 years
	Indirect evidence of progression	% bone loss / age	<0.25	0.25 to 1.0	>1.0
		Case phenotype	Heavy biofilm deposits with low levels of destruction	Destruction commensurate with biofilm deposits	Destruction exceeds expectations given biofilm deposits; specific clinical patterns suggestive of periods of rapid progression and/or early onset disease
Grade modifiers	Risk factors	Smoking	Non-smoker	<10 cigarettes/day	≥10 cigarettes/day
		Diabetes	Normoglycemic/no diagnosis of diabetes	HbA1c <7.0% in patients with diabetes	HbA1c ≥7.0% in patients with diabetes

The 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions was co-presented by the American Academy of Periodontology (AAP) and the European Federation of Periodontology (EFP).

Figure 16 American Association of Periodontology Periodontitis Grading Classification

Hard tissue examination was documented using the most common method of assessing dental caries prevalence as well as the treatment need amongst populations and has been used for over 75 years (Broadbent and Thomson, 2005). A probe, a mirror and a 3 in 1 syringe (lightweight budget air) were used to assess teeth during the dental examination and a count was made of the teeth that were decayed, missing (due to caries only) and filled teeth (DMFT). Exposure to fluoride in water and toothpaste was recorded alongside toothbrushing frequency and the use of interdental oral hygiene aids.

3.6 Data collection

Table 5 Data Collection

Demographics	**Oncodemographics**	**Referral Information**	**Oral Health Status**	**Dental Treatment Need**
Age	Diagnosis	Days awaiting dental assessment	Presenting complaint	Educational input
Gender	Additional treatments	GMP registration	Extraoral exam	Preventative input
Ethnicity	Stage	GDP registration	Intraoral soft exam	Restorative intervention
Smoking status	Allergies	GDP attendance	Periodontal assessment	Oral surgery intervention
Alcohol consumption	Planned BMA therapy	Covid-19 impact on attendance	Hard tissue assessment	Prosthetic intervention
Employment status	Date of BMA commencement	Referrer	Prosthesis assessment	Follow-on treatment
Barriers to care		Referral centre	Radiographic assessment	Dental Fitness
Family support				

3.7 Multivariate analysis

The table below summarises the potential explanatory variables assessed using statistical testing for the study population.

Table 6 Table of Analysed Explanatory Variables and Their Corresponding Comparison

Explanatory Variable	**Comparison**
Age	N/A (age is numeric, n=150)
Having a GDP	No (n= 65) vs Yes (n=84) or does not want to disclose (n=1)
GDP frequency	GDP every 2-4 year (infrequent, n=59) vs GDP every 6-12 months (frequent, n=46) GDP every 5 years or more (rare, n=45) vs GDP every 6-12 months (frequent, n=59)
Smoking status	Current smoker (n=37) vs never smoker (n=90) Ex-smoker (n=23) vs never smoker (n=90)
Barrier	No (n=131) vs yes barrier to care (language, n=11), (physical, n=6) and (transport, n=2)
Cancer diagnosis / stage	Breast cancer late stage (n=55) vs breast cancer early stage (n=41) All other cancers (n=54) vs breast cancer early stage (n=41)

Associations between binary response variables (a restoration treatment need and an oral surgery extraction treatment need) and the explanatory variables (Table 6) were assessed using binary logistic regression models. All statistical analyses were

performed in SAS® (Version 9.4). The level of significance used in all statistical tests was 5%.

3.8 Phase 2 qualitative analysis

Phase 2 includes the utilisation of both oncology patients and GDPs who are working in the CUDSH, to gain a clearer insight into BMA therapy in the general dental setting.

3.8.1 Patient cohort

The patient cohort included 10 patients who were happy to attend a focus group or engage in a telephone consultation regarding their experience of dental care as a component of their oncology plan. The influence of their pending BMA therapy was also explored, and the interactions were recorded anonymously for interpretation and analysis. Six patients took part in a focus group and four patients engaged in a recorded telephone discussion. The conversation was guided using a prepared topic guide (see appendix A).

3.8.2 General dental practitioners

The general dentist cohort included 20 staff members of the CUDSH who were also actively practicing dentistry in general dental practice. Three focus groups took place

(n=8, n=7 and n=5) in the CUDSH where the general dentists expressed their opinions and experiences of BMA therapy in general dental practice. The focus groups were recorded, and conservation was guided using the prepared topic guide (see appendix B).

Chapter 4

Results

4.1 Overview

The data presented includes an assessment of the study population's medical, social and dental history alongside clinical analysis of their oral health status and dental care treatment needs. Qualitative data gathered from patient and dentist focus groups highlights specific topics of interest surrounding the concept BMA therapy and its impact on patients in the dental setting. Data collection was achieved at 150 patients.

4.2 Patient demographics

4.2.1 Age

Data collection was achieved at 150 patients with a mean age of 61.5 years (range 18-87 years). There were 105 females and 45 males included in this study. Descriptive statistics for age amongst patients is summarised below, which also highlights age within gender in Table 7.

Table 7 Age Profile

Age (years)	**Total (N=150)**	**Females (N=105)**	**Males (N=45)**
Mean	61.5 years	60.6 years	63.5 years
SD	11.75	9.99	15.04
Range	18-87	34-87	18-87

The age profile of the population, males and females are depicted graphically on bar charts. The distribution of age is represented in decades on the bar charts and

highlights the distribution of males and females within their age categories at the time of presentation (figures 18 and 19).

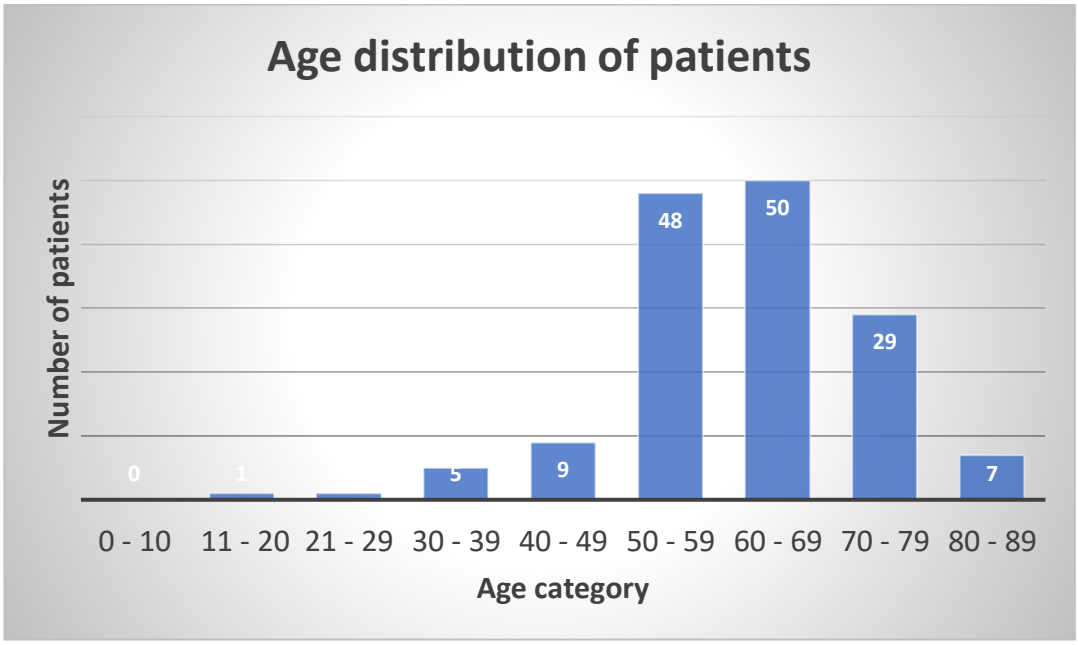


Figure 17 Age Distribution

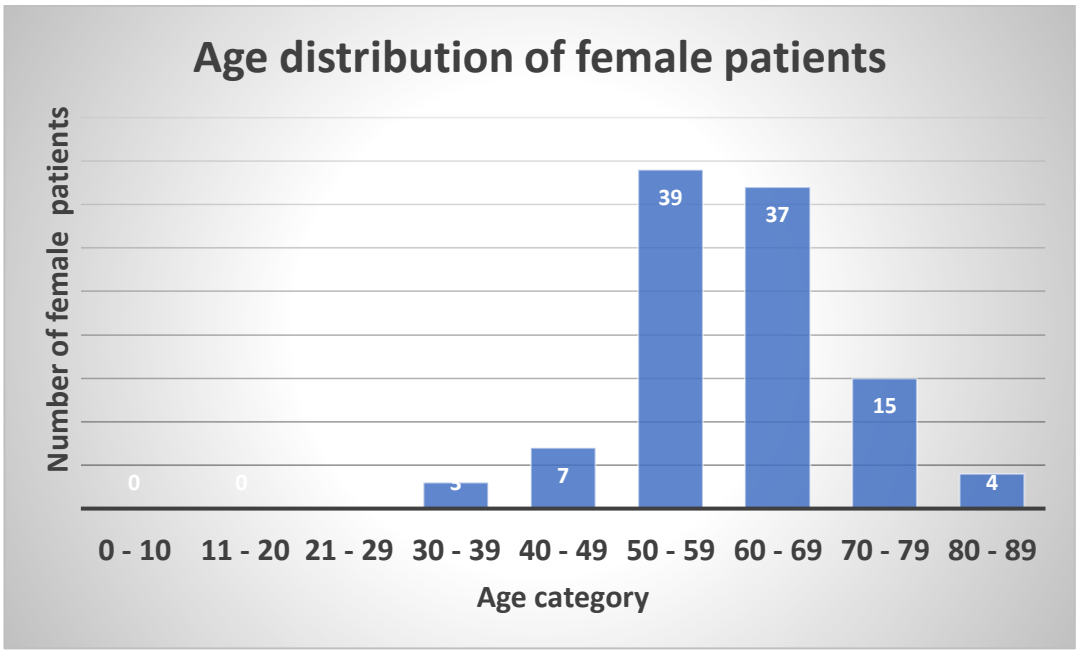


Figure 18 Female Age Distribution

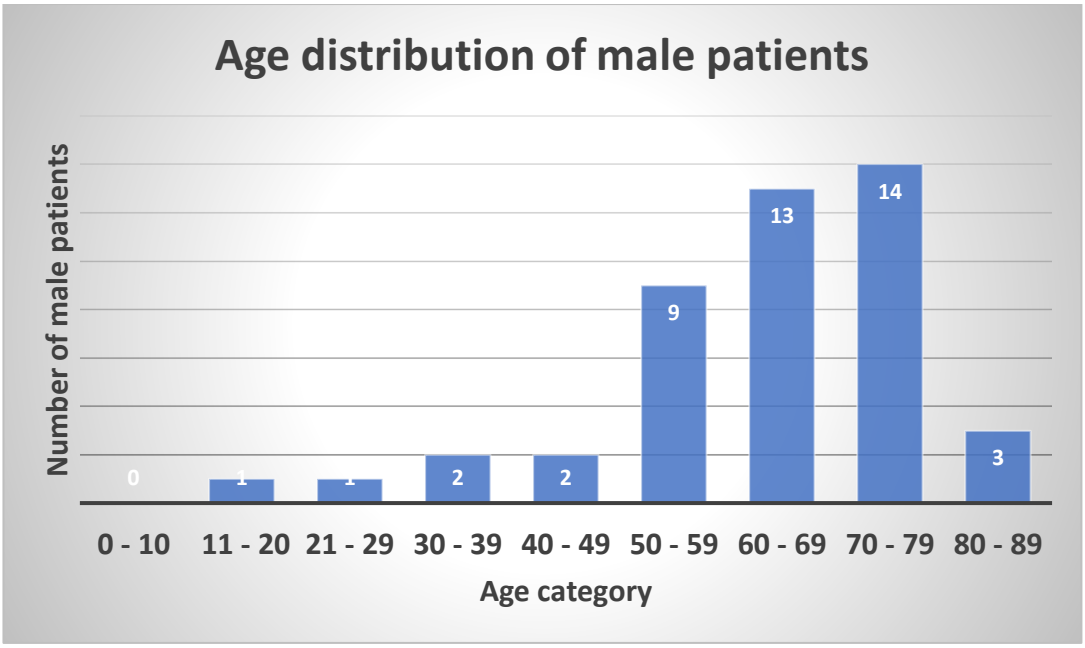


Figure 19 Male Age Distribution

4.2.2 Gender diagnosis

70% (n=105) of the population were females and 30% (n=45) were males. The cancer diagnosis of both males and females is represented in table 8 below.

Table 8 Gender Distribution of Diagnosis

Cancer	**Female (N=105)**		**Male (N=45)**	
	Frequency	**%**	**Frequency**	**%**
Breast	95	90.5%	1	2.2%
Prostate	-	0%	22	48.8%
Lung	4	3.8%	7	15.5%
Multiple Myeloma	4	3.8%	3	6.67%
Sarcoma	0	0%	5	11.2%
Renal	2	1.9%	3	6.67%
Lymphoma	0	0%	3	6.67%
Pheochromocytoma	0	0%	1	2.2%

4.2.3 Ethnicity

The population race included a predominance of Caucasians (n=140, 93.3%) followed by minorities of Asian (n=5, 3.3%), East Slavic (n=3, 2%), Arab (n=1, 0.675%) and Caribbean (n=1, 0.675%). The distribution is highlighted in table 9 below. The predominant race, Caucasian was further subdivided into country of origin in table 10. Ireland was represented the majority of patients in the study (n = 132, 94.2%).

Table 9 Race of Study Population

Race	**Frequency**	**%**
Caucasian	140	93.3%
Asian	5	3.3%
East Slavic	3	2%
Arab	1	0.67%
Caribbean	1	0.67%

Table 10 Country of Origin for Caucasian Patients

Caucasians – country of origin (N=140)	**Frequency**	**%**
Ireland	132	94.2%
United Kingdom	2	1.4%
South Africa	2	1.4%
Croatia	1	0.7%
Germany	1	0.7%
Hungry	1	0.7%
Italy	1	0.7%

4.2.4 Social information

Social parameters assessed during this study included smoking habits, alcohol consumption, employment status and home support. Current smokers included (n=37, 24.67%), ex-smokers (n=23, 15.3%) and non-smokers (n=90, 60.03%) which is represented in the bar chart in figure 20. A further assessment of smoking habit included quantification of cigarettes smoked (pack years) for the current smokers which is shown in figure 21. There was a degree of variation regarding the substance smoked by current smoker (n=37, 24.67%); including tobacco only (n=33, 89.2%), cannabis only (n=1, 2.7%), vaping (n=2, 5.4%), and tobacco / cannabis (n=1, 2.7%).

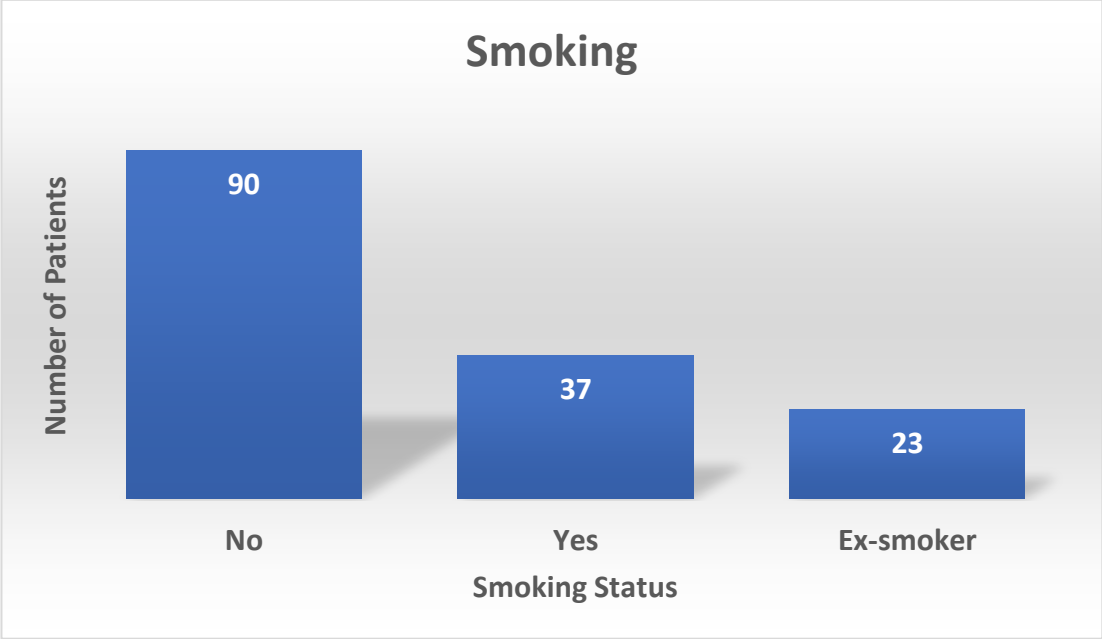


Figure 20 Smoking Status

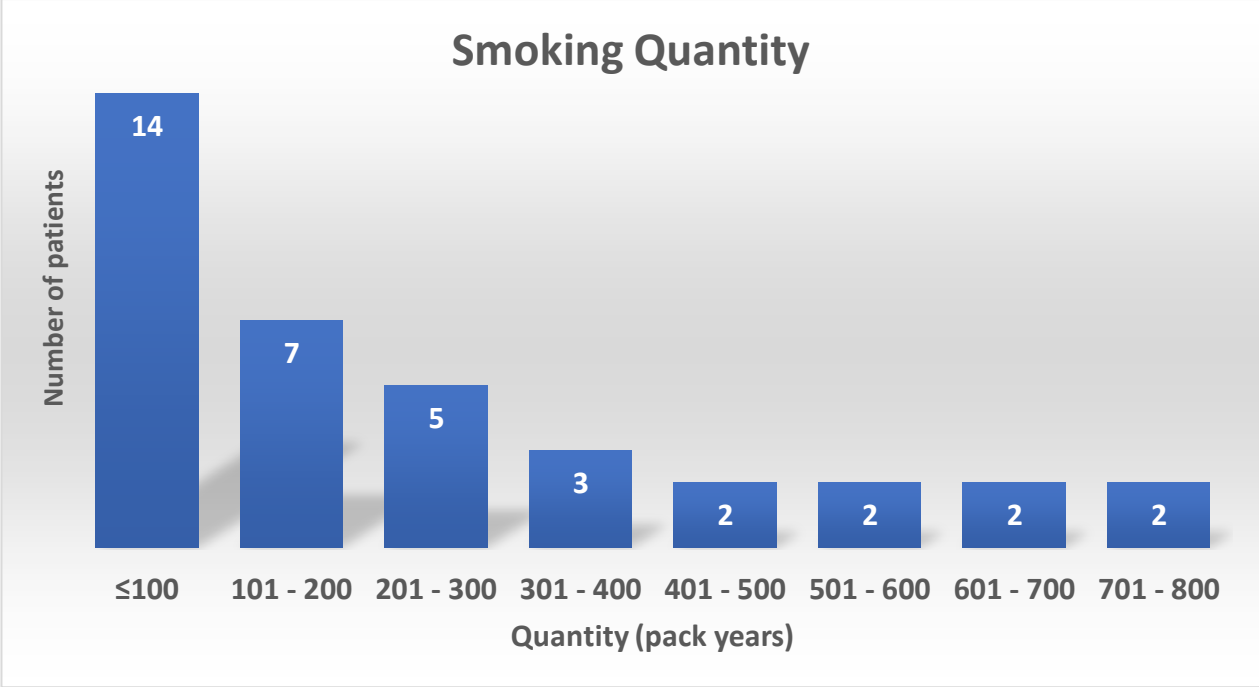


Figure 21 Quantity of Smoking for Current Smokers

Figure 21 shows the smoking quantity of the current smokers (n=37, 24.67%) is documented in cigarette pack years (number of packs smoked a day x numbers of years smoking = pack years). The majority of patients smoked less than 100 pack years (n=14, 37.8%).

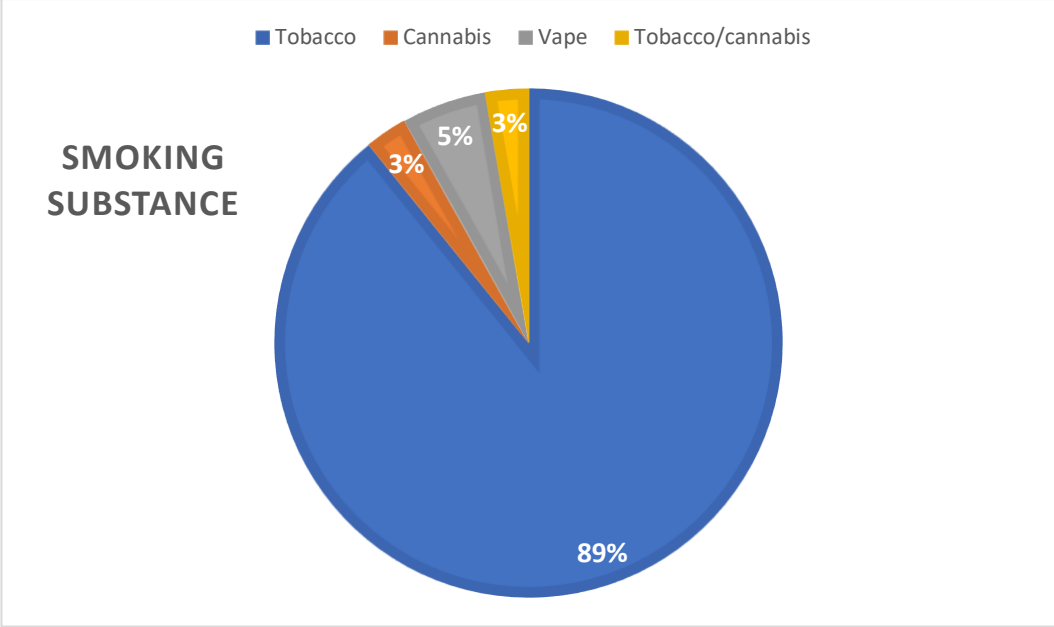


Figure 22 Smoking Substances for Current Smokers

The proportion of patients who consumed alcohol on a weekly basis included (n=93, 62%) and patients who refrained from alcohol consumption (n=57, 38%). There was a minority of patients who consumed in excess of the HSE average weekly low-risk alcohol guidelines, greater than 14 units per week included 5.4% of alcohol drinkers (*Weekly low-risk alcohol guidelines*, 2022).

Table 11 Alcohol Consumption

Characteristic	**Frequency**	**%**
Alcohol	93	62%
No alcohol	57	38%
Quantity (≤14 units per week)	88	94.6%
Quantity (≥14 units per week)	5	5.4%

4.2.5 Employment status

Employment status was assessed in conjunction with education and retirement status, where appliable. These figures are represented in table 12 which highlight a large proportion of patients (n=96, 64%) who were currently in employment at the point study enrolment.

