The dentist's role within the multi-disciplinary team maintaining quality of life for oral cancer patients in light of recent advances in radiotherapy

Précis: Multidisciplinary care of the oral cancer patient, including the role of the general dental practitioner in maintaining the patient's oral health post radiotherapy.

Abstract: Every year in Ireland over 400 people are diagnosed with head and neck cancer. Oral cancer, a specific type of head and neck cancer, is usually treated with surgery and often requires radiotherapy (RT). However, side effects of RT treatment, which include mucositis, xerostomia, radiation caries, trismus and osteoradionecrosis, can seriously compromise a patient's quality of life. Treatment for oral cancer patients is managed in a multi-disciplinary team. General dental practitioners (GDPs), consultant/specialist dentists and oral-maxillofacial surgeons play an important role in these patients' care.

Recent advances in the delivery of RT have not only improved loco-regional control and survival rates, but have also reduced the incidence and severity of RT-associated side effects; however, no mode of RT delivery has successfully eliminated side effects. The role of dentists is essential in maintaining oral health and all patients should be dentally screened prior to commencing RT.

Recent reports have attempted to standardise the quality of care for the oral cancer patient and have highlighted the significance of the role of the GDP. Despite the advancements in RT delivery, the dental team is still faced with a number of challenges, including the high number of patients lost to follow-up dental care, lack of an effective treatment for xerostomia, poor patient compliance, and a lack of standardised guidelines and funding.

Addressing these challenges will involve increased communication between all members of the multidisciplinary team and increased involvement of the GDP, thereby ensuring that dental care continues to evolve concurrently with new methods of RT delivery.

Sarah Brody
BDentSc BA BE PhD[1]

Osama Omer
BDS(Stat) MSc PhD FDS RCSI, FFD RCSI[1]

Jacinta McLoughlin
BDentSc MDS FDS FFD[1]

Leo Stassen
FRCS FDSRCS MA FTCD
FFSEM(UK) FFD RCSI[1,2]

1. Dublin Dental University Hospital, Lincoln Place, Dublin 2

2. St James's Hospital, James's Street, Dublin 8

Address for correspondence:
Prof. Leo Stassen
Oral and Maxillofacial Dept
Dublin Dental University Hospital
Lincoln Place
Dublin 2
T: 01-612 7200
F: 01-612 7296
E: stassenl@tcd.ie

Journal of the Irish Dental Association 2013; 59 (3): 137-146.

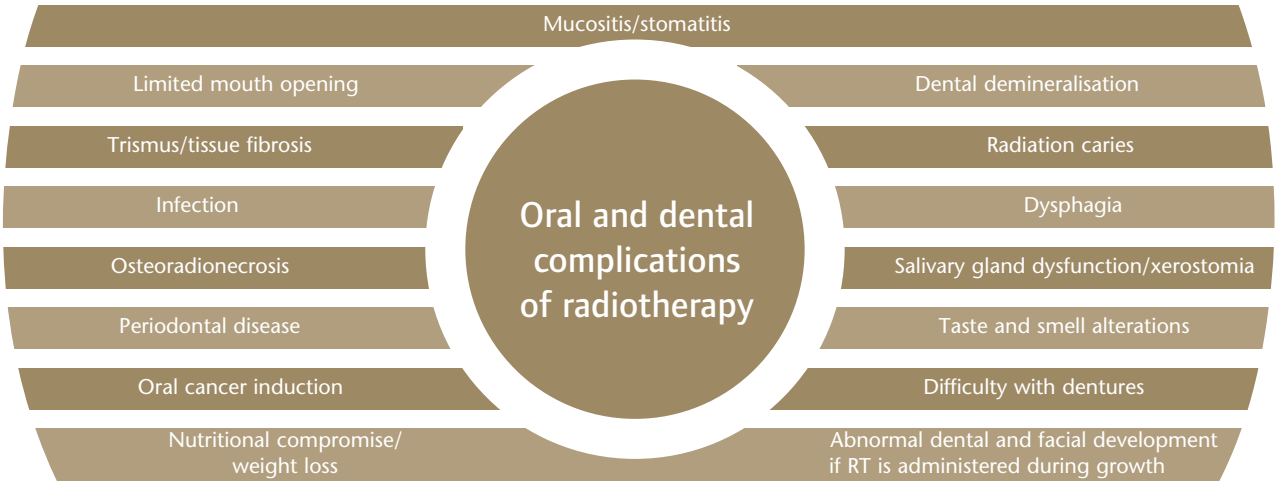

FIGURE 1: Oral and dental complications of radiotherapy (adapted from MacCarthy et al.*, 2005).*[5]

Introduction

Every year in Ireland more than 400 people are diagnosed with head and neck cancer.[1] The term 'intra-oral cancer' or 'oral cavity cancer' refers to particular forms of head and neck cancer, specifically those classified by the International Classification of Disease–O2 classification C01-C06.[2] Radiotherapy (RT) is used to treat intra-oral cancers as a primary treatment modality or as an adjuvant treatment pre or post surgery.[3,4] It is the ultimate aim of the RT team to deliver sufficient RT to control the tumour, while sparing as much normal healthy tissue from irradiation as possible.[3] Irradiation of susceptible tissues, including the mucosal lining of the mouth, nose and aero-digestive tract, the salivary glands and pharyngeal constrictor muscles, causes acute and late side effects (**Figures 1** and **2**).[3] Acute side effects, occurring within 90 