Table 12 Employment Status

	Employment status			
Category	Employed	Unemployed	Student	Retired
Number (N=150)	96	19	2	33
Frequency	64%	12.67%	1.3%	22%

4.2.6 Home support

The study also included an inclusion of home supports available to the study participants, which included family members who were capable of supporting the patient at the time of recruitment. A majority of patients (n=116, 77.3%) confirmed the presence of family support during this stage of their cancer care journey.

Table 13 Family Support in the Home

Characteristics	**Frequency**	**%**
Lives at home with family support	116	77.3%
Lives alone without family support	34	22.7%

4.3 Institutional information

4.3.1 Referrers and oncology centres

The referring centres are included below highlighting the institution from which their referral was made and also the health care member who made the referral. Oncology nurses referred the most patients (n=91, 60.7%) followed by medical oncologist consultants (n=44, 29.3%) and medical oncology speciality registrars (n=15, 10%). The referral basis included three hospital; CUH (n=97, 64.7%), SIVUH (n=49, 32.6%) and MUH (n=4, 2.7%).

Table 14 Referrer and Referral Basis

Oncology referrer basis	**Frequency**	**%**
Oncology nurse	91	60.7%
Consultant	44	29.3%
Speciality registrar	15	10%
Cork University Hospital	97	64.7%
South Infirmary Victoria University Hospital	49	32.6%
Mercy University Hospital	4	2.7%

4.3.2 Dental assessment referral time

Data were recorded from date of referral to date of assessment / provision of treatment. Patients were seen once weekly over a three hour clinical session. The date of referral was recorded as the date of initial correspondence from oncology containing the customised referral and the end-point was noted at the date of dental assessment. The distribution of time from referral to assessment is graphically represented in figure 23.

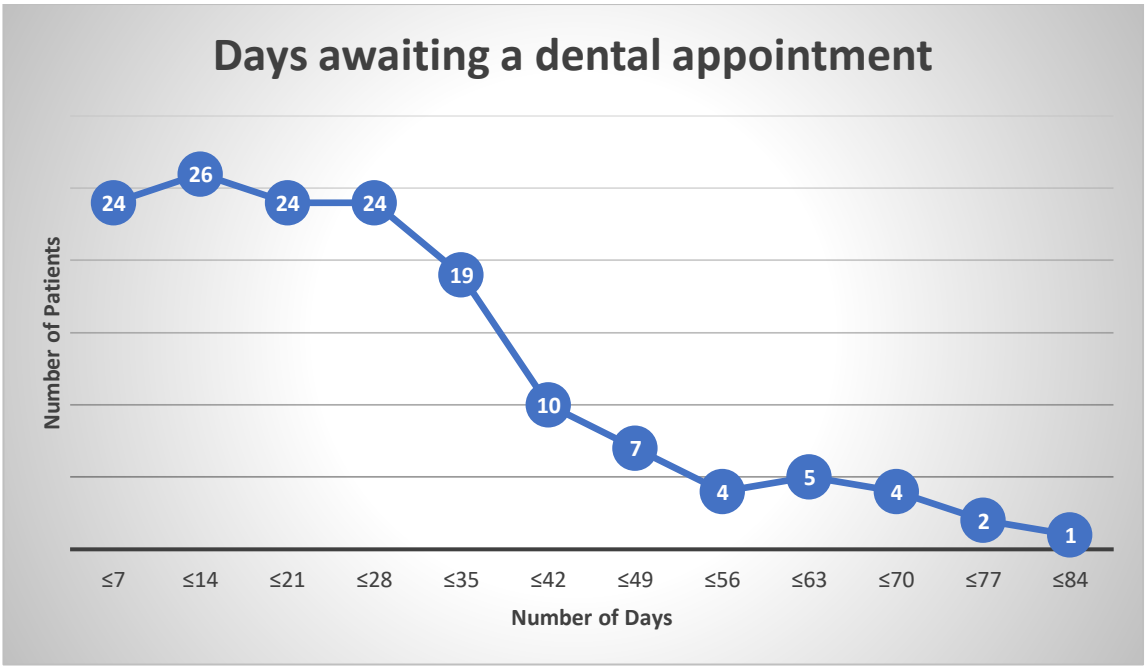


Figure 23 Waiting Time for Patients

Table 15 Accumulative Waiting Time

Numbers of days	**Number of patients**	**%**	**Accumulative (%)**
≤7 days	24	16%	16%
≤14 days	26	17.3%	33.3%
≤21 days	24	16%	49.3%
≤28 days	24	16%	65.3%
≤35 days	19	12.67%	77.97%
≤42 days	10	6.67%	84.64%
≤49 days	7	4.67%	89.31%
≤56 days	4	2.67%	91.98%
≤63 days	5	3.33%	95.31%
≤70 days	4	2.67%	97.98%
≤77 days	2	1.33%	99.33%
≤84 days	1	0.67%	100%

The content of the dental referrals contained information regarding the precise date for commencement of the BMA; noted in 16% (n=24) of cases. Otherwise, an approximate timeline was recorded or no timeframe was contained in the dental referrals (n=126, 84%).

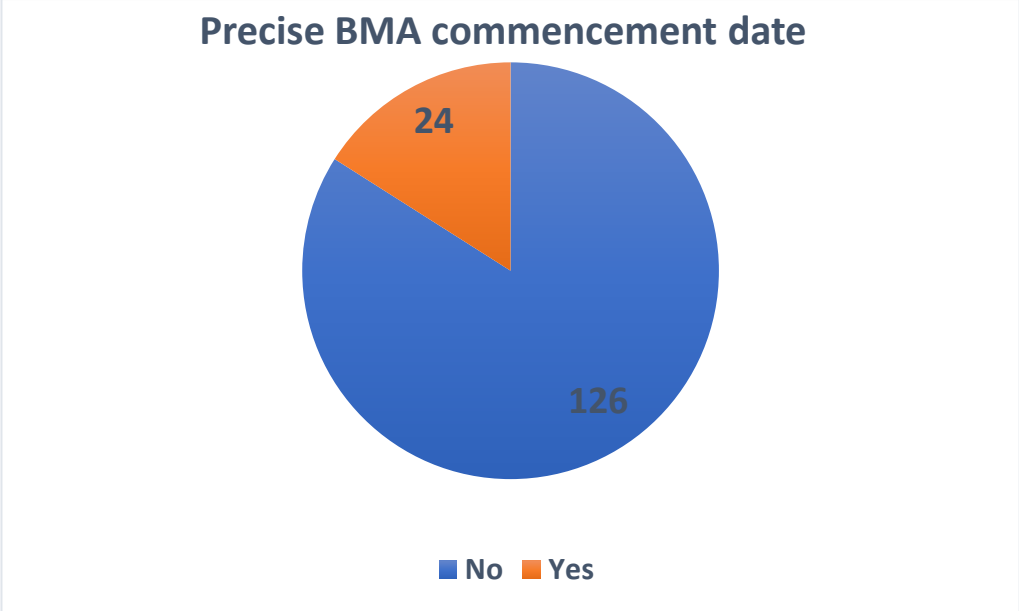


Figure 24 Precise Date for BMA Commencement

4.3.3 GMP registration

Registration with a general medical practitioner (GMP) was recorded in which the vast majority were registered and engaged with a GMP; 92.7% (n=139). There was a minority of patients, who were seeking refuge or moved to Ireland who did not have their registered GMP in Ireland; 4.7% (n=7).

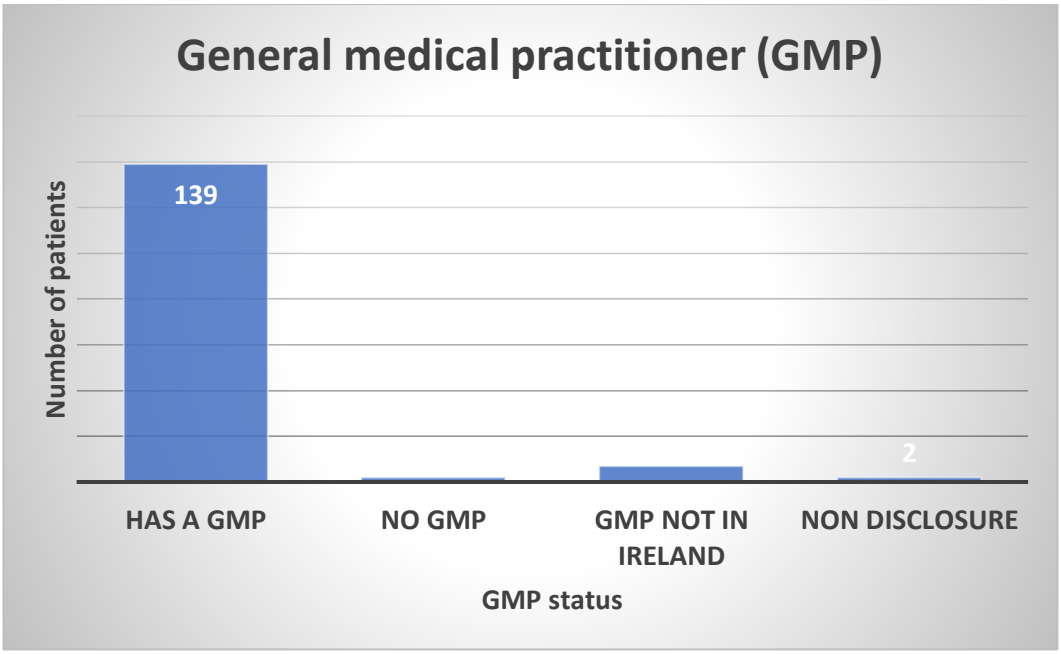


Figure 25 General Medical Practitioner Registration Status

4.3.4 GDP registration

The number of patients who were registered with a GDP included 56% (n=84). Patients who did not have access to a GDP or who were unhappy to disclose such information included 43.3% (n=65) and 0.67% (n=1), respectively.

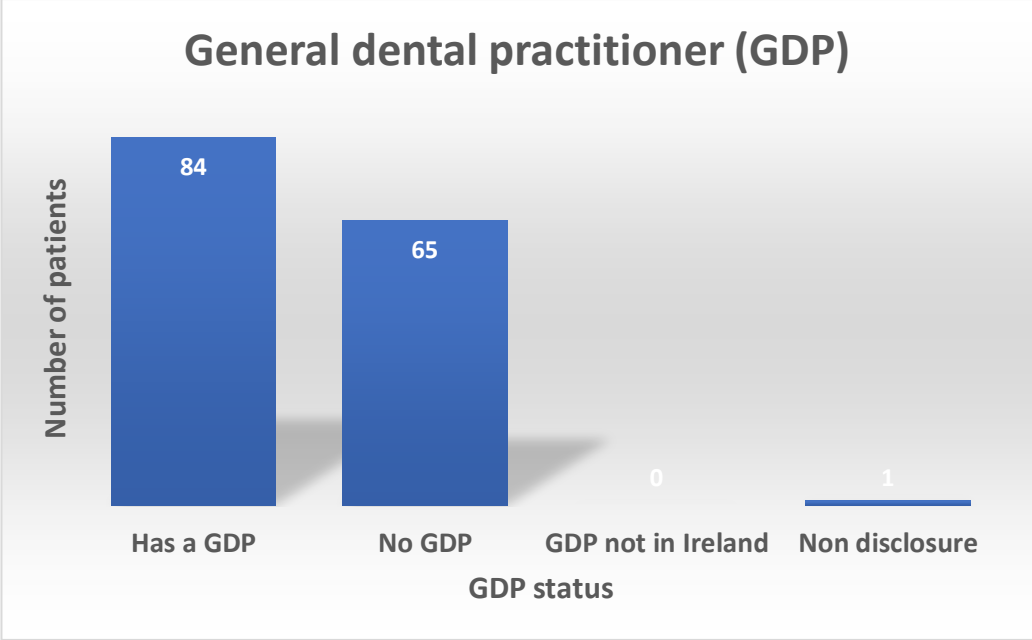


Figure 26 General Dental Practitioner Registration Status

4.3.5 Service barriers

Barriers to care were assessed within this study's population, which were divided into current transportation barriers (1.3%, n=2), language barriers (7.4%, n= 11) and physical barriers (4%, n=6).

Table 16 Barriers to Dental Services

Dental service barriers	**Frequency**	**%**
None	131	87.3%
Transport	2	1.3%
Language	11	7.4%
Physical immobility / wheelchair bound	6	4%

4.4 Oncodemographics

4.4.1 Oncology diagnosis

The distribution of cancer diagnoses are represented in the graph below (see figure 27). Breast cancer included the majority of patients (n=96, 64%) followed by prostate cancer (n=22, 14.7%), lung cancer (7.3%, n=11), multiple myeloma (4.7%, n=7), sarcoma (3.3%, n=5), renal cancer (3.3%, n=5), lymphoma (2%, n=3) and pheochromocytoma (0.67%, n=1).

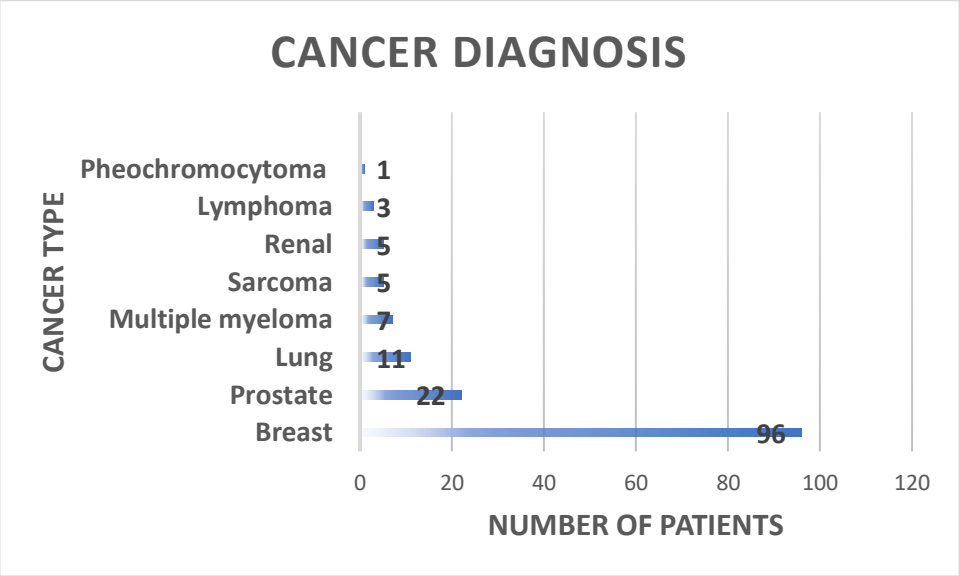


Figure 27 Cancer Diagnoses

The stages of cancer at dental assessment was recorded for the study population. Owing to the nature of BMA therapy, the majority of patients planned for BMA therapy had advance-staged disease (stage 4), accounting for 72% (n=108) of the population.

Table 17 Cancer Stage

Cancer stage	**Number of patients**	**Frequency**
2/3	42	28%
4	108	72%

4.4.2 Additional oncology treatments

Oncology patients in this study were also undergoing additional therapies for their cancer diagnosis. Table 18 below denotes the treatments also planned and completed as a component of their oncology care.

Table 18 Oncology Treatments

Characteristic	**Yes**	**%**	**No**	**%**
Oncology surgery	102	68%	48	32%
Chemotherapy	119	79.3%	31	20.7%
Radiation therapy	92	61.3%	58	38.7%
Hormone therapy	82	54.6%	68	45.4%
Immunotherapy	32	21.3%	118	78.7%

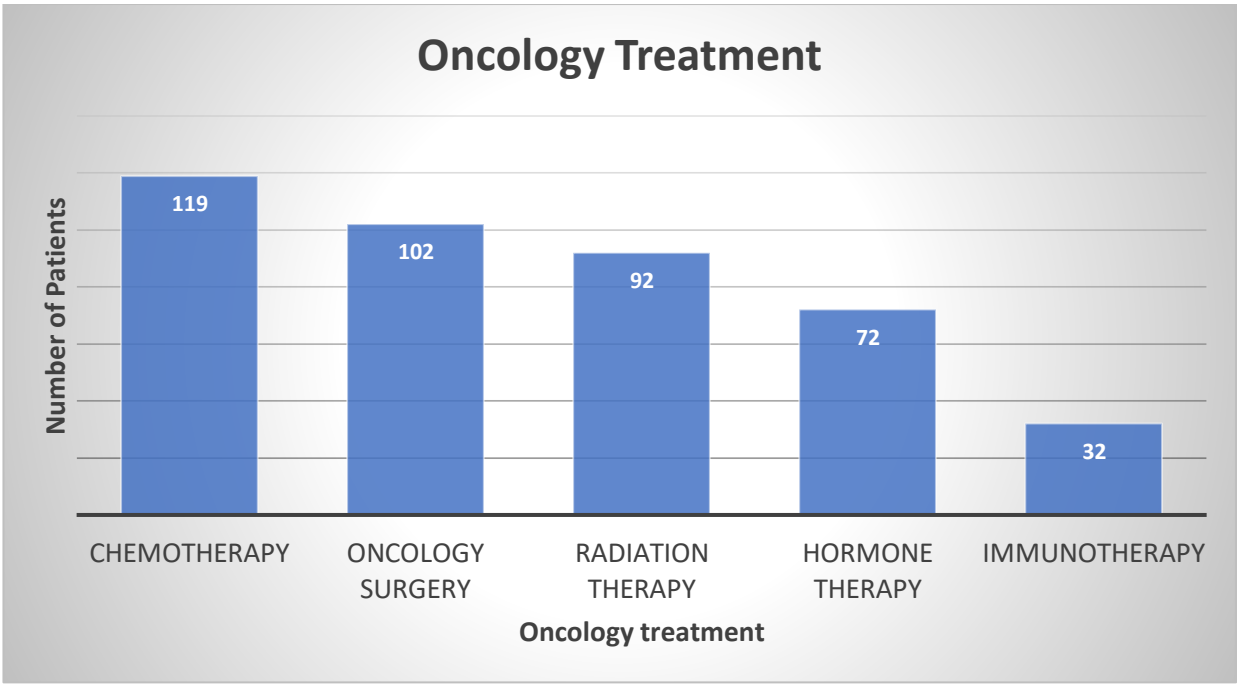


Figure 28 Additional Cancer Treatment Regimes

Figure 28 is a graphic representation of the overall oncology treatment plans for the study population, which included chemotherapy, surgery, radiation therapy, hormone therapy and immunotherapy

Patient allergies were documented for both known drug allergies (13.3%, n=20) and environmental allergies (8%, n=12).

Table 19 Known Drug and Environmental Allergies

Allergies	**Number of patients**	**Frequency**
Drugs	20/150	13.3%
Environmental	12/150	8%

4.2.3 Planned BMA therapy

Oncology regimes confirmed the intention to provide BMA treatment with either Zoledronic acid (94%, n=142) or Denosumab (6%, n=8).

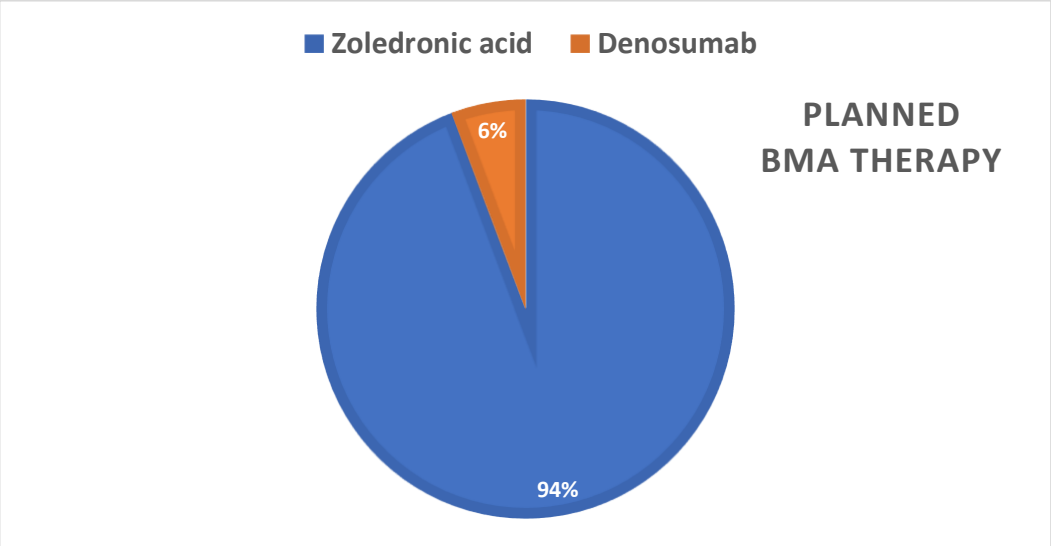


Figure 29 Planned BMA Therapy

4.5 Dental history

4.5.1 Previous dental engagement

Patient attendance with their registered general dentist or their prior attendance with a GDP was recorded. The graph below highlights the historic frequency of attendance with a GDP.

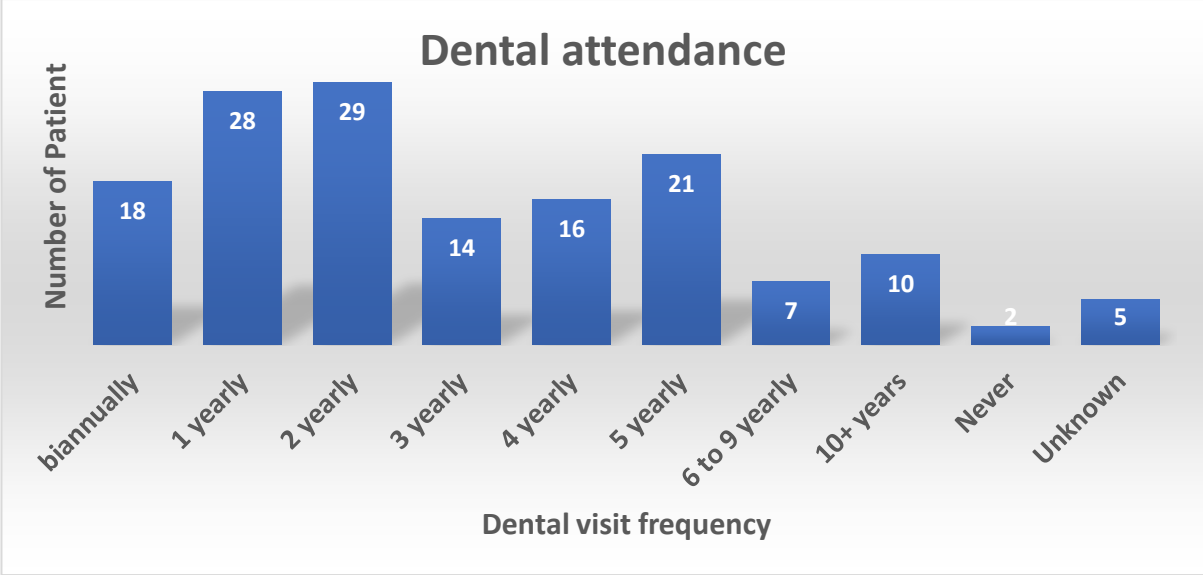


Figure 30 Historic Dental Attendance Frequency

During the time span of the study, which was midst the covid-19 pandemic, historic attendance with a GDP was affected by the covid-19 pandemic. This was reported by patients and demonstrated in the pie chart below.

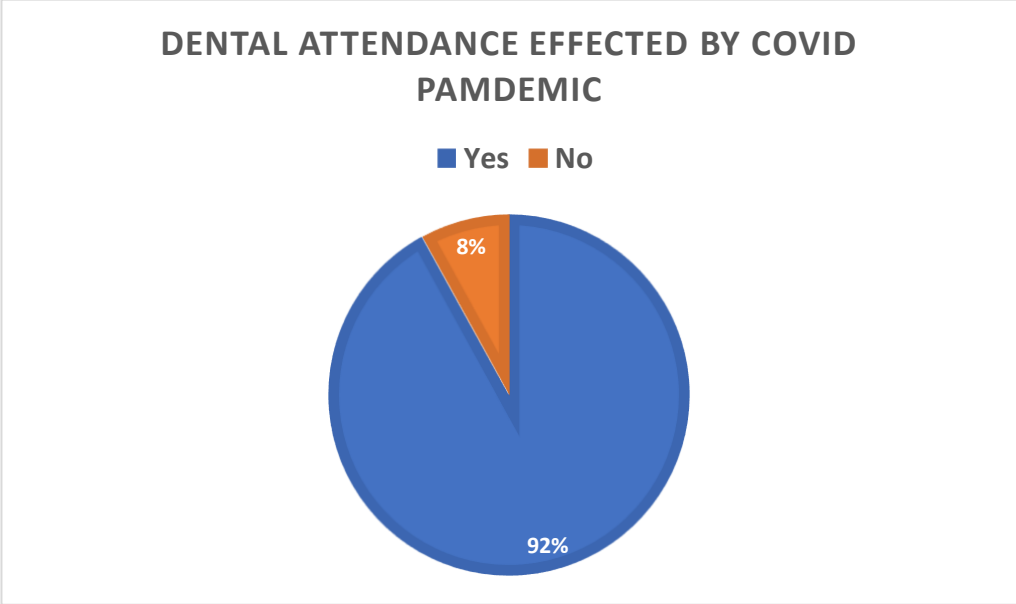


Figure 31 Reported Covid-19 Impact on Dental Attendance

4.5.2 Nature of presenting complaint

On presentation, patients expressed concerns surrounding a number of topics regarding their oral status and pre-existing dental issues. The nature of the presenting complains are highlighted below in figure 32. Presenting complaints were reported in 50% (n=76) of the time as a single concern (16%, n=250, or as multiple concerns about their oral cavity (34%, n=51).

Table 20 Presenting Complaint

Presenting complaint	**Frequency**	**%**
Yes	76	50%
Single concern	25	16%
Multiple concerns	51	34%

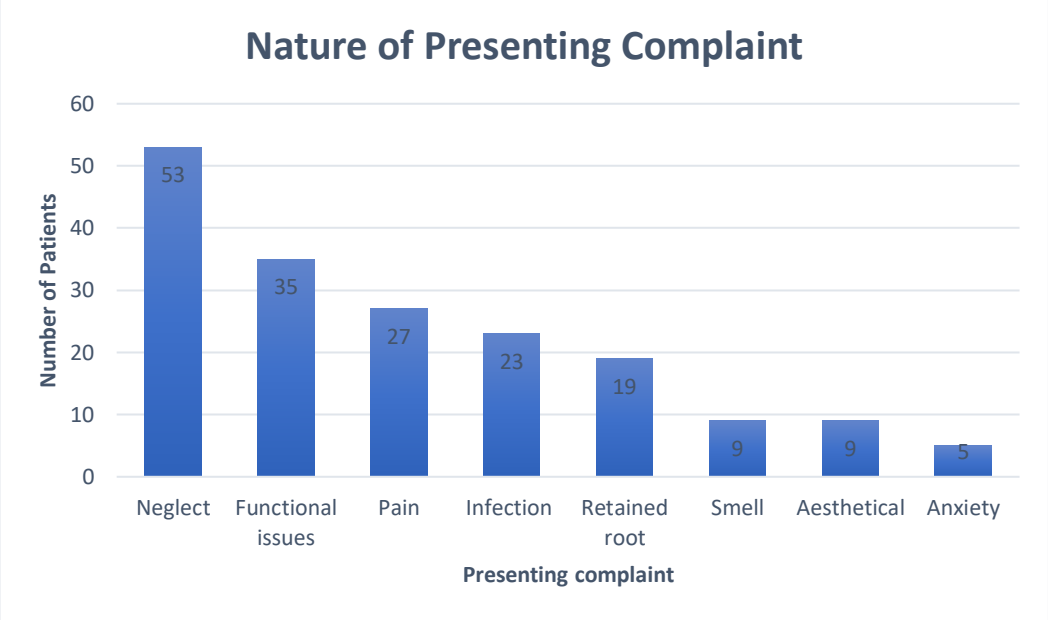


Figure 32 Nature of Presenting Complaint

4.6 Oral health status

4.6.1 Extraoral examination

A thorough clinical examination included both an extraoral and intraoral examination. On extraoral examination, specific examination of the cervical lymph nodes, facial skin, lips, temporomandibular joints, muscles or mastication were examined. Other difficulties such as excessively high or low Body Mass Index (BMI), disease-related issues, infective and physical mobility issues were recorded where necessary.

Table 21 Extraoral Findings

Extraoral Finding	**No (N,%)**	**Yes (N,%)**	**Nature (N, %)**	**Nature (N, %)**
Cervical Lymphadenopathy	148	2	Infective (1, 50%)	Neoplastic (1, 50%)
Facial skin pathology	138	12	Benign (4, 33.3%)	Premalignant (8, 66.6%)
Lip pathology	117	33	Benign (11, 33.3%)	Premalignant (22, 66.6 %)
TMJ pathology	146	4	Degenerative (3, 75%)	Inflammatory (1, 25 %)
Muscles of mastication	136	14	Inflammatory (2, 14.3%)	Hypertrophy (12, 85.7%)
Other clinical concern	138	12	BMI excess (2, 16.7%)	Disease-related (4, 33.3%)
			Infective (1, 8.3%)	Physical disability (5, 41.7 %)

4.6.2 Intraoral soft tissue examination

An intraoral examination included a thorough clinical assessment of the soft tissues of the oral cavity. These were categorised into the buccal mucosae, tongue, floor of mouth, labial mucosae, hard/soft palate and oropharynx. Predominantly, parafunctional frictional keratosis was noted on the buccal mucosae (23.3%, n=35). Frictional and benign soft tissue pathology accounted for 43% (n=48) and 9.3% (n=14) of soft tissue findings, respectively.

Smoking related changes accounted for 8% (n=12) of the soft tissue pathology reported and infective soft tissue findings accounted for 7.3% (n=11) of soft tissue changes noted on intraoral examination.

Table 22 Intraoral Findings

Soft tissue	**No abnormal finding N (%)**	**Frictional N (%)**	**Infective N (%)**	**Smoking-related N (%)**	**Benign N (%)**
Buccal mucosa	103 (68.7%)	35 (23.3%)	6 (4%)	2 (1.3%)	4 (2.7%)
Tongue	138 (92%)	5 (3.3%)	1 (0.7%)	0 (0%)	6 (4%)
Floor of mouth	149 (99.3%)	0 (0%)	1 (0.7%)	0 (0%)	0 (0%)
Labial	138 (92%)	4 (2.7%)	1 (0/7%)	5 (3.3%)	2 (1.3%)
Hard / soft palate	125 (83.3%)	4 (2.7%)	1 (0.7%)	5 (3.3%)	2 (1.3%)
Oropharynx	150 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4.6.3 Hard tissue examination

The DMFT was used to measure the historic treatment caries treatments and presence of decay in the study population. A caries risk assessment grading (low, moderate, high) was calculated and designated to each patient appropriately. Fluoride intake was also noted in the form of water source and tooth paste used by the study population. Daily tooth brushing regimes were also recorded, both tooth brushing frequency and interdental hygiene aids.

4.6.3.1 Caries risk assessment

The caries risk assessment proportions are noted for the entire cohort of 150 patients. The majority of patients (68%, N=102) were in the high caries risk category, alongside 26% (N=39) and 6% (N=9) were categorised in the moderate and low caries risk categories at the time of examination.

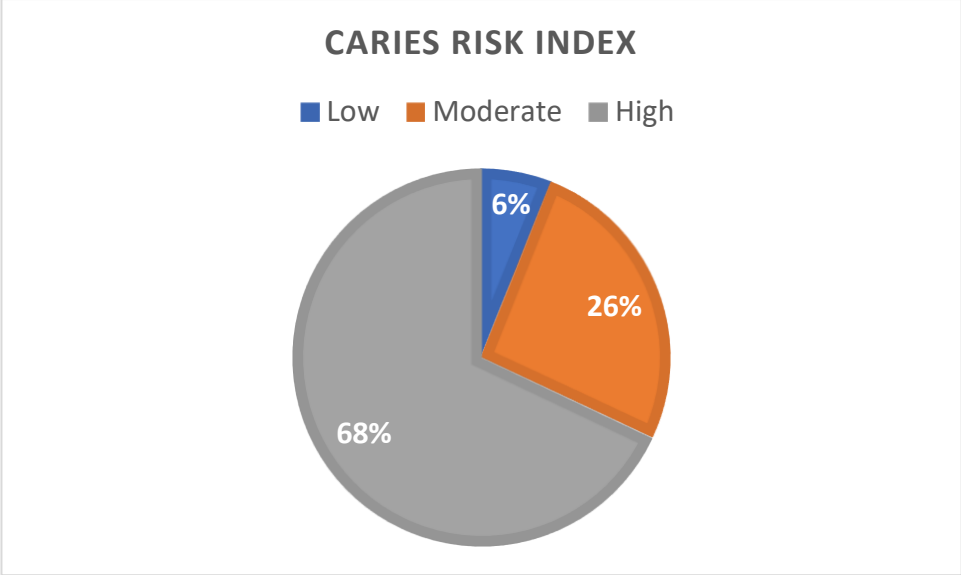


Figure 33 Caries Risk Assessment

4.6.3.2 DMFT assessment

The DMFT measurements for the permanent dentition of the cohort are included in the table below (see table 23). There was an average of 1.16 decayed teeth, 10.59 missing teeth and 5.9 filled teeth recorded in this cohort. The total DMFT average was 17.68.

Table 23 Decayed, Missing and Filled Teeth

	Total teeth	**Decayed**	**Missing**	**Filled**	**Total DMFT**
Total	3176	174	1589	886	2652
Mean	21.17	1.16	10.59	5.9	17.68
Range	(0-32)	(0-12)	(0-32)	(0-20)	(0-32)
Median	24	0	8	5.5	17
SD	8.26	1.86	8.22	4.69	7.85

4.6.3.3 Fluoride exposure and oral hygiene regime

Exposure to fluoride therapy both in drinking water and tooth paste was recorded for the population, alongside their frequency of brushing and using interdental aids. Tap water was consumed by 59.3% (n=89), bottled water by 30.7% (n=46) and well-water by 10% (n=15) of the population. There was a majority of patients who reported twice daily tooth brushing (52%, n=78), followed by once daily (26.5%, n=40), every second day (16%, n=24), once weekly (4%, n=6) and never (1.3%, n=2). The use of interdental oral hygiene aids were rarely used; 16% (n=24).

Table 24 Fluoride Exposure and Oral Hygiene Habits

Fluoride - water	**Number (%)**	**Fluoride - toothpaste**	**Number (%)**
Well water	15 (10%)	No toothpaste / non-fluoride containing	10 (6.7%)
Bottled water	46 (30.7%)	Fluoride tooth (1450ppm)	140 (93.3%)
Tap water	89 (59.3%)		
Tooth brushing frequency		**Interdental hygiene aids**	
Twice daily	78 (52%)	Yes	24 (16%)
Once daily	40 (26.7%)	No	126 (84%)
Every second day	24 (16%)		
Once weekly	6 (4%)		
Never	2 (1.3%)		

4.6.4 Periodontal examination

Periodontal examination included a screening assessment using the PSR screening tool and AAP/ EFP classification system.

4.6.4.1 Periodontal screening examination

The periodontal screening record (PSR) was used to screen the dentition for periodontal disease and help guide management for these patients.

Table 25 Periodontal Disease Distribution

Periodontal health	**Number**	**%**
Gingivitis	3	2%
Mild periodontitis	32	21.3%
Moderate periodontitis	104	69.3%
Severe periodontitis	11	7.4%

4.6.4.2 Periodontal classification

Periodontal classification was completed using the AAP/ EFP classification.

Table 26 American Association of Periodontology Staging and Grading Summary

Stage	**Grade**	**Number**	**% of total population**
1	A	13	8.7%
1	B	19	12.7%
2	A	45	30%
2	B	55	36.6%
2	C	4	2.7%
3	B	7	4.9%
4	B	4	2.7%

Table 27 Periodontal Disease Severity and Treatment Need

Periodontal health	**Treatment need**	**% of total population**
Gingivitis	Tooth debridement, OHI, smoking cessation and review	2%
Mild Periodontitis	Tooth debridement, OHI, smoking cessation and review	21.3%
Moderate Periodontitis	Root debridement, OHI, smoking cessation and review	69.3%
Severe Periodontitis	Intensive quadrant root debridement, OHI, smoking cessation and review	7.4%

4.6.5 Bleeding and plaque scores

Bleeding and plaque score were reported for all patients where appropriate. The corresponding average bleeding score was 30% (range 5%-75%) and plaque score 28% (10%-60%). The graph below highlights the distribution of patients within both indices (see figure 34).

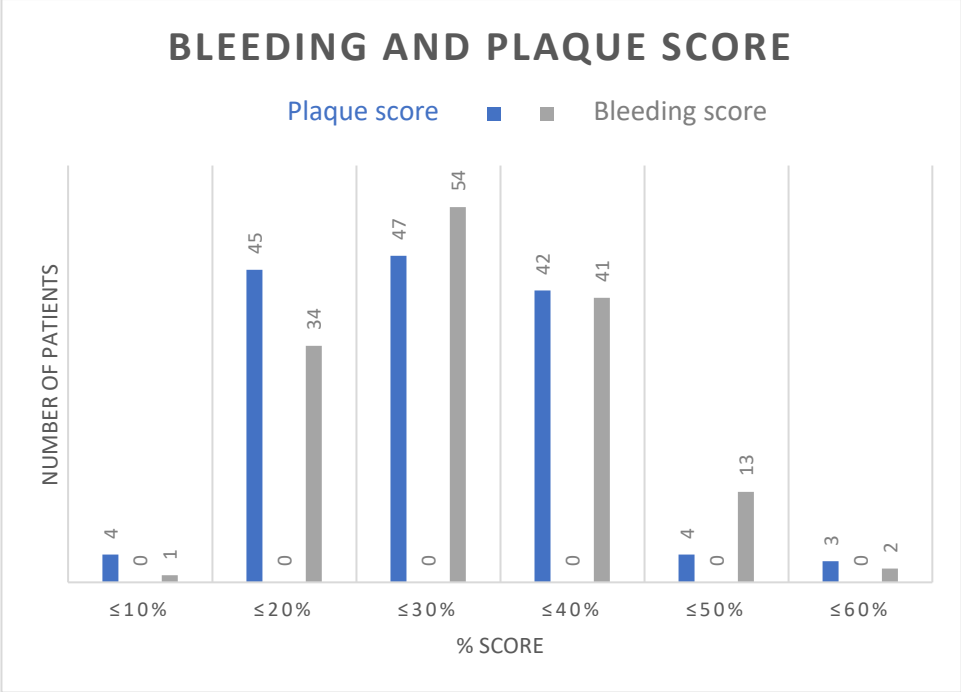


Figure 34 Bleeding and Plaque Scores

4.6.6 Denture examination

Removable prostheses were noted in 20% of the cohort and there was a varying degree of both complete and partial dentures for one or two arches. The most common prosthesis was a partial denture in a single arch (8%, n=12), followed by a complete denture in a single arch (6.67%, n=10), a complete and partial denture (2.67%, n=4), complete dentures (1.33%, n=2) and two partial dentures (1.33%, n=2).

Table 28 Removable Prostheses

Removable prosthesis	**Frequency**	**%**
None	120	80%
Complete (single arch)	10	6.67%
Partial (single arch)	12	8%
Complete and partial (double arch)	4	2.67%
Complete (double arch)	2	1.33%
Partial (double arch)	2	1.33%

Following an assessment of the dentures within the study (20%, n=30), the majority of dentures were well fitting with sufficient denture hygiene standards (75%, n=22), 16% (n=5) had unsatisfactory hygiene regimes and 9% (n=3) were not suitable for function and had an unsatisfactory fit.

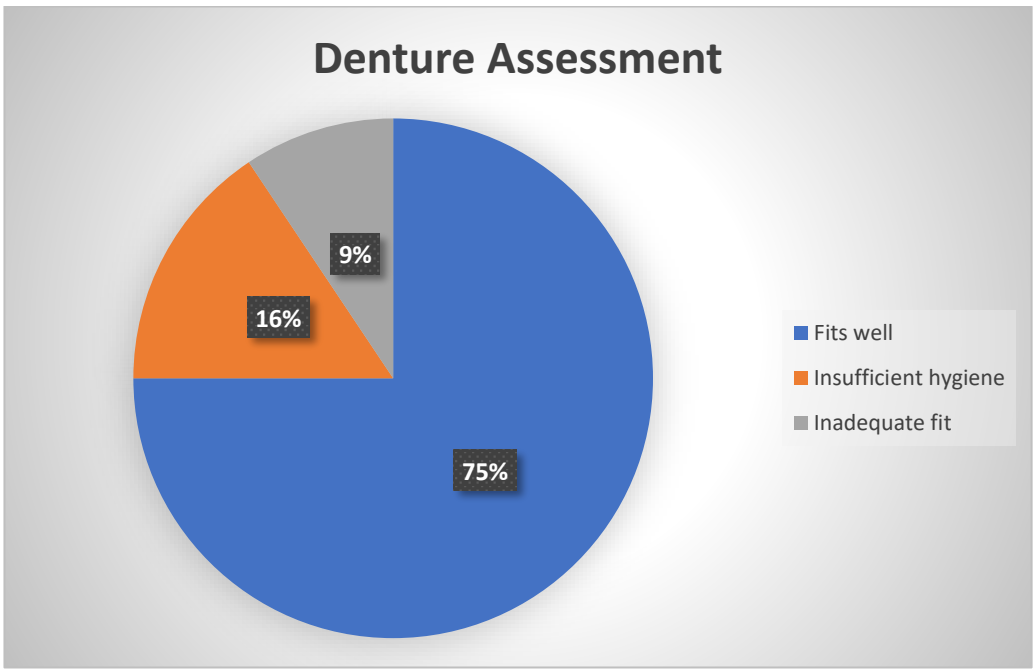


Figure 35 Denture Assessment Findings

4.6.7 Radiographic examination

Radiographic examination of patients included an orthopantomogram for patients where appropriate. Additional imaging was utilised including intraoral plain film radiographs. The table below highlights the radiographs taken over the course of the study (see table 29). One patient was physically unable to undergo an orthopantomogram due to wheelchair restrictions and physical immobility outside of the wheelchair (0.67%, n=1).

Table 29 Radiograph Summary

Radiograph	**Number**	**%**
OPG	149	99.3%
Intraoral Periapical	14	9.3%
Anterior occlusal	2	1.3%
Cone Beam CT	1	0.67%

4.7 Dental care treatment needs

Dental care treatment needs includes two elements of care; educational and preventative treatment provided to all patients and interventional treatments to treat dental disease (periodontal disease, dental decay, periapical infection and soft tissue mucosal changes).

4.7.1 Educational input

Educational input was standardised for all patients in which they received a standard package of information and oral hygiene aids following completion of their dental treatment. An information leaflet regarding the aims of the study and information on MRONJ was provided. *Curaprox soft* tooth brushes and appropriate sizes of *Tepe* interdental brushes were also given to patients on departure. Each patient was coached on accessing a GDP every 3 months following completion of their dental treatment at the CUDSH. Integration into the community and follow-on care was discussed with patients prior to discharge from the study.

4.7.2 Preventative intervention

Preventative treatment included topical fluoride application and where appropriate, a prescription as provided for *Duraphat* toothpaste. Patients were subcategorised into high or low fluoride requirement based on their caries risk assessment and clinical parameters for topical fluoride usage.

Table 30 Fluoride Application

Topical Fluoride requirement	**Number**	**%**
Duraphat prescription (2800ppm)	118	78.6%
Topical fluoride application	118	78.6%
None	32	21.4%

4.7.3 Restorative intervention

Periodontal disease and dental decay were prevalent amongst the patients (see tables 23, 25,and 26). Gingivitis and mild periodontitis was addressed with a tooth debridement (23.3%, n=35) or a root debridement depending of periodontal risk factors or the overall clinical picture (69.3%, n=104). Advanced stage periodontal disease which require staged-quadrant debridement included 7.4% (n=11). The bar chart below demonstrates the periodontal therapy that was completed during the study.

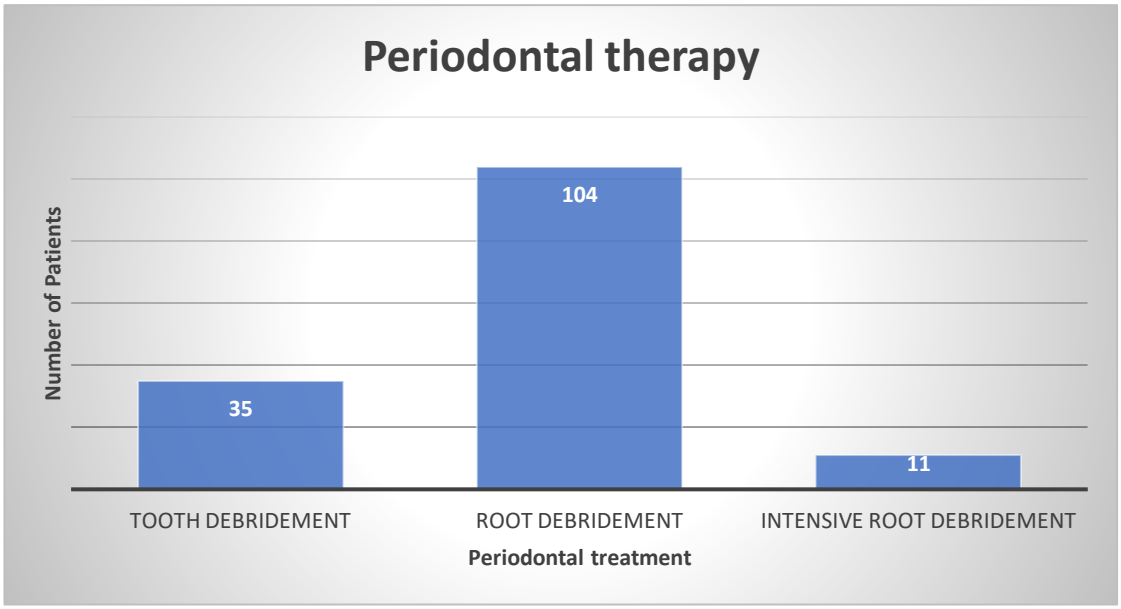


Figure 36 Periodontal Therapy

Dental restorations were completed for patients using two material, a light-cured resin based glass ionomer or a composite resin. Dental restorations were subcategorised into single or multiple restorations depending on the case demands. Glass ionomer restorations were used in 23 patients and composite restorations were used in 19 patients (total n=42 patients). There was a similar number of patients who had a single

vs multiple glass ionomer restoration, 28.5% (n=12) and 26.2% (n=11) respectively. Multiple composite restorations were completed more often than single, accounting for 26.2% (n=11) versus 19% (n=8) for single composite restorations.

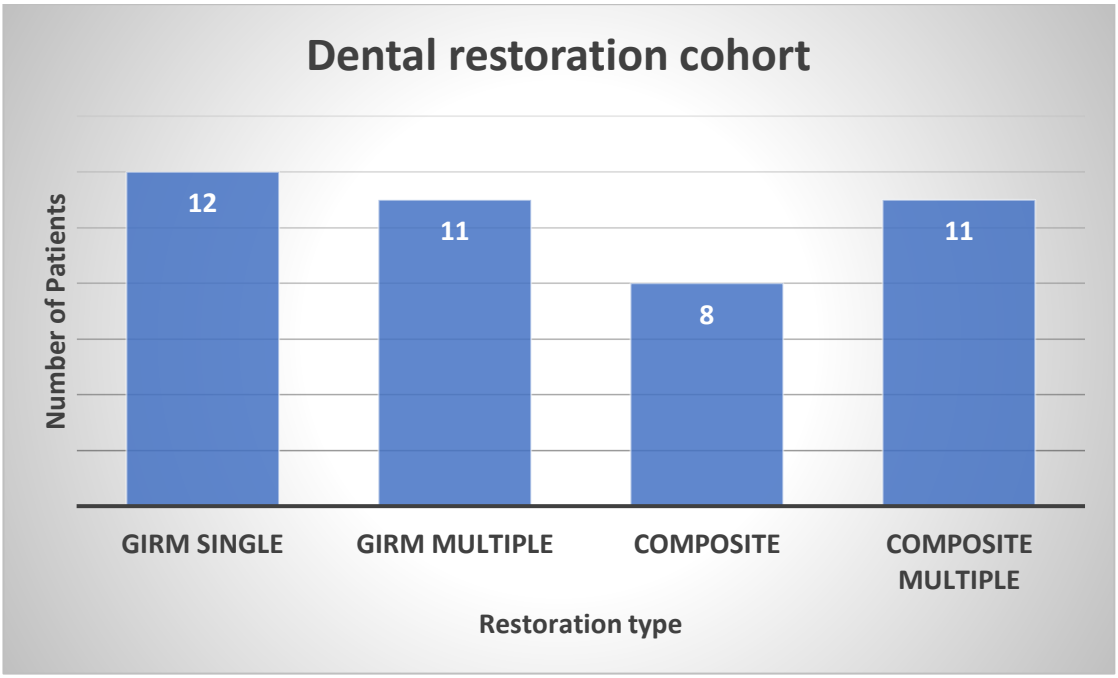


Figure 37 Patients who Received a Dental Restoration using Glass Ionomer Resin Modified or Composite

Total restorations placed was 86 restorations for the cohort who required a restoration (n=42). This figure was split evenly between both GIRM restorations (50%, n=43) and composite restorations (50%, n=43).

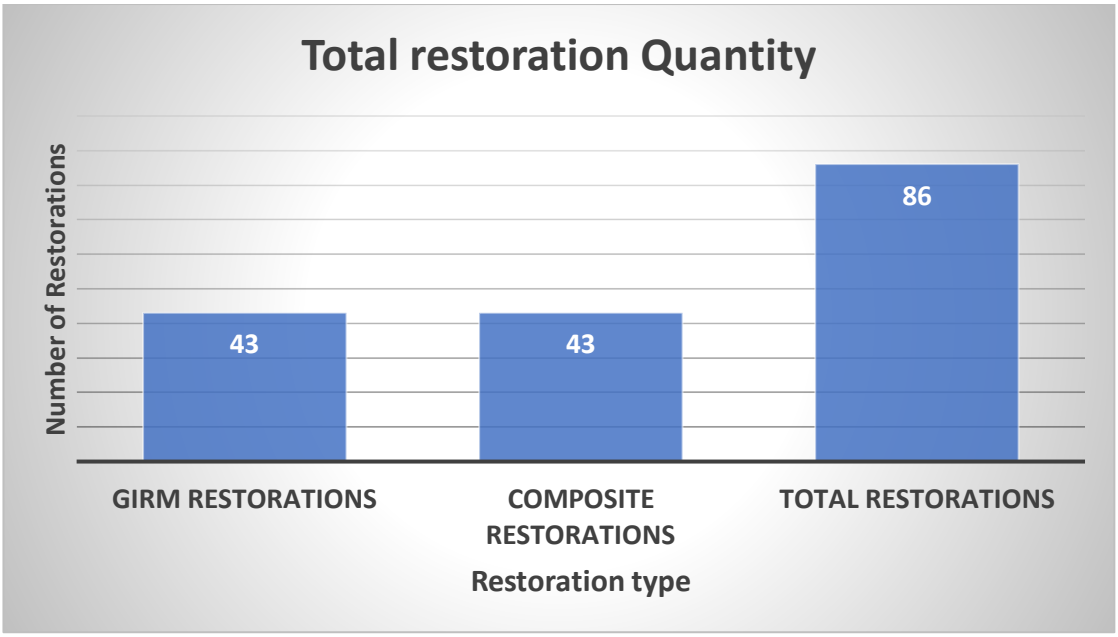


Figure 38 Number of Completed Restorations

4.7.4 Oral surgery intervention

Dental extractions were completed in 76 patients (50.7% of the total cohort). A larger proportion of the population required multiple extractions (32%, n=48) compared to a single extraction (18.7%, n=28). The average number of dental extractions was 3.

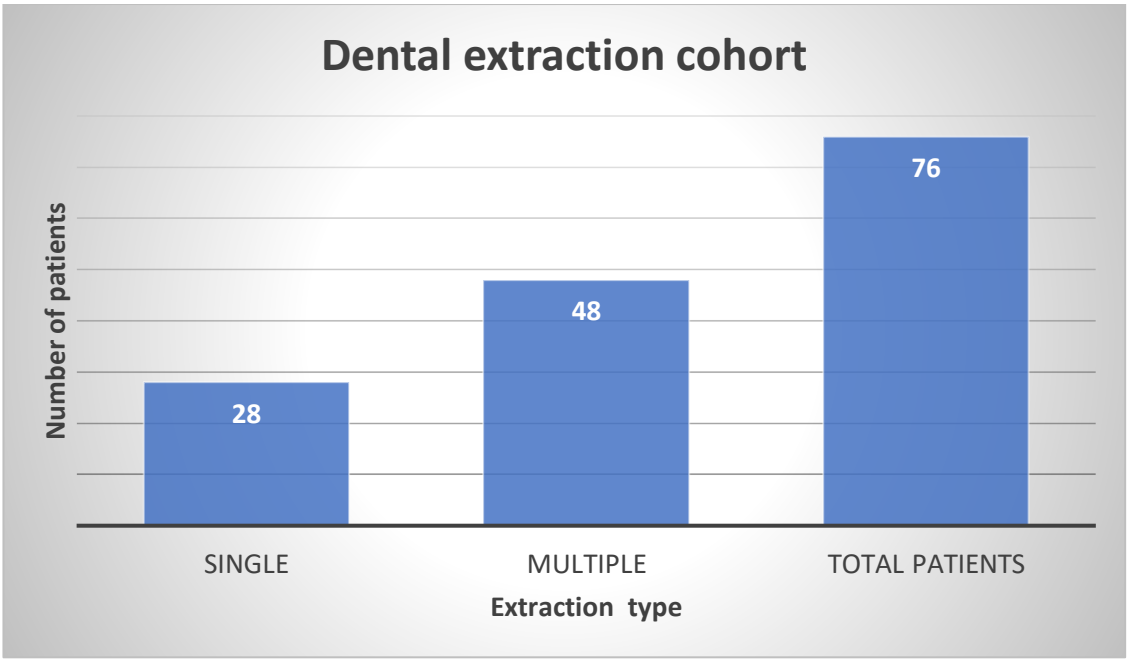


Figure 39 Total Patients to Undergo an Extraction

The total number of extractions completed was 188 in 76 patients. There was a large discrepancy in the number of teeth extracted during a single extraction (18.67%, n=28) compared to multiple extractions (81.33%, n=160). Hence, a majority of patients who required an extraction, required multiple extractions.

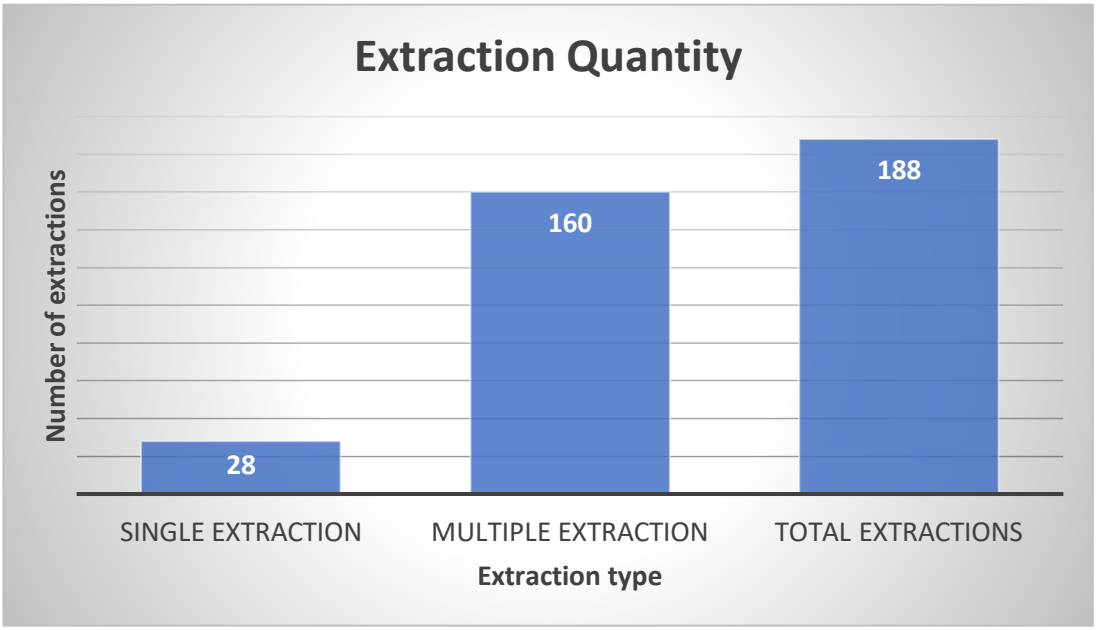


Figure 40 Number of Completed Extractions

Oral cavity soft tissue biopsies were completed for 8 patients. Their treatment and outcome are summarised below in table 31.

Table 31 Soft Tissue Procedures

Biopsy type	**Number (%)**	**Result**	**Outcome**
Incisional biopsy	2 (25%)	Mild / moderate dysplasia	Oral medicine follow-up
Excisional biopsy	4 (50%)	Benign pathology	No intervention required
Debridement of socket	2 (25%)	Granulation tissue	No intervention required

Table 32 Indication for an Extraction (Periodontal Disease or Decay) and for a Dental Restoration (Primary or Secondary Decay)

Treatment	**Dental disease**	**Single (%)**	**Multiple (%)**	**Quantity**
Extraction	Periodontal disease	20 (10.6%)	101 (54.3%)	121 (64.4%)
	Decay	22 (11.7%)	45 (23.4%)	67 (35.6%)
Total				188
Restoration	Primary decay	18 (20.9%)	64 (74.4%)	82
	Secondary decay	2 (2.3%)	2 (2.3%)	4
Total				86

4.7.5 Prosthetic intervention

The total number of dentures included 30 dentures in 26 patients. A denture was completed for each patient including an assessment of the quality of denture retention / resistance, the standard of denture hygiene and the suitability to replace the denture where necessary. The bar chart below highlights the interventions for the dentures. Denture fabrication included 4 immediate dentures completed by the operator (Dr Harriet Byrne) and 3 dentures were completed with the assistance of a student undergraduate clinic.

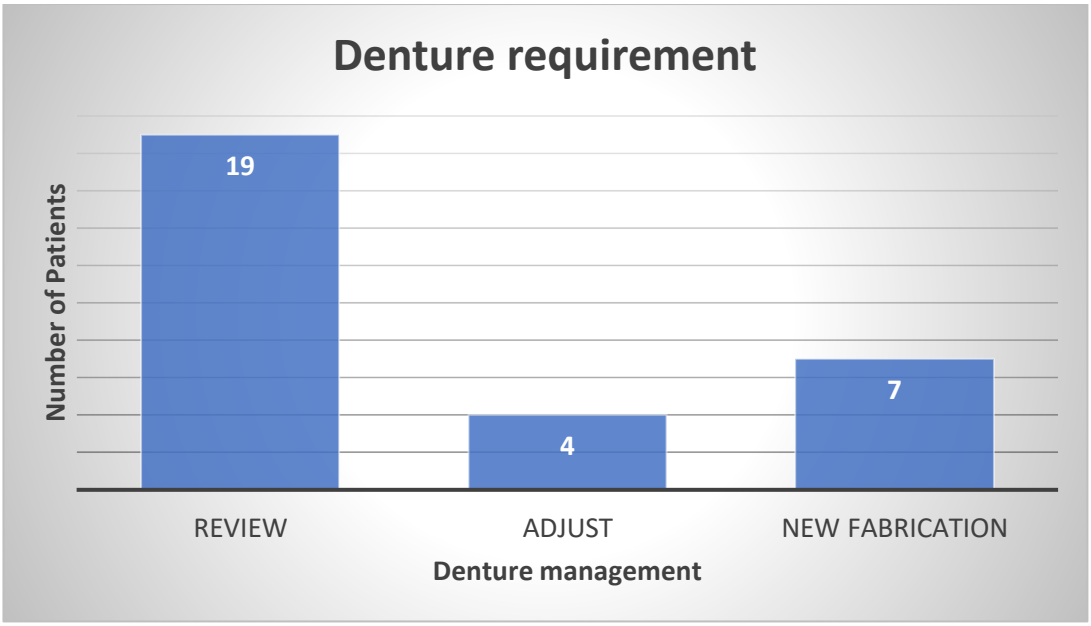


Figure 41 Denture Intervention

4.7.6 Follow-on dental collaboration

Assistance was required during stages of the study to collaborate and utilise the expertise of dental colleagues. The table below includes follow-on treatment required for patients to achieve dental fitness or following completion of treatment in the study in which they gained dental fitness. 28 patients (18.67%) required further follow-up with other dental colleagues.

Table 33 Follow-Up Management

Follow-on care	Number	%	Reason
Student undergraduate dental clinic	18	12%	Financial burden of dental care
Endodontic specialist	4	2.67%	Retention of tooth with root canal therapy
Prosthodontist	4	2.67%	Fixed prostheses following dental extractions
Oral medicine	2	1.33%	Oral dysplasia confirmed on biopsy

4.7.7 Dental fitness

Dental fitness includes patients who at the time of discharge from the study, were suitable dentally to commence a BMA. Unfortunately, 3 patients (2%) refused dental intervention and were not deemed dentally fit to commence a BMA. 147 patients (98%) achieved dental fitness prior to their BMA (see figure 34).

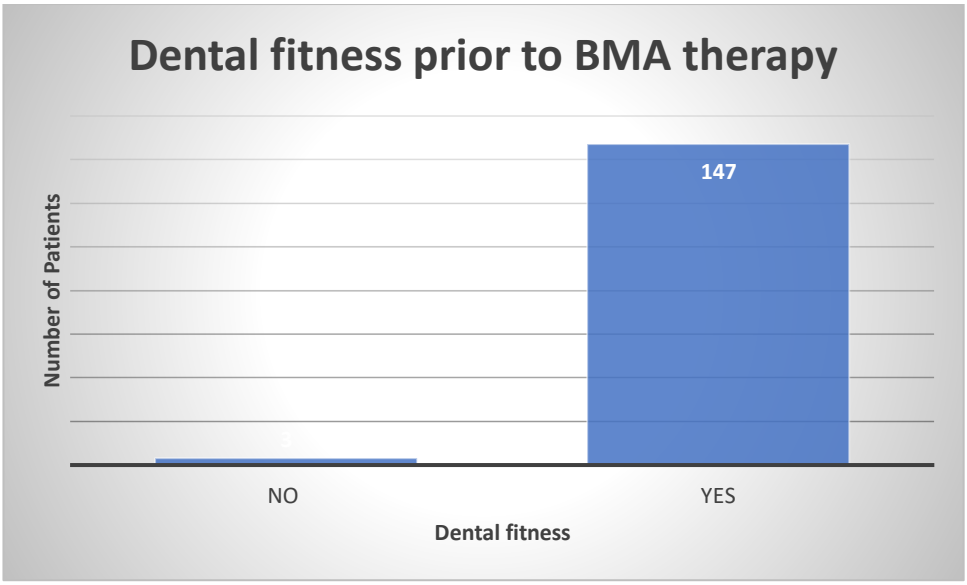


Figure 34 Dental Fitness Prior to BMA Treatment

4.8 Qualitative assessment

The researcher performed semi-structured 45-minute qualitative interviews with 20 dentists and 10 patients. Informed consent was gained from each participant.

Semi-structured interview questions are attached (see appendices A and B) for dentist and patient cohorts. Interviews (in person and phone interviews) were recorded, and a transcription service (*GoTranscript*) used to ensure accurate, verbatim transcription of interviews. The transcript was analysed using thematic analysis, and dentist / patient themes documented below.

4.8.1 Patient focus group analysis

10 patients were interviewed regarding their routine dental care, the potential impact of BMA therapy on their oral health, their dental treatment requirements and awareness of MRONJ. Six patients were included in a focus group and four patients were contacted via telephone.

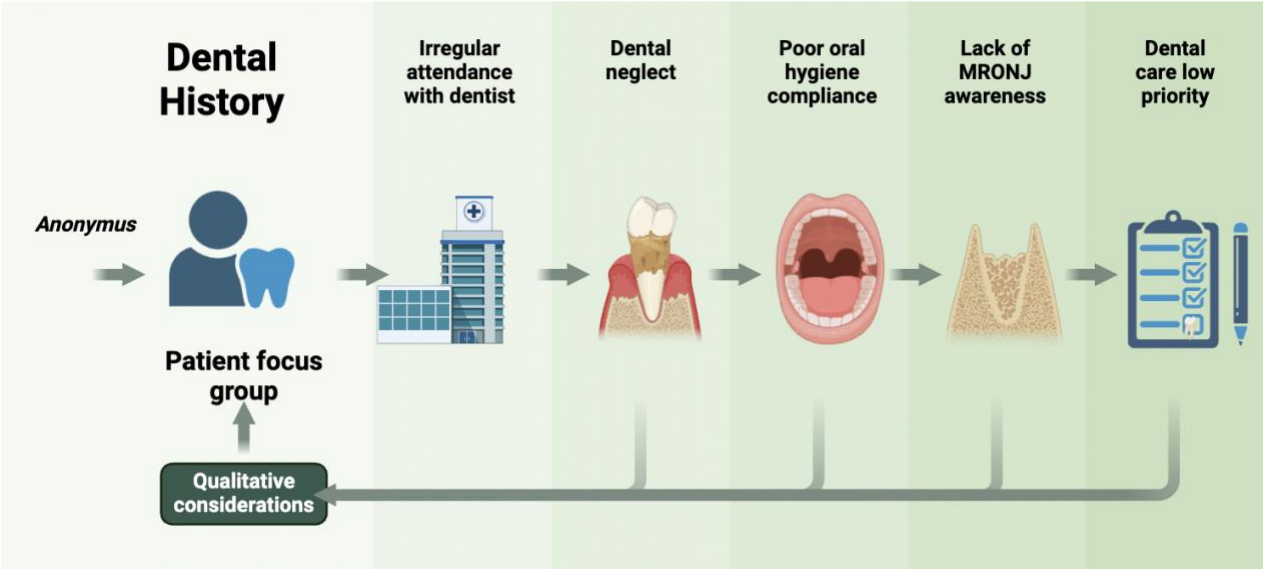


Figure 42 Patient Focus Group - Dental History

Table 35 Patient Focus Group - Dental History Topic

Dental History	Dental History
Variability regarding GDP registration	Irregular dental attender
Unaware of dental implication with cancer treatment	Emergency based attendance
Historic driven adverse dental events	Dental anxiety about treatment
Aware of negative effects of sugar diet on dental health	Symptom driven attendance
Dental care was a minor priority in treatment	Dental neglect
Poor prior knowledge about MRONJ	Poor compliance with oral hygiene habits
Unaware of dental status	

Input from patient transcriptions were included which highlighted the lack of education and knowledge of MRONJ in this cohort prior to BMA therapy.

"No, I wasn't aware until I went to you – and I wasn't even sure why I was being sent to you, I hadn't really looked it up. But then you explained the link with the Zometa and the dental issues".

Patient perception of dental care prior to commencement of a BMA impacts their future projection of dental care. Dental disease and the chronic effects of poor dental can dictate their motivation for dental care and engagement following BMA administrations.

"I couldn't tell you that now, being honest, I never was keen to go to the dentist. I had no real interest in looking after my teeth, which I should have, really. But I never did, being honest".

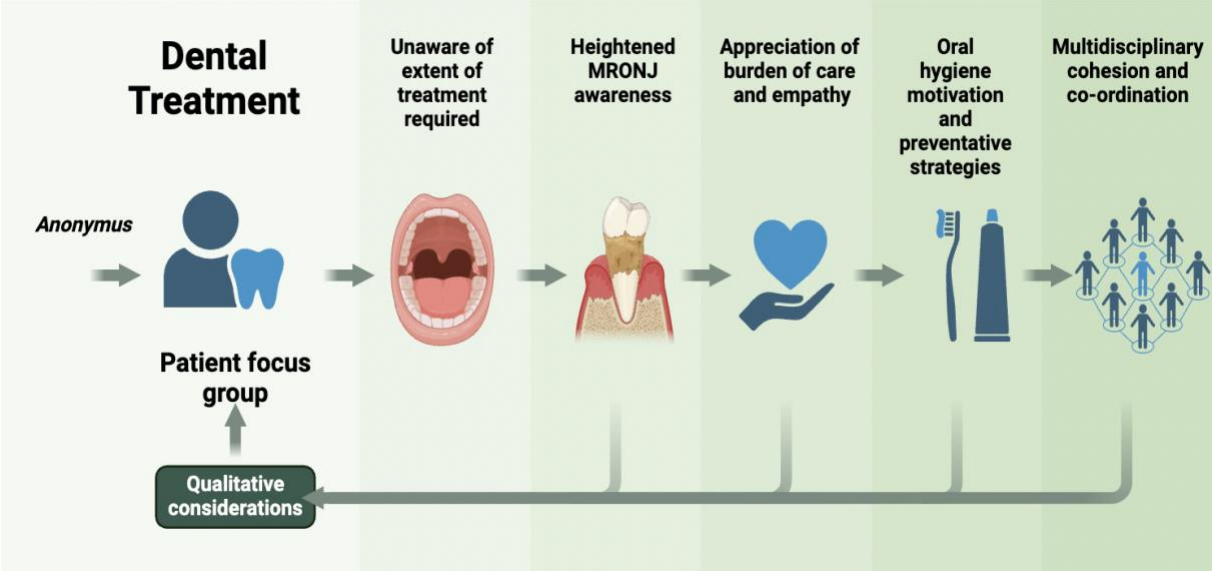


Figure 43 Patient Focus Group - Dental Treatment

Table 36 Patient Focus Group - Dental Treatment Topic

Dental treatment	Dental treatment
Confidence in dental care with collaborative approach	Unaware of extent of dental treatment that was necessary prior to "dental fitness"
Encouraged when received all information about BMA therapy and dental effects / MRONJ	Shock about scale of treatment required
Cohesion with communication and oncology nurses	Encourages and motivates oral hygiene habits
Burden of oncology care and inclusion of dental another challenge	Unaware of dental treatment performed in short space of time
Organised to engage with GDP since dental assessment	Aesthetic deficiency most worrisome issue following removal of teeth
Risk of MRONJ changes attitude to dental care and proactivity	Reassured that dental practitioner was knowledgeable about BMA treatment and overall oncology structure
Psychological burden of care, particularly during chemotherapy	Dental – oncology cohesion very reassuring
Hard copy paper leaflets are helpful to read at home about MRONJ risk	Comfortable in the dental setting, positive experience
Dental empathy and kindness made process enjoyable	

4.8.2 GDP focus group analysis

Dentists (n=20) engaged in a focus group surrounding the topic guide (see appendix B) specifically about their knowledge of MRONJ and their experience of treating this cohort in general dental practice. Each member of the focus group was both a general dental practitioner and employed by the Cork University Dental School and Hospital on a part time basis. Two members of the dentist group had higher training in prosthodontics.

Recurrent themes emerged which are highlighted in figure 44.

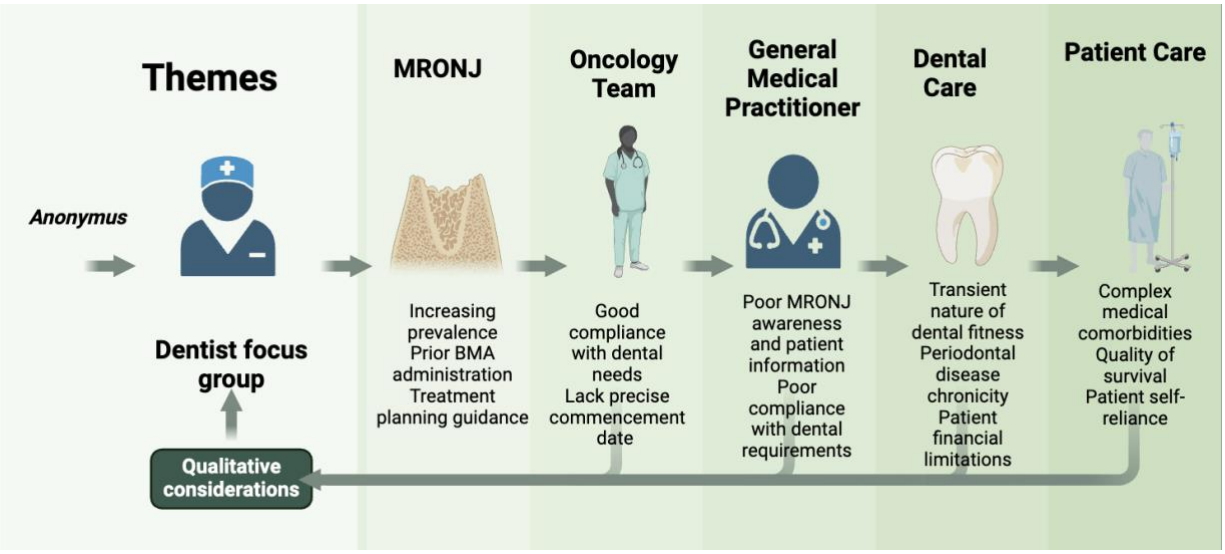


Figure 44 Dentist Focus Group Themes

The burden of dental treatment amidst oncology care is demanding and patients remarked on the impact of this additional facet of care. The importance of multidisciplinary driven care was considered important by patients. Cohesion of care amongst professionals remains an important aspect of oncology care for patients.

"Like, they're going through an awful traumatic time, a lot of them have cancer treatments – and then you must tell them that they're going to have all these teeth removed, it's a double whammy for them. But some communication with the consultant is nice to have, and I suppose when we're writing these letters we'll say, at this moment in time, their mouths are healthy, which is all you can do".

The importance of MRONJ education was highlighted as an important aspect of care and the appreciation of education was acknowledged by patients.

“They usually have no idea and come to you for a letter. They don’t know why they’re turning up. Doctor needs a letter, like, and then why. But the risk of osteonecrosis is played down”.

The challenges of dental fitness and the parameters that define dental fitness remain challenging. Treatment planning, dental prognosis and co-ordination of dental care present challenges for the dental profession. Often, dental disease such as periodontitis is a long-standing, chronic, inflammatory condition that cannot be resolved prior to dental fitness.

“I think the problems start when you get a letter saying can you give us a cert or whatever, to say that they’re dentally fit – but it’s very hard. I always found that very difficult to predict. So, I don’t know if there were guidelines to guide treatment, but the guidelines aren’t there, you don’t want to be too aggressive either. It’s a balance”.

“It does put you under a lot of pressure to do it, and to decide what’s best to do. In my opinion, if its any way borderline, my opinion is to remove the tooth”.

Table 37 Dentist Focus Group Themes

Topic	Comment
Medication – related osteonecrosis of the jaw	Concern about intravenous BMA
	Transitioning from oral BMA to intravenous / subcutaneous forms
	Historic BMA not investigated prior to extraction
	Increasing prevalence of MRONJ seen in practice
Oncology team	Good compliance with dental assessments prior to BMA commencement
	Poor to comment on a planned date of commencement
	Do not start unless dental letter received
General medical practitioner (GMP)	Poor knowledge of MRONJ amongst GMPs
	Poor knowledge of MRONJ potential relayed to patients
	Denosumab more prevalent amongst GMPs and very few dental assessments prior to administration
Dental Care	Dental fitness is transient
	Treatment planning compromised teeth for long term viability
	Treatment planning challenges / lack of guidance
	Management of periodontally involved tooth
	Denture management and loss of teeth
	Comfortable timing extractions with denosumab
	Unknown protocol for treatment of MRONJ or management by the dentist
	Definition of “dentally fit”
	Treatment protocol following administration of BMA and dental pain
	Limitations of the medical card
	Hygiene appointment intervals
	Affordability to attend private oral surgeon for extractions
Patient care	Loss of function and quality of life important to GDP
	Breaking news regarding multiple extractions
	Both regular and emergency patients for dental assessment prior to a BMA

	Emergency with dental fitness and cancer cases compared to the osteoporotic patient
	Immunocompromised patient needs / complex medical history
	Waiting list times for extractions with oral surgery services
	Aware of burden of care for oncology cohort
	Patient motivational factors and self-reliance

4.9 Multivariate analysis

The findings of the multivariate analyses are represented in the tables below.

4.9.1 Treatment need for a restoration (Yes/No)

Table 38 Logistic Regression Model Parameter Estimates to Assess the Treatment Need for a Restoration (P-Value in Bold are Significant or Close to Significant at 5%)

Explanatory Variable	DF	Estimate	Standard Error	P-value	Odds Ratio	95% Confidence Limits	
Age	1	0.1309	0.1665	0.4317	1.140	0.822	1.580
GDP (No)	1	0.7525	0.4278	**0.0786**	2.122	0.918	4.908
GDP every 2 – 4 years	1	0.5401	0.4971	0.2773	1.716	0.648	4.547
GDP every 5 or more years	1	-0.0875	0.5736	0.8788	0.916	0.298	2.820
Smoking (Yes)	1	0.5499	0.4507	0.2224	1.733	0.716	4.192
Smoking (Ex)	1	0.4232	0.5356	0.4295	1.527	0.534	4.362
Barrier (Any)	1	-0.8535	0.6880	0.2148	0.426	0.111	1.641
Cancer Breast (Late)	1	-0.1432	0.5176	0.7820	0.867	0.314	2.390
Cancer (All Others)	1	0.1731	0.5085	0.7335	1.189	0.439	3.221

Patients that did not have a GDP were more likely to need restorations (OR = 2.122, 95% CI: (0.918, 4.908) but the difference was marginally non-significant (p = 0.0786).

4.9.2 Treatment need for restorations

Table 39 Poisson Regression Model Parameter Estimates to Assess the Treatment Need for Restorations (P-Value in Bold are Significant or Close to Significant at 5%)

Explanatory Variable	DF	Estimate	Standard Error	P-value	Ratio of Means	95% Confidence Limits	
Age	1	0.0524	0.0934	0.5750	1.054	0.877	1.266
GDP (No)	1	0.5161	0.2412	**0.0324**	1.675	1.044	2.688
GDP every 2 – 4 years	1	0.6727	0.3362	**0.0454**	1.960	1.014	3.787
GDP every 5 or more years	1	0.4102	0.3683	0.2653	1.507	0.732	3.102
Smoking (Yes)	1	0.6036	0.2611	**0.0208**	1.829	1.096	3.051
Smoking (Ex)	1	0.8578	0.2743	**0.0018**	2.358	1.377	4.037
Barrier (Any)	1	-0.5528	0.4377	0.2065	0.575	0.244	1.357
Cancer Breast (Late)	1	0.1551	0.3345	0.6429	1.168	0.606	2.250
Cancer (All Others)	1	0.5477	0.3141	0.0812	1.729	0.934	3.200

Patients that did not have a GDP needed more restorations (ratio of means = 1.675, 95% CI: (1.044, 2.688) and the difference was significant (p = 0.0324). Patients who were current smokers needed more restorations than never-smokers (ratio of means = 1.829, 95% CI: (1.096, 3.051) and the difference was significant (p = 0.0208). Patients that were ex-smokers needed more restorations than never-smokers (ratio of means = 2.358, 95% CI: (1.377, 4.037) and the difference was significant (p = 0.0018).

Patients that attend their GDP every 2 to 4 years needed more restorations than those that attend at least annually (ratio of means = 1.960, 95% CI: (1.014, 3.787) and the difference was marginally significant (p = 0.0454).

4.9.3 Treatment need for a dental extraction (Yes/No)

Table 40 Logistic Regression Model Parameter Estimates to Assess the Treatment Need for an Extraction (P-Value in Bold are Significant or Close to Significant at 5%)

Explanatory Variable	DF	Estimate	Standard Error	P-value	Odds Ratio	95% Confidence Limits	
Age	1	0.0207	0.0159	0.1939	1.021	0.990	1.053
GDP (No)	1	0.6264	0.3949	0.1127	1.871	0.863	4.057
GDP every 2 – 4 years	1	0.9162	0.4533	**0.0433**	2.500	1.028	6.078
GDP every 5 or more years	1	1.2257	0.5031	**0.0148**	3.407	1.271	9.132
Smoking (Yes)	1	1.2337	0.4536	**0.0065**	3.434	1.412	8.353
Smoking (Ex)	1	0.2373	0.5045	0.6381	1.268	0.472	3.408
Barrier (Any)	1	-0.3565	0.5555	0.5210	0.700	0.236	2.080
Cancer Breast (Late)	1	0.0160	0.4685	0.9727	1.016	0.406	2.545
Cancer (All Others)	1	-0.1651	0.4780	0.7298	0.848	0.332	2.164

Patients that were current smokers were more likely to need extractions than never-smokers (OR = 3.434, 95% CI: (1.412, 8.353) and the difference was significant (p = 0.0065). Patients that attend their GDP every 2 to 4 years were more likely to need extractions than those that attend at least annually (OR = 2.500, 95% CI: (1.028, 6.078) and the difference was marginally significant (p = 0.0433). Patients that attend their GDP every 5 years or more were more likely to need extractions than those that attend at least annually (OR = 3.407, 95% CI: (1.271, 9.132) and the difference was significant (p = 0.0148).

4.9.4 Treatment need for dental extractions

Table 41 Poisson Regression Model Parameter Estimates for Extractions (P-Value in Bold are Significant or Close to Significant at 5%)

Explanatory Variable	DF	Estimate	Standard Error	P-value	Ratio of Means	95% Confidence Limits	
Age	1	0.0115	0.0066	0.0819	1.012	0.999	1.025
GDP (No)	1	0.0833	0.1622	0.6077	1.087	0.791	1.494
GDP every 2 – 4 years	1	0.5555	0.2175	**0.0107**	1.743	1.138	2.669
GDP every 5 or more years	1	0.7808	0.2305	**0.0007**	2.183	1.390	3.430
Smoking (Yes)	1	0.7274	0.1689	< **0.0001**	2.070	1.486	2.882
Smoking (Ex)	1	0.5339	0.2008	**0.0078**	1.706	1.151	2.528
Barrier (Any)	1	-0.0426	0.2364	0.8571	0.958	0.603	1.523
Cancer Breast (Late)	1	0.4344	0.2189	**0.0471**	1.544	1.006	2.371
Cancer (All Others)	1	0.3957	0.2199	**0.0720**	1.485	0.965	2.286

Patients that were current smokers needed more extractions than never-smokers (ratio of means = 2.070, 95% CI: (1.486, 2.882) and the difference was significant ($p < 0.0001$). Patients that were ex-smokers needed more extractions than never-smokers (ratio of means = 1.706, 95% CI: (1.151, 2.528) and the difference was significant ($p = 0.0078$). Patients that attend their GDP every 2 to 4 years needed more extractions than those that attend at least annually (ratio of means = 1.743, 95% CI: (1.138, 2.669) and the difference was significant ($p = 0.0107$). Patients that attend their GDP every 5 years or more needed more extractions than those that attend at least annually (ratio

of means = 2.183, 95% CI: (1.390, 3.430) and the difference was significant (p = 0.0007). Patients that were diagnosed with late-stage breast cancer needed more extractions than those diagnosed with early-stage breast cancer (ratio of means = 1.544, 95% CI: (1.006, 2.371) and the difference was marginally significant (p = 0.0471). Patients that were diagnosed with cancer other than breast cancer needed more extractions than those diagnosed with early-stage breast cancer (ratio of means = 1.485, 95% CI: (0.965, 2.286) but the difference was marginally non-significant (p = 0.0720).

4.9.5 Treatment need for dental extractions due to periodontal disease

Table 42 Poisson Regression Model Parameters to Assess the Treatment Need for Number of Extractions Due to Periodontal Disease (P-Value in Bold are Significant or Close to Significant at 5%)

Explanatory Variable	DF	Estimate	Standard Error	P-value	Ratio of Means	95% Confidence Limits	
Age	1	0.1925	0.0853	**0.0239**	1.212	1.026	1.433
GDP (No)	1	0.0380	0.2005	0.8497	1.039	0.701	1.539
GDP every 2 – 4 years	1	1.0075	0.3043	**0.0009**	2.739	1.508	4.973
GDP every 5 or more years	1	1.2657	0.3199	< **0.0001**	3.545	1.894	6.636
Smoking (Yes)	1	0.8887	0.2098	< **0.0001**	2.432	1.612	3.669
Smoking (Ex)	1	0.5439	0.2533	**0.0318**	1.723	1.049	2.830
Barrier (Any)	1	-0.4656	0.3408	0.1719	0.628	0.322	1.224
Cancer Breast (Late)	1	0.5845	0.2763	**0.0344**	1.794	1.044	3.084
Cancer (All Others)	1	0.2767	0.2833	0.3287	1.319	0.757	2.298

Older patients needed more extractions due to periodontal disease (ratio of means for a 10-year increase in age = 1.212, 95% CI: (1.026, 1.433) and the difference was significant (p = 0.0239). Patients that were current smokers needed more extractions due to periodontal disease than never-smokers (ratio of means = 2.432, 95% CI: (1.612, 3.669) and the difference was significant (p < 0.0001). Patients that were ex-smokers needed more extractions due to periodontal disease than never-smokers (ratio of means = 1.723, 95% CI: (1.049, 2.830) and the difference was significant (p = 0.0318). Patients that attend their GDP every 2 to 4 years needed more extractions due

to periodontal disease than those that attend at least annually (ratio of means = 2.739, 95% CI: (1.508, 4.973) and the difference was significant (p = 0.0009).

Patients that attend their GDP every 5 years or more needed more extractions due to periodontal disease than those that attend at least annually (ratio of means = 3.545, 95% CI: (1.894, 6.636) and the difference was significant (p < 0.0001). Patients that were diagnosed with late-stage breast cancer needed more extractions due to periodontal disease than those diagnosed with early-stage breast cancer (ratio of means = 1.794, 95% CI: (1.044, 3.084) and the difference was significant (p = 0.0344).

4.9.6 Treatment need for dental extractions due to decay

Table 43 Poisson Regression Model Parameters to Assess the Treatment Need for Number of Extractions Due to Decay (P-Value in Bold are Significant or Close to Significant at 5%)

Explanatory Variable	DF	Estimate	Standard Error	P-value	Ratio of Means	95% Confidence Limits	
Age	1	-0.0250	0.1029	0.8085	0.975	0.797	1.193
GDP (No)	1	0.1244	0.2755	0.6516	1.132	0.660	1.943
GDP every 2 – 4 years	1	-0.0171	0.3277	0.9583	0.983	0.517	1.869
GDP every 5 or more years	1	0.1245	0.3471	0.7198	1.133	0.574	2.236
Smoking (Yes)	1	0.4592	0.2897	0.1129	1.583	0.897	2.793
Smoking (Ex)	1	0.5247	0.3298	0.1117	1.690	0.885	3.226
Barrier (Any)	1	0.5276	0.3367	0.1172	1.695	0.876	3.279
Cancer Breast (Late)	1	0.1440	0.3651	0.6932	1.155	0.565	2.362
Cancer (All Others)	1	0.6016	0.3497	0.0854	1.825	0.920	3.621

Patients that were diagnosed with cancer other than breast cancer needed more extractions due to decay than those diagnosed with early stage breast cancer (ratio of means = 1.825, 95% CI: (0.920, 3.621) but the difference was marginally non-significant (p = 0.0854).

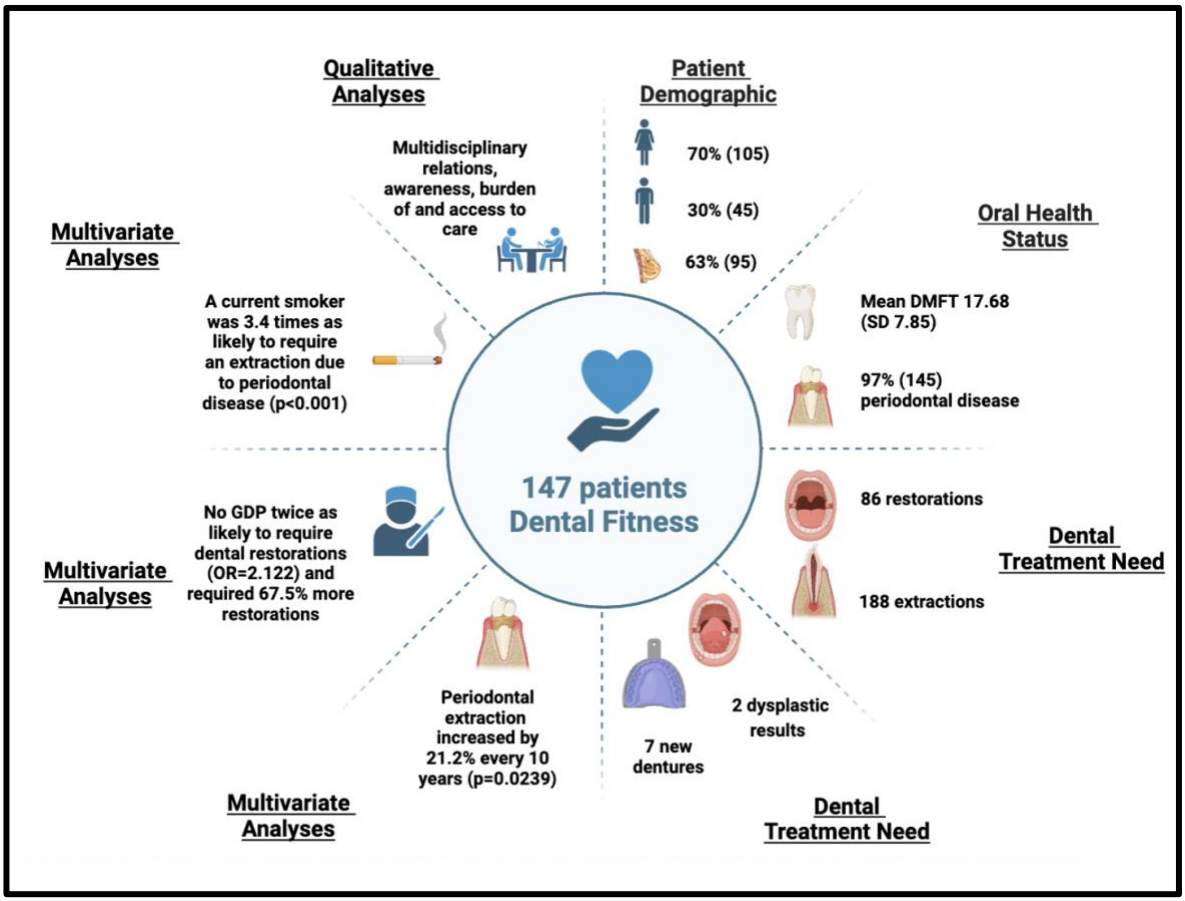


Figure 45 Key Project Findings

Chapter 5

Discussion

5.1 Overview

Research, both from an epidemiological and clinical perspective, has highlighted the critical link between oral health and systemic health. Evidence of association has been established between oral disease and diabetes, renal disease, rheumatoid arthritis and Alzheimer's disease (Kapila, 2021). In spite of this established link between oral disease and systemic wellbeing, oral health is often not seen as a priority during cancer therapy (Hartnett, 2015). This is the first study to explore oral health status and dental health needs of oncology patients planned for BMA therapy in the Republic of Ireland.

5.1.1 Oral health status

The oral health analysis included an assessment of oral health parameters such as periodontal (PSR, AAP/EFP periodontal classification), and hard tissue structures (DMFT). A thorough extraoral and soft tissue intraoral examination concluded the clinical measurements. The standard criteria used for comparison with other studies included research on caries readings (DMFT), periodontal scores (EFP / AAAP) scores and the Scottish Dental Clinical Effectiveness Programme (2011), to assist comparison of similar studies in the literature (R. N. Patel *et al.*, 2016; Botelho *et al.*, 2020).

Soft tissue intraoral structures yielded some interesting results based on a thorough clinical examination, which includes screening for oral cancer. In two cases, speckled mucosal changes, possibly indicative clinically of a premalignant / malignant disorder, proceeded to a biopsy which yielded two intraoral samples from one patient (candidate

54) following histopathology examination revealed mild and moderate dysplasia alongside mild dysplasia of the lower lip for candidate 121. Attendance at a GDP irrespective of planned BMA therapy includes an oral cancer screening and 69.3 (n=104) attend a GDP every 2 years or more, which lies above the recommended frequency of attendance. The relevance of early cancer diagnosis or identification of premalignant clinical disorders/risk factors is of utmost importance, given the high mortality of oral cancer . The NICE guidance for the *suspected cancer: recognition and referral*, most recently updated in October 2023, advocates urgent referral of an erythroleukoplakia and a non-healing ulcer (candidate 54, and 121 respectively) to a specialist secondary care centre for management (*NICE*, 2015). The yearly malignant transformation rate of mild dysplasia (1.7%), and moderate dysplasia (3.57%) coupled with positive risk factors for oral cancer, leave patients with a likelihood of progression to an oral cancer (Iocca *et al.,* 2020). Presentation to a dental setting for routine oral cancer screening is an important aspect of the study irrespective of pre-emptive BMA treatment. Our study highlights the vigilance required to ensure thorough oral examinations and oral cancer screenings are completed for all patients (Iocca *et al.,* 2020).

A Cochrane Systematic Review was published in 2020 assessing recall intervals for oral health in primary care centres in relation to the development of decay, periodontal disease and effects on oral health related quality of life (Fee *et al.*, 2020). The study had high certainty for one of the outcomes that there was little to no difference in oral health related quality of life between 6 months and 24 month recalls. They also found that there was no difference between the groups assessed at 6 months and 24 months regarding percentage of sites with gingival bleeding (high certainty) or prevalence of

moderate-extensive caries between 6 months and 24 months (moderate certainty). Our study highlights the sensitivity of dental attendance and time, which is evident across both restorative and extraction treatment needs for patients. Patients who attended a GDP every 2-4 years required more restorations compared to the regular attenders (every 6-12 months) (ratio of means = 1.675, 95% CI: (1.044, 2.688) and the difference was significant (p = 0.0324). Also, comparing the standard of attending a GDP every 2-4 years to every 6-12 months, there was a 96% chance of requiring a greater number of restorations with a significant value of P=0.0454. The data also demonstrated a higher treatment need for dental extractions in patients that attend their GDP every 2 to 4 years compared to those that attend at least annually (ratio of means = 1.743, 95% CI: (1.138, 2.669) and the difference was significant (p = 0.0107). Our data suggests there is a time sensitive nature of dental reviews and its impact on treatment need (both restorations and extractions). Our data opposes the Cochrane Systematic Review (2020) and the sensitive nature of timely dental reviews (versus Cochrane 6-24 months) however it was noted that our data is not entirely comparable due to the difference in maximum time in both categories; 24 months versus 4 years. The burden of dental treatment needs for this vulnerable oncology cohort is suggestive that at least 6-12 monthly dental reviews can influence dental treatment need and 3-monthly are recommended, being the recommended, optimum timeframe for dental reviews in this cohort (Yarom *et al.*, 2019). Inherent characteristics of our cohort include an aging population and as a consequently possess a potentially higher dental treatment need than that of the general population (Lauritano *et al.*, 2019).

The study also continues to highlight the sensitivity of engaging with a GDP within a recommended, specific timeframe and its impact on treatment need. The statistical

testing for extraction numbers continued to increase as patients attended a GDP less frequently (every 5 years or more) compared to regular attenders, requiring three times more extractions. The impact of preventative dental strategies and its reduction on both treatment following a BMA and reduced likelihood of MORNJ development has been highlighted in the literature in a randomised control trial by Mücke et al (2016) over 6 years in prostate cancer patients receiving zoledronic acid (Mücke *et al.*, 2016). Pre-BMA dental care and 3 monthly dental reviews was associated with a 2.59 relative-risk reduction in MRONJ and a 82% reduction in reported MRONJ cases (Mücke *et al.*, 2016).

Definition of the oral health status of oncology patients requiring a BMA has been sparsely reported in the literature albeit the literature is rife with papers defining the risk of MRONJ and preventative/management therapies for MRONJ (Kuchuk *et al.*, 2013a; Yarom *et al.*, 2019; Ruggiero *et al.*, 2022a). Oral health has been assessed in breast cancer patients specifically related to periodontal health and oral health related quality of life (Taichman et al., 2015; Taichman et al., 2016). Taichman et al. (2015) did not demonstrate any negative oral health effects following breast cancer treatment with regard to gingivitis, periodontitis and poor self-perceived oral health (Taichman et al., 2015; Taichman et al., 2016). Interestingly, 50% (n=76) of our cohort had a presenting complaint and 35.3% (n=53) reported dental neglect as a presenting complaint at the initial appointment. This poor perception of oral health was contrasting to results reported by Taichman et al., (2015) (Taichman, 2015). The oral health status of multiple myeloma patients was assessed predominantly due to the involvement of the oral cavity in initial presentation of multiple myeloma, which was reported in 14.1% of cases (Epstein et al., 1984). There was no statistical difference

noted in DMFT scores for multiple myeloma patients compared to paired controls. This was also true when decayed and missing teeth were compared between both cohorts, concluding the caries history and treatment need of multiple myeloma patients was similar to the control group in this study (Feitosa *et al.*, 2020). Multiple myeloma patients are frequently placed on BMA due to skeletal involvement noted in 85% due to osteolytic lesions (Tanveer *et al.*, no date). Antiresorptive treatment minimises SREs, has an excellent risk-profile for long-term use however subjects patients to the risk of MRONJ (Feitosa *et al.*, 2020). Our study included 7 (4.67%) multiple myeloma patients, where 1 patient (candidate 103) had maxillofacial evidence of multiple myeloma following radiographic examination.

A subsequent study published in 2024 by Olofossen et al. assessed the oral health, and prospective incidence of MRONJ in multiple myeloma patients who had received a bisphosphonate, chemotherapy, corticosteroids and had an invasive dental procedure. They ascertained a combination significant risk when patients had missing teeth ($p<0.01$), moderate – severe periodontitis ($p<0.001$) and dental treatment following administration of a bisphosphonate ($p<0.001$). The incidence of MRONJ was 6.3% of 144 patients (Olofsson *et al.*, 2024). Spontaneous MRONJ development was noted in 3.2% of this cohort (Olofsson *et al.*, 2024). Although studies cannot be compared directly due to the nature and heterogeneity of cohorts, this study highlights aspects of dental health that remain indicative of MRONJ development. However, similar measurements of the oral health status was reported between our cohort and the cohort (Olofsson *et al.*, 2024) where the median number of teeth (24 vs 24 teeth), and median decayed teeth (0 vs 0) were identical however missing teeth was greater for our cohort (8 vs 4) and decayed teeth were less for our cohort compared to the

published data by Olofsson et al (5.5 v 14). The periodontal status of these groups are documented below where similarities are noted in the distribution of mild and severe periodontal disease however our cohort displayed more moderate periodontal disease.

Table 44 Distribution of Periodontal Disease in our Study compared to Olofsson et al. (2024)

Periodontal disease	**Byrne et al. (2024)**		**Olofsson et al. (2024)**	
	Number	%	Number	%
Mild periodontitis	32	21.3%	48	33.3%
Moderate periodontitis	104	69.3%	26	18.1%
Severe periodontitis	11	7.4%	9	6.3%

The oral health status of the study population demonstrated a high prevalence of periodontal disease as seen above (see table 44), a caries risk assessment of predominantly moderate (n=39, 25%) and high (n=102, 68%) caries risk, and mean DMFT scores of total (17.68), decayed (1.16), missing (10.59), and filled (5.9). The European assessment of oral health, Dental Caries in European Adults and Senior Citizens 1996-2016, published in 2018, assessed the oral health habits of European adults (35-44 years) and senior citizens (65-74 years) over a 20 year period (Carvalho and Schiffner, 2018).

Table 45 DMFT Records, Tooth Brushing Regime and Fluoride Toothpaste usage in the Study populations compared to Larger European Cohorts

	EU adults	**EU senior citizens**
Mean DMFT	6.6 – 17.6	14.6 – 25.8
Median DMFT	12.1	22
Tooth brushing twice daily	33-81%	Not recorded
Fluoride tooth paste	33-81%	Not recorded

Filled teeth made-up the majority of DMFT scores in EU adults, except Azerbaijan majority was missing teeth. Missing teeth accounted for the majority of DMFT in senior citizens except for Switzerland and the Netherlands where filled teeth were the largest component. A remark based on studies from European countries (n=23) included the improvement of oral hygiene habits and the expectant impact on DMFT is seen over time, improving in more recent measurements of DMFT across Europe. Examples of improvement in European DMFT scores include a study on caries trends in 35-year-old Norwegians which declined from 14.8 in 1993 to 11.7 in 2003 (Skudutyte-Rysstad and Eriksen, 2007). Also a study from Sweden (1993 and 2003) which assessed DFT scores in 30- and 40-year-olds also declined in mean DFT scores from 11.8 to 7.8 (30 year olds) and from 16.3 to 11.5 (40 year olds). This study also assessed caries experience and DFT scores in 60- and 70-year-olds which decreased from 14.1 and 15.8 (1993) to 12.3 and 15.3 (2003) (Hugoson and Koch, 2008).

These similar trends were ultimately noted in 12 other countries for caries trend in senior citizens, demonstrating a decreasing European trend in caries experience and DMFT scores (Carvalho and Schiffner, 2018). The data presented in this documented reported a 20% reduction in DMFT scores from 1996 to 2016 for adults (35-44 years)

and less marked reduction of 13% for senior citizens (65-74 years) referring to countrywide data (Carvalho and Schiffner, 2018). The mean and median scores of the European DMFT scores may be over-estimated when used as reference points for the oncology cohort in this research project, however a positive finding for patients at risk of MRONJ. A change was also noted from a predominantly based missing teeth to filled teeth, shifting from extraction to restorative based treatments.

Dental decay can be considered a behavioural dependent, non-communicable disease, where regular tooth brushing with fluoride containing toothpaste has been strongly related to lower caries experience (Figuero *et al.*, 2017). Opportunities can be gained by improving oral hygiene habits which is evident in our study population, similar to the European Adult and Senior Citizen statuses. This current review did not comment on the periodontal health of European countries, which is a more accurate predictor of extractions, and MRONJ development in severe periodontal cases (Kwoen *et al.*, 2023). Periodontal involved teeth are more likely to be extracted compared to non-periodontal involved teeth which was noted in 27,168 patients analysed following administration of bisphosphonates for at least 1 year. MRONJ was nearly twice as common in teeth which were periodontally involved (0.58%) compared to non-periodontal involved teeth (0.31%) (Kwoen *et al.*, 2023). This study also indicated some interesting figures regarding an increased risk of MRONJ with dental extractions (hazard ratio = 1.61, 95% confidence interval: 0.74–3.52), periodontal disease without dental extraction also indicated a similar risk (HR = 1.68, 95% CI: 0.86–3.28) of MRONJ incidence. Interestingly, there was a greater increased noted for MRONJ development when both periodontal disease and tooth extraction was present, the HR significantly increased to 2.55 (95% CI: 1.41–4.64)(Kwoen *et al.*, 2023). This study

highlights the importance of including periodontal disease as an independent entity for MRONJ development (oral health status) alongside its implication in dental extractions too (treatment need). These accumulative factors allow us to develop pre-emptive risk factors for MRONJ in this patient cohort.

Our study's data confirmed the impact of periodontal disease on dental extractions and consequently dental treatment needs. Periodontal disease accounted for 64.9% (N=121) of dental extractions and 101 of those extractions were included as a "multiple extraction" case. Patients with periodontal involved teeth required more extractions than single extraction in patients with periodontal disease (single extractions, N=20, 10.6%). Our study's results correspond to the work of Kwoen et al (2022). There was a high treatment need in patients with periodontal disease noted in our study. Moderate and severe periodontal disease included 77.7% of the population in this project. The oral health status of older patients remains poorer than younger cohorts noted in both dental decay and periodontal scores (Carvalho and Schiffner, 2018; Eke, Borgnakke and Genco, 2020). Our multivariate analyses concluded for dental extraction attributed to periodontal disease (n=121) that older patients needed more extractions due to periodontal disease with a ratio of means for a 10-year increase by 21.1% and the difference was significant ($p = 0.0239$). Age-related oral health factors commonly develop poor dexterity, poorer physical and mental states which commonly impacts the standard of oral health seen in this band of the population. Specifically, to the older population in Ireland, the Oral Health and Wellbeing in Older Adults In Ireland (2017) alongside *Health in Ireland, (Key Trends 2022*) echoed the work from the European publication on oral health, *Dental Caries in European Adults and Senior Citizens 1996-2016,* highlighting the poorer oral health noted in the aging

population (Razak *et al.*, 2014; O Connell et al., 2017; May *et al.*, 2022). 18% of Irish adults over 54 years are edentulous, tooth loss increased with age, who reported 40% of those aged 75 years and over having no natural teeth compared to 7% of those aged 54 to 64 years. The Oral Health and Wellbeing in Older Adults In Ireland (2017) report also noted older adults who have lost their teeth are more likely to be current smokers, than those who have retained them and the difference is particularly noted in those aged 54 to 64 years (40% versus 15%) (O Connell et al., 2017). Ireland's aging population is constantly increasing, which most recently noted as a 36% increase in 65 years and older since 2012 to 2022 (May *et al.*, 2022). This is no coincidence that 57.3% (n=86) are 60 years and older. The patient demographic places a majority of the cohort in an aging, older population where oral health status can deteriorate, with increased dental treatment needs (Wu *et al.*, 2014; Dye et al., 2019; May *et al.*, 2022).

5.1.2 Treatment need

The treatment need of the cohort included generic educational and preventative interventions to holistically reduce the risk of future caries experience and periodontal disease. The dental education included information about MRONJ, oral hygiene advice, and attendance with a GDP for continuation of dental care and community integration. Oral health education delivered by dental professionals has the capacity to improve knowledge (Nakre and Harikiran, 2013). However, education also serves a purpose to change attitudes, motivate and change oral hygiene habits (Kay and Locker, 1996; Nakre and Harikiran, 2013). A systematic review by Harikiran et al. (2013), demonstrated some quantitate effects of different forms of educational based

interventions. These effects were assessed clinically regarding gingival health and plaque scores. 90% of the studies assessing plaque score demonstrated a significant improvement (Nakre and Harikiran, 2013). Bleeding on probing scores also reduced from baseline readings by 33.2% (95% < I: 29.1 to 37.3%) and 40.5% (95% < I: 35.9 to 45.8%) following the provision of one versus two oral hygiene education sessions, respectively. This systematic review demonstrates the impact of dental education and in particular improvement in toothbrushing frequency in our cohort. However, oral health education can be of limited value in long term environments if not supported by oral health promotion efforts to reinforce educational benefits. This objective was demonstrated in Glasgow, following oral health education and oral health promotion in school-based environments which reported a 20% reduction in dental decay after a 6-year study. Consistent oral health promotion was a salient feature of this preventative strategy (Blair *et al.*, 2006). Inclusion of patients at risk of MRONJ with a GDP every 3 months remains a valuable, effective preventative asset to patients who require consistent oral health promotion benefits (Mücke *et al.*, 2016).

Preventative treatments were also performed for all patients including the provision of oral hygiene aids, and topical fluoride treatment (5% sodium fluoride 22,600ppm) where necessary. The beneficial effects of fluoride therapy is undisputed (Medjedovic *et al.*, 2015). Two Cochrane systematic reviews advocated the preventative effects of dental decay with the use of fluoride varnish (Marinho *et al.*, 2002; Group, Board (HRB) and Cork (UCC), 2009; Clarkson JE, Marhino VCC, Worthington HC, 2013). There was a reported mean reduction in caries increment of 46% (95% CI, 30–63%; $p<0.0001$) in permanent teeth, based on the results of seven trials involving 2,278 children. This corresponds to a NNT of 3.2 to prevent one DMFS in a population

(Marinho *et al.*, 2002). This data was assessed for children and adolescent and not in the adult population, however the data cannot be disregarded for the adult population (Gkekas *et al.*, 2022).

Restorative treatment was completed on 42 patients, in which 95.3% (n=82) of restorations were placed due to primary carious lesion. There was a minority replaced due to secondary decay (4.5%, n=4). However, dental extractions were also completed due to decay; 11.7%(n=22) as single extraction cases and 23.4% (n=45) as multiple extractions per case. Overall, 86 restorations and 67 extractions were completed due to dental decay. Unmet dental health care is evident for this cohort due to the extent of dental treatment required by this group of oncology patients (Aleksejuniene and Brukiene, 2009). However, addressing a comprehensive, accurate scale to define and compare indices of oral treatment need remain challenging. Dental disease is multifactorial in nature which remains integral to the challenges of standardisation of treatment need indices. The DMFT index was used to measure caries experience in the study which was adapted by the WHO (Organization, 2013) and widely used for over 70 years. It was dual purpose describing the past caries experience and unmet dental decay treatment needs. Difficulties arise when comparing between countries of different socioeconomic standards, such that developing countries and industrialised countries may not be comparable due to access to health services and dental provisions. The DMFT figure does not distinguish between past and current dental decay, nor is the summative value specific enough to define treatment need (Aleksejuniene and Brukiene, 2009). The Significant Caries Index (SiC) was derived from the DMFT and accounts for the mean DMFT highest third of at risk patients (Bratthall, 2000). Its preventative and prognostic values are more sensitive than that

of DMFT and its use is indicated in high risk categories from different countries (Marthaler et al., 2005). Its limitation lies within normative or total treatment burdens (Aleksejuniene and Brukiene, 2009). Simplified quantitative indices such as subjective (self-perceived) or objective (dentist assessed treatment need) can be biased, and the extent of treatment need can be flawed.

5.2 Multivariate analysis – conclusion on each potential explanatory variable

Multivariate analyses can allow us to identify certain characteristics that may highlight patients with added risk factors for dental disease and potential treatment need. We assessed the following characteristics statistically to investigate this aspect of the project. See table 6 for explanatory and comparison characteristics.

5.2.1 Age

In the data presented, age did approach significance with regard the requirement for a dental extraction due to periodontal disease. 84.6% (n=127) of the study population were between ages 50-79 years on initial presentation, which shows that the data for age is skewed towards older adults while younger patients (0-50 years) are sparsely represented. Age is strongly related to incidence rates of cancer, noted predominantly in patients aged 85 to 89, however age specific cancers rates most significantly begin to rise from age 55 to 59 (*Cancer incidence by age*, 2015). Women have a higher incidence of cancer at a younger age and lower at an older age compared to males (*Cancer incidence by age*, 2015). Our data coincides with the literature, in which

females were most commonly diagnosed in their 5th and 6th decade whilst the male population were most commonly diagnosed in their 6th, 7th and 8th decade.

The WHO (2010) categorised the aging population as patients of 60 years and above (*Ageing: Global population,* 2010). Within developed regions of the world, patients over 60 years are expected to increase by 45% in 2050, rising from 287 million in 2013 to 417 million in 2050 (*World Population Prospects, the 2012 Revision*, 2013). According to the United Nations, the most rapidly growing cohort are people aged 80 years and older which is expected to grow by 400% to 400 million by 2050 (*World Economic and Social Survey,* 2007). Ireland is expected to experience the greatest population growth in Europe, with an expected population of 5.5 million in 2035 and 6.5 million in 2060 (Eurostat, 2011).The global trends of increasing aging population are also reported for Ireland, where those aged 65 year and older are expected to increase from 532,000 persons of that age in 2011 to over 1.4 million in 2046 (*Press Release Population and Labour Force Projections 2016-2046 Central Statistics Office*, 2013). The concept of increasing public health demands in the older population is not a new phenomenon and oral health is no exception (Kennedy, C., 2014). European data has highlighted a high burden of dental disease and treatment needs in senior citizens (65 to 74 years)(Carvalho and Schiffner, 2018). The oral health of the aging population has been placed as a priority by the WHO since 2003 (Petersen et al., 2003) which has also been emanated in our National Health Policy, Smile agus Sláinte (Department of Health, 2019). Albeit our data is not completely comparable to aging populations in such documents, we can appreciate that an older population is predominantly represented in our study (84%, n=127). In the data presented, age did approach significance with regard to the requirement for a dental extraction due to

periodontal disease which noted an increase of 21.1% every 10 years. The oral health treatment need in Ireland's aging population (over 65 years) have been a priority for almost the past two decades (Whelton *et al.,* 2007). DMFT was one index used to measure oral health status. The DMFT of Ireland's aging population (DMFT 25.9) compared unfavourable to 35-44 year olds (DMFT 15) (Whelton *et al.,* 2007.) Chronic dental conditions such as periodontal disease are prevalent in aging populations (Tadjoedin *et al.,* 2017). A publication published by Tadjoedin et al. (2017) noted an increasing incidence of chronic periodontal disease with increasing age from 59% of adolescents, 73% adults and 82% (Tadjoedin *et al.,* 2017). Our cohort includes a majority of patients within the aging population. This is a concern when placing such patients on a BMA due to increased treatment needs of the older population, which is globally and nationally increasing with time (Kennedy, C., 2014). Our data coincides with the literature and notes age as a characteristic for increasing extractions due to periodontal disease.

5.2.2 Engagement with a GDP

The data presents a patient's response, whether they had a GDP or not. Accessing dental services is an important aspect of an oncology patient's care prior to and following BMA therapy. Our study aimed to investigate an association between having a GDP or not, and a patient's dental treatment needs. Not having a GDP noted a marginally non-significant association with the requirement of one or more restorations ($p=0.0786$) and an odds ratio which indicated such patients were twice as likely to require dental restorations ($OR=2.122$). A significant association was also

observed between not having a GDP and the number of restorations required; the difference was significant ($p = 0.0324$) and such patients required 67.5% more restorations. An association was not evident for dental extractions and not having a GDP. Oral health is an integral part of general health and accessibility to a GDP is important to ensure dental disease is treated. Prevention of dental disease is also imperative for patients commencing a BMA. Oral disease are the fourth most costly disease to treat in industrialised countries, and preventative strategies can reduce this healthcare burden (Petersen *et al.*, 2005; Kumar, 2019). The 74th World Health Assembly Report (2021) has reinforced the importance of moving away from curative dental approaches as a predominant form of dental care and shifting towards preventative dental strategies and inclusion in primary healthcare systems (World Health Assembly, 2021). The current model of oral health delivery known commonly as the westernised model of modern dentistry does not meet oral health needs globally, which is an unsustainable model to correct rising oral disease figures (Peres *et al.*, 2019). Globally, over 3.5 billion people have unmet dental disease which is chronic, progressive and preventable in nature (Beltrán-Aguilar *et al.*, 2005; Peres *et al.*, 2019). Accessing a GDP is an important aspect of their care and our study has highlighted the influence of not having a GDP on a patient's dental treatment needs. The study highlights an area of vulnerability in an oncology patient's care and greater emphasis is required to ensure patients have a GDP prior to commencing BMA treatment.

5.2.3 Frequency of attendance with a GDP

Attendance is a significant factor affecting the treatment need of extractions in our cohort. The data shows that with increasing infrequency, there is an increasing treatment need for an extraction. Patients that attended on an irregular (every 2-4 years) were 2.5 times and rare (5 years or more) basis were 3.4 times as likely to require an extraction compared to frequent attenders (OR=2.5 and OR=3.407), respectively. A significant association was also seen between the number of extractions and the frequency of attendance. Attendance on an irregular basis required 74.3% more extractions and attendance on a rare basis required 118.3% more extractions compared to frequent attenders. This trend was also significantly associated with a higher requirement of extractions due to periodontal disease for patients attending on an irregular and rare basis (p=0.009 and p=0.001), respectively. We know that periodontal disease is prevalent in Europe (50% of population, 10% severe periodontitis). Our data corresponds to the literature that periodontal disease is prevalent, coincides with an aging population (70-85%) and consequentially places a demand on dental extractions (Tadjoedin *et al.*, 2017; Lauritano *et al.*, 2019). Unfortunately, dental caries also is the highest non-communicable disease worldwide and the European region has the second greatest proportion of tooth loss amongst the six WHO world regions, 25.2% tooth loss in about 88 million people over 25 years, translating to double the figure of the global prevalence (*WHO,* 2019). These figures from 2019 ignited a global announcement in April 2023 identifying key aspects of health care discrepancies and inadequacies (*WHO,* 2019). Albeit, European countries can be considered in the industrialised world, 50% of the European region have major oral disease, which prompted the Global Oral Health Status report, European region

(2023-2030). Affordable, essential oral health care and addressing oral health inequalities were the two critical aims of this report (WHO, 2022). Definition of vulnerable cohorts such as oncology patients on BMA therapy requires oral health policies, to begin to identify these requirement in vulnerable groups of patients. Attendance at a GDP on a regular basis is accountable with a reduced treatment need, which is an important aspect of the prevention of MRONJ, particularly regarding dental extractions.

5.2.4 Smoking status

Interestingly, a current smoker was 3.4 times as likely to require an extraction however no significant association was noted for ex-smokers requiring an extraction compared to never smokers. This finding coincides with reports in the literature which notes the improvement in a patient's periodontal health following cessation of smoking (Alexandridi et al., 2018). Periodontal pocket probing depths and radiographic analysis of bone levels were assessed in two longitudinal studies over 10 and 20 years which noted a 30% reduction in bone loss in ex-smokers compared to current smokers and a significant reduction in periodontal pocket probing depths (Bergström et al., 2000; Thomson *et al.*, 2007). These findings reinforce the importance of smoking cessation for their future oral health. Smoking has deleterious effects on the periodontium (Machuca *et al.*, 2000). The literature has reported a positive association between smoking and the risk of periodontal disease which both affects the incidence and progression of periodontal disease (Leite *et al.*, 2018). Our data demonstrates a significant association between smoking status and extractions due to periodontal

disease; current smokers required 143.2% and 72.3% more extractions due to periodontal disease in current and ex-smokers, respectively. The literature has also shown a higher self-perception of dental care needs in smokers than non-smokers. Our presenting complaints in the smoking cohort (24.6%, n=37), noted dental neglect (38%,N=14) as the most common presenting complaint expressed by the smoking cohort. This correlates to publications in the literature surrounding the self-perception of oral treatment needs in smokers (Dye and Thornton-Evans, 2010).

5.2.5 Cancer diagnosis

We know oncology treatment regimens can vary depending on tumour characteristics and stage, depending on the intensity of BMA therapy and potential concurrent immunosuppressive therapies such as corticosteroids (AlRowis *et al.*, 2022a; Ruggiero *et al.*, 2022a). This concept allowed us to form the basis of cancer diagnosis division into specific exploratory (late stage breast cancer and all other cancers) and reference variables (early breast cancer). The oncology diagnosis did not bear any significance to treatment needs for restorations or the requirement for an extraction however there was a significant relationship between the number of extractions required which was increased for late stage breast cancer (54.4%) compared to early breast cancer. This figure was not quite significant for all other cancers (p=0.0720). Late breast cancer patients displayed a higher treatment need for extractions due to periodontal disease requiring 79.4% more periodontal extractions compared to early stage breast cancer patients. In summary, there wasn't any significant results with respect to dental treatment however quantification of treatment need displayed a

marginally significant result. The literature does not have sufficient data regarding the oral health status and treatment needs of breast cancer patients however one study did assess the impact of breast cancer treatment on post-menopausal breast cancer survivors. Their data demonstrated that the diagnosis and treatment of breast cancer increased the odds of gingivitis, periodontitis or poorer self-perceived oral health (Taichman, Griggs and Inglehart, 2015). This data was taken in conjunction with the 1999-2004 National Health and Nutrition Surveys (Taichman, Griggs and Inglehart, 2015).

5.2.6 Barriers to dental service

A minority of patients reported barriers to dental service (n=19). Barriers did not show any relationship to treatment needs. Our data had relatively few patients that reported barriers to dental services, which could have reduced the power of the statistical comparisons to demonstrate a difference for those that had barriers. The literature in comparison highlights the significance of barriers to oral health care, which are most prevalent in the older population (Awano *et al.*, 2008; Kandelman et al., 2008; Lauritano *et al.*, 2019). Factors that can influence access to dental care include socioeconomic factors, age, finance, physical barrier, comorbidities and geography which are consistently shown throughout Europe (Winkelmann *et al.*, 2022). Barriers to care are significantly prominent in the displaced population including refugees and immigrants (Banihashem Rad *et al.*, 2023).

5.3 Vulnerable cohorts

A growing additional facet of dental oncology is the care of the displaced cancer patient. Based on Data from the United Nations High Commissioner for Refugees (UNHCR), 110 million people are forcibly displaced and 36.4 million refugees world-wide in mid-2023 (*UNHCR*, 2023). Since Russia's military aggression on Ukraine in February 2022, Europe has received the largest influx of people fleeing war since World War II. Oncology services must begin to accept the increased prevalence of refugees and the necessity to facilitate healthcare for this cohort of patients (Ledoux *et al.*, 2018). Ireland remains prominent in the promotion of inclusive policies to facilitate "intercultural healthcare" specifically targeting migrant's health (Ledoux *et al.*, 2018; Villarroel *et al.*, 2019; MacFarlane *et al.*, 2023). Irish society has become increasingly diverse related to immigrants, people seeking asylum and the impact of war in neighbouring continents (*Central Statistics Office*, 2023). Translation, transport, and communication challenges healthcare provision to refugees. In Ireland, major oncology centres have access to two dental hospitals in Dublin and Cork. Relationships and co-located dental-oncology services require the uptake of facilities, finance, structural and organisational initiatives to foster improvements in healthcare (Bledsaw *et al.*, 2023b). However, global studies have highlighted substandard access particularly in mental health and dental care services within migrant populations (Lebano *et al.*, 2020). Oral health tends to be poorer in refugee populations. A study of 12 year old migrants in Austria demonstrated 42% higher rate of decay, and more affected by gingivitis in migrant children compared to children with no migrant background in general (Lebano *et al.*, 2020; Banihashem Rad *et al.*, no date). The pre-existing oral health status and the social upheaval of displacement remain significant

factors for displaced populations (Lebano *et al.*, 2020; MacFarlane *et al.*, 2023). Language barriers significantly impact the quality of care in refugees. Cross-cultural consultations can be hindered by lack of healthcare staff awareness of resources, societal racism, ethnocentrism, engagement of senior HSE and governmental offices and the financial myth of professional interpreting services were shown to hinder service provision (Puthoopparambil, Phelan and MacFarlane, 2021; MacFarlane *et al.*, 2023). Poor service provision and access to adequate dental health care, is largely coupled by a high burden of dental disease and limited access to oral health in their native country (Keboa, Hiles and Macdonald, 2016). Barriers to care have translational consequences for outcomes in oncology care are noted in migrant populations, particularly an earlier age of breast cancer diagnosis, poorer survival in women, variable mortality patterns and differences in treatment modalities (Ikram *et al.*, 2016; von Au *et al.*, 2016; Van Hemelrijck *et al.*, 2020). Migrants' vulnerabilities prevail to poorer psychological and health related quality of life outcomes (Sze *et al.*, 2015). Professional interpreters, funding, research and awareness can facilitate communication and integration of healthcare for a multicultural nation. Our cohort included 5 refugees, each of whom required translational services. The greater extent of patients included 18 patients of non-Irish origin. An interesting remark included the three patients who did not achieve dental fitness due to refusal of dental treatment. Two patients fled from countries of war and were residing in Ireland, and the final patient was a recent refugee due to social unrest in Ukraine. Each of these patients required translational service, nor were they registered with a GDP in Ireland. All three patients refused dental treatment. This subgroup of patients remain vulnerable to accessing dental services, translational services, financial support and service barriers. Perception of cultural sensitivities to reduce the burden and inequalities of oral health

is an important concept cited in the literature (Marcus *et al.,* 2023). Poor English proficiency can influence a multitude of factors such as oral health attitudes, lack of awareness of public health dental programmes, low esteem and self-efficacy to navigates dental systems, traditional home remedies to resolve dental issues and the competing demands of daily living (Marcus *et al.,* 2023). Cultural, psychological, communication, system determinants and affordability pose difficulties for a subgroup of our oncology cohort and this potentially contributed to their unwillingness to proceed with dental treatment prior to BMA therapy (Nam *et al.*, 2016; Tiwari *et al.*, 2018).

5.4 Project outcomes

The project proposes two outcomes including customised referral and discharge forms for the BMA cohort alongside training for health care workers (HCWs) regarding the prescription of BMAs and dental demands of patients within the oncodental interface.

5.4.1 Referral and discharge forms for oncology / community dental integration

The study has added valuable insight into the oral health status and treatment need of a small section of oncology patients in Ireland planned for BMA therapy. Our data has demonstrated key components of a patient's history, social status, past dental experience and clinical findings that heighten their risk of MRONJ development. The data highlights significant information such as age, smoking status, registration with a GDP, frequency of dental visits, stage of cancer and certain barriers to care such as

communication barriers that may infer significance for both oncology and dental teams. The study outcome includes a customised oncology referral sheet for the oncology team and a dental discharge sheet for their community dentist / dental provider following dental fitness prior to BMA treatment. This project would aim to integrate these forms in national cancer frameworks and oral care strategies for cancer patients. The National Cancer Control Programme endorses a baseline assessment form for patients and the section on oral health has been included in appendix F and G. The project wishes to influence the long term care of oncology patients and our data highlights valuable aspects prior to BMA that may be indicative of an increased treatment need. The discharge form aims to encourage integration and cohesion between the interface of oncology and dental specialities.

5.4.2 Education for HCWs

The thematic assessment of the qualitative data highlighted some valuable opinions from patients and dentists. Their views included deficiencies in communication, education and accessible dental services . Educational initiatives were included in this study by visual and verbal instruction via power-point presentation prior to recruitment of patients from oncology clinic. Patients were given written leaflets on MONRJ and verbal instructions surrounding their current and future dental care requirements. The research shows us that patient's awareness of MRONJ following BMA can be poor. Knowledge basis was greater in educated females however awareness levels were recorded at 33.82% (Al Abdullateef and Alhareky, 2020). Similar figures were noted by Bauer et al. (2012) following a questionnaire review of

patients on bisphosphonates in which 32% were aware of MORNJ, 62% received their information from medication packaging and 80% of dental intervention was continued without modification (Bauer *et al.*, 2012). Dental input on the prevention of MRONJ is an integral component of patient care particularly via the implementation of prophylactic dental assessment and enhanced preventative dental intervention (Sim *et al.*, 2015). The impact of dental preventative therapies was shown to effectively reduce the prevalence of MRONJ with an odds ratio of 0.24 in a study by Sim et al. (2015) (Sim *et al.*, 2015). Dental education and oral health promotion encompass preventative strategies. Dental education and knowledge was also shown to reduce the severity of MRONJ treatments in two cohorts who were exposed to a preventative programme or not (La Verde *et al.*, 2008). Dental auxiliaries have been utilised effectively in some European countries to target these patients specifically to MRONJ prevention (Mauceri *et al.*, 2022). Alongside dental auxiliaries, oncology nurses and GMPs are another cohort of HCWs that can implement MRONJ educational strategies (Drudge-Coates *et al.*, 2020). Oral Health Education and Promotion Interventions (OHEPIs) have been extensively documented in the literature (Ghaffari *et al.*, 2018). Educational information can take many forms including verbal instruction, written instruction, video demonstration, physical demonstration, group discussion and campaigns (Nakre and Harikiran, 2013). A systematic review by Nakre et al. (2013) demonstrated that oral health education and promotion displayed positive impacts in change of knowledge and attitude of patients ranging from 7% to 85% improvement (Nakre and Harikiran, 2013). Long term behavioural changes, assessed at 6 years, were only effective when accompanied by continuous oral health promotion, a study by Tai et al. (2001) which demonstrated a 74% immediate improvement in oral hygiene measures following intervention which decreased to 17% at year 6 follow-up (Tai *et*

al., 2001). The systemic review did not comment on the efficacy of mode of delivery of oral health education however frequency and reinforcement were highlighted as the most powerful influencers of changing oral health behaviours (Nakre and Harikiran, 2013). This insight signifies the importance of consistent reinforcement of oral health behaviours by both an educated oncology and dental team to ensure maximum input of preventative measures and appropriate care.

The requirement for educational and informative dental preventative strategies is also echoed by patients at risk of MRONJ. Sturrock et al. (2019) reported on four important categories including improvement in perception of knowledge of BMA prescription, quality of life effects of MRONJ, interprofessional management and service provision addressing dental barriers and vulnerable cohorts (Sturrock *et al.*, 2019). We accept educational intervention stems from poorer quality evidence and longitudinal data is not readily available to accurately assess the impact on MRONJ development specifically (Beth-Tasdogan *et al.*, 2022a). However, robust and improving levels of evidence are available most notably from the United States of America (USA) where a randomised open labelled clinical trial conducted at 269 centres across the USA which reported similar outcomes for skeletal complications at 12 weeks versus 4 weekly zoledronic acid interventions (Himelstein *et al.*, 2017). More importantly, there was a 50% reduction in MRONJ incidence with the lower dosing regime, and prophylactic, preventative dental intervention serves as a positive standing for dental engagement with patients prior to intervention (Himelstein *et al.*, 2017). This study highlighted the benefit of a multidisciplinary management schedule between oncology, dentistry and obligatory dental clearance interventions prior to BMA administration (Himelstein *et al.*, 2017).

Our study proposes the engagement of dental preventative care amongst multiple layers of health care workers. An initiative will include local information based sessions to standardise oral health promotion and education for HCWs in both oncology and dental disciplines ensuring cohesion of care for at risk patients. Addressing the potential of MRONJ prior to BMA administration remains paramount to MRONJ prevention.

5.5 Service provision in Ireland

Ireland does not have a formalised route for oncology patients prior to BMA therapy. Their care is largely patient led and self-reliance is an mitigating factor for their oral health (Bledsaw *et al.,* 2023a). The Royal College of Physicians (2019) document offers a collaborative approach to reduce the risk of MRONJ and integrate dental preventative service into oncology regimes (*UKCB, 2019*). In the United States, the MASCC/ISOO/ASCO Clinical Practice Guideline on Medication-Related Osteonecrosis of the Jaw published in 2019 has also provided clinical guidance for oncologists on best practice to prevent MRONJ in oncology (Yarom *et al.,* 2019). Introduction of a standardised pathway for oncology patients and considerations of real-time challenges is an important step towards the optimal standard of care for this cohort (Kuchuk *et al.,* 2013a). Alternative avenues to combat MRONJ rates includes the 360 degree survey which constitutes a risk reduction pathway between general, community and hospital dental services in the UK (Muthukrishnan *et al.,* 2017). The National Cancer Strategy (2017-2026), published by the National Cancer Control Programme (NCCP) in Ireland, has included a note on the importance of regular oral cancer screenings with a dentist and the inclusion of pre-radiation dental assessments

prior to head and neck radiation. Omissions such as dental care for patients prior to BMA therapy and post treatment dental regimes were not included (*National Cancer Strategy,* 2017). Our National Oral Health Policy, *Smiles agus Sláinte* references the skillset within the workforce to support policy and provide care to vulnerable cohorts and the aging population, however service provision for patients at risk of systemic oncology treatments including BMA treatment are not referenced for inclusion (Department of Health, 2019). The Irish oral healthcare system has wavered in direction as our formalised oral health policy change was set in motion in 2019, *Smile agus Sláinte*, following a 25 year wait (McAuliffe *et al.*, 2022). McAuliffe et al. (2022) accurately defines the lack of national drive and direction to reduce marginalised populations, progress preventative schemes and political intent (McAuliffe *et al.*, 2022). This echoes the epitome of disconnect between oncology and dental specialties for influential intervention (Bledsaw *et al.*, 2023a). The Irish Longitudinal Study on Ageing (TILDA) have highlighted this shift in population following a microsimulation projecting health related outcomes in the older population in Ireland (2018-2040) (May *et al.*, 2022). An increasing aging population, places significant demands on the long-term effects of chronic conditions and aftermath of oncological treatment, including MRONJ. Improvement in adjuvant therapies and increasing life expectancy in BMA cohorts, indicates growing populations of patients at risk of MRONJ (Jung *et al.*, 2022; Byrne *et al.*, 2023). 91% of non-metastatic breast cancer patients survive over 5 years and the 10 year survival is 85% (Patel *et al.*, 2015). Dental preventative strategies play a pivotal role in these populations and their subsequent oral health related quality of life. This population will see an increase in healthcare utilisation, functional limitations and burden of chronic illness impact our service provision in the future (May *et al.*, 2022).

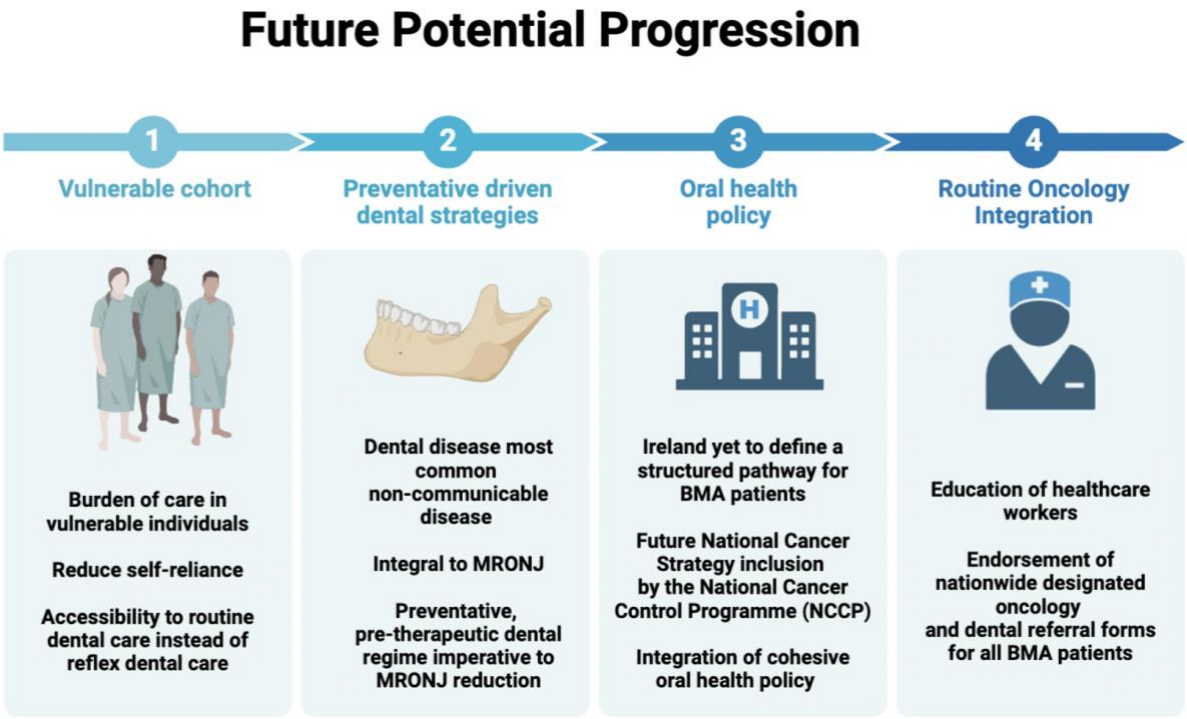


Figure 46 Future Progression for the Onco-Dental Interface

5.6 Study Strengths

Our study was conducted over a 22-month period and clinically assessed (n=150). 147 patients were deemed dentally fit to commence BMA therapy. Recordings of the oral health status and completion of dental treatment was performed by a single operator in a tertiary dental centre (CUDSH). Standard, clinical protocols were used to measure the oral health status. Treatment need was completed as a standard of care for these patients to ensure they were dentally fit prior to a BMA. Patient recruitment was based on a randomised allocation of patients from three main oncology centres in Cork (CUH, SIVUH and MUH). All candidates were anonymised which helped reduce bias for data analysis.

To the authors knowledge, there has been no other study to define the oral health status dental care treatment needs in this defined cohort of cancer patients planned for BMA treatment. Albeit, research has investigated the prevalence of MRONJ development following preventative strategies (Vandone *et al.*, 2012b), assessed heterogenous groups of patients prior to BMA therapy for cost analyses investigation (Chang *et al.*, 2017), and managed reduction risk pathways (Muthukrishnan *et al.*, 2017); definition of an oncology based population's oral health status and dental treatment needs is sparsely studied. We hope to address this gap in knowledge.

5.7 Study limitations

The study only captures a small proportion of patients at a single site in the Republic of Ireland, which creates challenges when applying the results to the wider population.

The Covid-19 pandemic influenced patient's dental engagement prior to recruitment which could influence the data captured regarding frequency of attendance with a dentist and their overall dental treatment needs. The operator (Dr Harriet Byrne) was not calibrated against a gold standard assessor for the detection of caries and periodontal tools used in this study. The Missing element of the DMFT may be flawed due to the exact inability to define whether previous teeth were loss due to decay, periodontal disease or trauma. Dental service limitations were capped to a single 3 hour clinical session which impacted the timeframe from referral to dental assessment. A greater access to facilities and staffing resources would allow patients to be seen more frequently and with less time delays.

Provision of services for the project did not allow the progression of treatment to extend beyond immediate dental fitness. The chronicity of periodontal disease in particular cannot be under-estimated and periodontal treatment needs were effect due to the nature of the study design.

5.8 Future recommendations

5.8.1 Future care of this cohort

The importance of dental care in oncology is paramount for patients on BMAs (Hartnett, 2015). Patients diagnosed with cancer rise from the 5th to the 8th decade and so also does the dental treatment need of the aging population (Kuchuk *et al.*, 2013b; Lauritano *et al.*, 2019; Miglietta *et al.*, 2022). We have identified a vulnerable cohort of cancer patients due to their dental treatment needs and the requirement to commence a BMA. Timely dental treatment is imperative and accessing resources for timely dental care remains challenging. Oral care provision is necessary to achieve these goals which relies heavily on health care policy motivation (McAuliffe *et al.*, 2022). Formalisation of a dental care pathway for oncology patients prior to a BMA on a national oral health level can benefit this group of patients.

Our study has developed a strategic, customised referral and discharge form to ensure appropriate information is recorded by both oncology and dental specialities (see appendices F and G). These forms aims to develop cohesion between BMA prescribers and dentists, which also serve as a template for community integration following administration of a BMA. We would hope endorsement of such documents can be

achieved in the future. Our data has also highlighted from qualitative assessments, that educational and oral health promotion amongst health care workers, predominantly dentists and oncology staff members, remains deficient. We aim to commit to offering educational seminars to provide further education to HCWs as they support patients through their oncology journey.

5.8.2 Future research in this field

Robust data has begun to emerge in the area of MRONJ. Treatment strategies and response to medical and surgical intervention remain heterogenous, however preventative dental strategies remain paramount to the overall management of these patients (Campisi *et al.*, 2011; Yarom *et al.*, 2019; Ruggiero *et al.*, 2022b). The importance of preventative therapies remains paramount and efforts to integrate dental prevention remains the dominant challenge in this aspect of MRONJ.

The literature is rife with revisions of low quality evidence in the field of MRONJ, and similar data has been recycled throughout the literature. In the oncology cohort, often surgical management may not a suitable treatment option for advanced stages of MRONJ in palliative patients; and management relies on antiseptic routines, and medical management of MRONJ. Similar to the RAPTOR trial for patients with osteoradionecrosis, collaboration between multiple centres, can produce high quality, randomised data to treat ORN (*Kanatas,* 2024). MRONJ management would benefit from a similar approach to encourage collaboration and production of high quality evidence. Randomised data has been recently published for the efficacy of teriparatide

in the management of MRONJ, which could benefit from larger scale investigations (Sim *et al.*, 2020; Ferreira *et al.*, 2022).

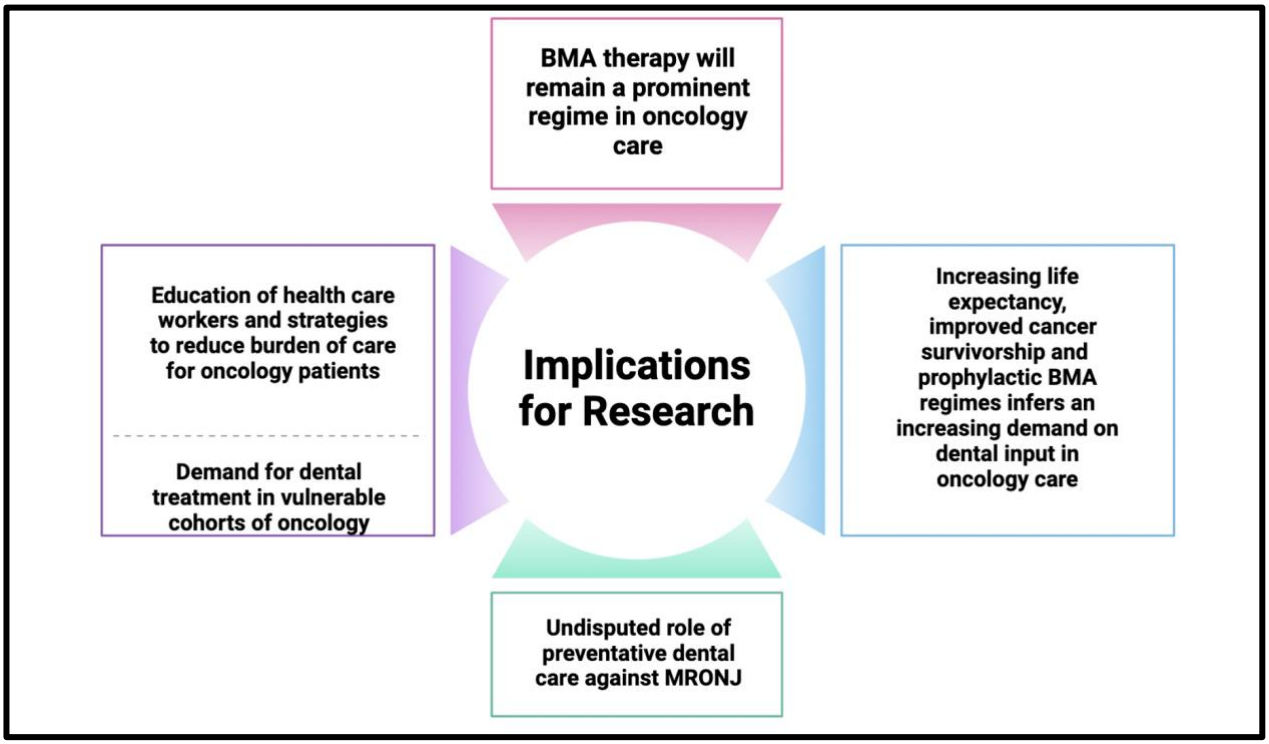


Figure 47 Future Implications Summary

Chapter 6

Conclusions

6.1 Conclusions

This study achieved the aims outlined and uncovered some interesting observations about the oral health status and dental care treatment needs of this oncology cohort.

Patient characteristics such as smoking status, registration with a GDP, and frequency of attendance with a GDP each displayed significant statistical results related to the treatment need of restorations. Smoking status, frequency of attendance with a GDP, age and stage of cancer diagnosis in particular late stage breast cancer each demonstrated statistical significance in relation to dental extractions.

This data allows both the dental and oncology communities to extrapolate important information about their BMA-requiring cohort which may help to guide their management prior to BMA administration. These clinical findings facilitated the development of an evidence-based, customised referral and discharge forms for use amongst the oncodental community. We hope to endorse these forms for future use.

The qualitative aspect of our project weighted heavily on thematic emergence of important dentist and patient derived topics which were grossly centred on patient support pathways, education and multidisciplinary lead care. We know from the literature that patients value these principles of care (Bauer *et al.*, 2012; Sturrock *et al.*, 2019; Al Abdullateef and Alhareky, 2020). We aim to complete educational and training sessions with health care workers in this facet and delivery of information for the introduction of compulsory prophylactic dental intervention and preventative

dental measures prior to administration of a BMA (AlRowis *et al.*, 2022b; Bacci *et al.*, 2022b). This outcome will help reduce the burden of patient-lead oral care in oncology (Bledsaw *et al.*, 2023a) and optimise oral health service for marginalised populations within our healthcare system (Ripamonti *et al.*, 2009; Bramati *et al.*, 2015; Di Fede *et al.*, 2018; Agrasuta *et al.*, 2021; McAuliffe *et al.*, 2022).

Chapter 7

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Chapter 8

Appendices

8.1 Appendices

Appendix A

Oral Health Status and Dental Care Needs of Oncology Patients Receiving Bone Modifying Agents.

Moderator Introduction and Purpose of Group (2 minutes)
Hello. My name is Harriet. I'd like to start off by thanking each of you for taking time to participate today. We'll be here for about forty-five minutes.

The reason we're here today is to gather your opinions about your knowledge of MRONJ and experience of dental care before receiving your intravenous cancer therapy.

I'm going to lead our discussion today. I will be asking you questions and then encouraging and moderating our discussion.

I would like you to know that this focus group will be voice recorded. The identities of all participants will remain confidential, each of you will be allocated a number. The recording allows us to revisit our discussion to ensure we have interpreted your comments correctly and the results can then be used for developing research papers and presentations.

I will cross check the you against the list of patients who consented to participate, and we will be ready to start.

Ground rules (3 minutes)

To allow our conversation to flow more freely, I'd like to go over some ground rules.

1. Only one person speaks at a time. This is doubly important as our goal is to make a written transcript of our conversation today. It is difficult to capture everyone's experience and perspective on our audio recording if there are multiple voices at once
2. Please avoid side conversations.
3. Everyone doesn't have to answer every single question, but I'd like to hear from each of you today as the discussion progresses.
4. This is a confidential discussion in that I will not report your names or who said what to anyone. Names of participants will not even be included in the final report about this meeting. It also means, except for the report that will be written, what is said in this room stays in this room.
5. We stress confidentiality because we want an open discussion. We want all of you to feel free to comment on each other's remarks without fear your comments will be repeated later and possibly taken out of context.
6. There are no "wrong answers," just different opinions. Say what is true for you, even if you're the only one who feels that way. Don't let the group sway you. But if you do change your mind, let me know.
7. Let me know if you need a break. The bathrooms are…
8. Are there any questions?

Introduction of participants (3min)

Before we start, I'd like to know a little about each of you. Please tell me:

1. Your name

Focus Group Questions (35 minutes)

1. ***Personal history and knowledge about dental care***
    i. ***How often do you attend your dentist?***
    ii. ***Is dental care an important factor to you?***
    iii. ***Did you know about the oral complications of your IV cancer therapy?***

2. ***Dental care experience prior to intravenous (IV) cancer therapy***
    i. ***Are you aware you require a pre-therapy dental examination and necessary treatment before your IV cancer therapy?***
        1. ***Who informed you about your basic dental assessment?***
        2. ***How did you access a dental service?***
        3. ***What difficulties did you experience in the process of accessing a dental service? Availability restrictions? Financial restrictions? Travel? Aftercare support?***
        4. ***Did you attend the dental assessment and if not, why so? Travel? Anxiety? Did not feel it was necessary?***

3. ***Basic treatment requirements***
    i. ***What treatments did you receive?***
    ii. ***Satisfaction with treatment***
        1. ***Was it successful?***
        2. ***What do you understand about success of the dental treatment?***
        3. ***Are you aware of classic signs and symptoms of MRONJ?***

4. ***Treatment outcomes***
    i. ***Do you have a long-term review regime in place?***
        1. ***Do you consider regular dental reviews necessary while taking you IV cancer therapy?***
    ii. ***Has the process of attending a dental review prior to IV cancer therapy influence your oral health?***

5. ***Has the process of a dental assessment prior to IV cancer therapy increased your awareness of MRONJ?***

Closing (2 minutes)

Thanks for coming today and talking about your knowledge of MRONJ and experience of pre-therapy dental assessments. Your comments have given us lots of valuable information. I thank you for your time.

Appendix B

Oral Health Status and Dental Care Needs of Oncology Patients Receiving Bone Modifying Agents.

Moderator Introduction and Purpose of Group (2 minutes)
Hello. My name is Harriet. I'd like to start off by thanking each of you for taking time to participate today. We'll be here for about 45 minutes.

The reason we're here today is to gather your opinions about your knowledge of MRONJ and experience of treating this cohort prior to bone modifying agents (BMAs).

I'm going to lead our discussion today. I will be asking you questions and then encouraging and moderating our discussion.

I would like you to know that this focus group will be voice recorded. The identities of all participants will remain confidential, each of you will be allocated a number. The recording allows us to revisit our discussion to ensure we have interpreted your comments correctly and the results can then be used for developing research papers and presentations.

I will cross check the you against the list of patients who consented to participate, and we will be ready to start.

Ground rules (3 minutes)
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10. Please avoid side conversations.

11. Everyone doesn't have to answer every single question, but I'd like to hear from each of you today as the discussion progresses.
12. This is a confidential discussion in that I will not report your names or who said what to anyone. Names of participants will not even be included in the final report about this meeting. It also means, except for the report that will be written, what is said in this room stays in this room.
13. We stress confidentiality because we want an open discussion. We want all of you to feel free to comment on each other's remarks without fear your comments will be repeated later and possibly taken out of context.
14. There are no "wrong answers," just different opinions. Say what is true for you, even if you're the only one who feels that way. Don't let the group sway you. But if you do change your mind, let me know.
15. Let me know if you need a break. The bathrooms are…
16. Are there any questions?

Introduction of participants (3min)

Before we start, I'd like to know a little about each of you. Please tell me:

6. Your name

Focus Group Questions (35 minutes)

1. ***Personal history and knowledge of patients prior to receiving a BMA?***
    i. ***Are you aware of bone modifying agents?***
    ii. ***Have you treated a patient prior to their administration?***
    iii. ***Did you know about the oral complications of BMAs?***

7. ***Dental care experience prior to intravenous (IV) cancer therapy***
    i. ***Are you aware this cohort require a pre-therapy dental examination and basic dental treatment before their IV cancer therapy?***

1. ***Who informed you about their basic dental requirements?***
2. ***How did they access your dental service?***
3. ***What difficulties did you experience while treatment planning and treating this cohort?***
4. ***Did you consider this treatment planning process beyond you scope of capabilities?***
5. ***How do you educate you patient on the oral complications of BMAs?***

8. ***Basic treatment requirements***
    i. ***What treatments did they receive?***
    ii. ***Satisfaction with treatment***
        1. ***Was it successful?***
        2. ***What do you understand about success of the standard dental treatment in this cohort?***
        3. ***Are you aware of the presentation of MRONJ?***
        4. ***What protocol do you adhere to with regard to the management of MRONJ?***

9. ***Treatment outcomes***
    i. ***Do you have a long-term review regime in place for these patients?***
    ii. ***What resources do you recommend to you patients for further education regarding BMAs and oral complications?***

10. ***Has the dental profession provided additional CPD courses or resources to manage this cohort of patients?***

Closing (2 minutes)

Thanks for coming today and talking about your knowledge of MRONJ and experience treating this cohort prior to BMA therapy. Your comments have given us lots of valuable information. I thank you for your time.

Appendix C

Dental Oncology Referral Form

NOTABLE Study dental referral form

Patient details

Name
Date of Birth
Hospital number
Nationality
Phone number
Address

Next of kin

Phone number

Cancer

Consultant _____
Diagnosis _____
Bone Modifying Agent _____
Additional therapy _____
Stage _____
Commencement date _____
Comments _____

Medical Practicioner:

Dental Practitioner:

Pharmacist:

Referrals returned to:
harriet.byrne@ucc.ie

Fax: 021-4901179

Appointment:
Cork Dental Hospital,
Wilton,
Co.Cork.
T12E8YV

Harriet Byrne to contact patient prior to their dental appointment

Appendix D

CONSENT BY SUBJECT FOR PARTICIPATION IN RESEARCH STUDY

<u>Project:</u> Oral Health Status and Dental Care Needs of Oncology Patients receiving Bone Modifying Agents.

Name of Chief Investigator: Dr Richeal Ní Ríordáin

Contact Number for Chief Investigator: 021-4901174

You are being asked to participate in a research study. The doctors at Cork University Dental School and Hospital want to explore your oral health status and treatment needs prior to commencing your intravenous cancer therapy. In order to decide whether or not you want to be a part of this research study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. This consent form gives detailed information about the research study. The Chief Investigator will also discuss the study with you in detail. When you are sure you understand the study and what will be expected of you, you will be asked to sign this form if you wish to participate.

NATURE AND DURATION OF PROCEDURE(S):

Medication-related osteonecrosis of the jaw (MRONJ) is a condition that can happen after you receive medications called bone modifying agents (BMAs). These drugs are used to strengthen your bones. Dental procedures such as an extraction, gum cleaning, implant placement or an ill-fitting denture lead to the development of MRONJ. The condition can also spontaneously occur following BMA therapy. MRONJ can be difficult to treat. The standard of care for every patient receiving BMAs is to try

prevent the development of MRONJ. A standard dental examination with appropriate dental treatment, before starting the BMA therapy, can help prevent MRONJ. As an aspect of your preparation prior to BMA therapy, every patient should have a dental assessment by their dentist. This also allows a dentist to carry out any necessary dental treatments before you start your BMA therapy and to improve your oral health status. This study will perform the basic dental examination and basic dental treatment where appropriate.

POTENTIAL RISKS AND BENEFITS:

We do not foresee any risks in participating in this study. There is no intervention in this study and therefore no side effects are expected. We hope to explore the oral health status of patients receiving a BMA, and to treat their basic oral health treatment requirements. Developing this understanding can help us to develop better long-term treatment strategies.

POSSIBLE ALTERNATIVES:

You may choose not to participate in this study. Participation is entirely voluntary.

AGREEMENT TO CONSENT

The research project and the treatment procedures associated with it have been fully explained to me. All experimental procedures have been identified and no guarantee has been given about the possible results. I have had the opportunity to ask questions concerning all aspects of the project and any procedures involved. I am aware that participation is voluntary and that I may withdraw my consent at any time. I am aware that my decision not to participate or to withdraw will not restrict my access to health care services normally available to me. Confidentiality of records concerning my involvement in this project will be maintained in an appropriate manner. When required by law, the records of this research may be reviewed by government agencies and sponsors of the research.

I understand that the sponsors and investigators have such insurance as is required by law in the event of injury resulting from this research.

I, the undersigned, hereby consent to participate as a subject in the above described project conducted at Cork University Dental School and Hospital. I have received a copy of this consent form for my records. I understand that if I have any questions concerning this research, I can contact the Chief Investigator listed above. I understand that the study has been approved by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC) and if I have further queries concerning my rights in connection with the research, I can contact CREC at Lancaster Hall, 6 Little Hanover Street, Cork, 021 4901901 or email crec@ucc.ie.

Statement of consent	**Yes**	**No**
I have read and understand the study		
I agree to participate in this research		
I understand that all medical information pertaining to me will be protected by the principles of confidentiality and both National and EU Data Protection Legislation.		
I agree to the storage of my personal information (**excluding my name or my address)** on computers of Cork University Dental School and Hospital, for a period of 10 years, as per UCC policy, after the end of the study.		

Chief Investigator Signature: _____

Signature of Study Participant: _____

Witness Signature (if applicable): _____

Date: _____

Appendix E

Data Collection Sheet

Data Collection Sheet **NOTABLE study**

Name
Date of Birth
Gender

Nationality
Martial status
Address

General Practicioner

Dental Practitioner

Medical History

Medications

Surgeries
Allergies

Cancer
Diagnosis
BMA
Additional therapy
Stage
Commencement date
Duration

Social History
Smoking
Alcohol
Recreational drugs
Occupation
Residence

Dental History
Brushing regime
Interdental aids
Sources of fluoride
Dental attender
Hygiene attender
Removable prosthesis
Implants
Perio treatment
Caries risk assessment

Low	
Moderate	
High	

Data Collection Sheet **NOTABLE study**

Clinical Exam

Extraoral Tissues

Intraoral Soft Tissues

Prosthesis

Hard tissues

DMFT

DMFT

Periodontal tissues

Mobility
PPD

PPD
Mobility

BPE		

Plaque Index	
DRI	

Radiograph	

Data Collection Sheet **NOTABLE study**

Diagnosis

Soft tissues	
Hard tissues	
Periodontal tissues	

Treatment Plan		**Completion**
Education		
Prevention		
Basic Dental Care		
Post Operative Leaflet		
Review Date		

Clinician	
Date	

Appendix F

Dental oncology referral form

Dental Oncology Referral Form

CUH/UCC CANCER CENTRE

Patient details
Name:
Date of Birth:

Contact
Phone Number:
Address:

Next of kin
Phone number:

Translational services required:
Yes ☐ No ☐
Language: _____

Oncology
Cancer diagnosis:
_____
Stage _____

Prior Bone Modifying Agent (BMA):
Yes ☐ No ☐
Type _____

Intended start date for BMA therapy:
_____

Intended Bone Modifying Agent:
Yes ☐ No ☐
Type _____

Intent of BMA therapy:
_____

Intended duration of chemotherapy:
_____

Chemotherapy start date:
_____

Smoking: _____
Pack years: _____

Anticoagulants:
_____

Antibiotic prophylaxis required:
Yes ☐ No ☐

Current Medications:
_____
_____
_____
_____

Allergies:
_____

Dental Practitioner:
_____

Medical Practicioner:
_____

Frequency of attendance:
≤ once yearly ☐ ≥ once yearly ☐

Pharmacy:
_____

Referring Consultant:
_____

Contact details:
_____

Signature:
_____

Appendix G

Dental oncology discharge form

Dental Oncology Discharge Form

CUH/UCC CANCER CENTRE

Patient details
Name:
Date of Birth:

Contact
Phone Number:
Address:

Next of kin
Phone number:

Translational services
Yes ☐ No ☐
Language: _____

Dental Practitioner:

_____

Next dental appointment:

_____

Periodontal status (PSR):

Commence Bone Modifying Agent (BMA):
Yes ☐
No ☐
When _____

Caries Risk Assessment
Low ☐
Moderate ☐
High ☐

Denture
Yes ☐
No ☐
Adequate fit _____

Dental treatment comments:

_____

Completed dental treatment:

_____

Current medications:

_____

Smoking: _____
Pack years: _____

Oncology follow-up:

_____

Teeth under review:

_____

BMA interval:

_____

Community-based dental follow-up:

_____

Oncology Consultant:

_____

Signature:

_____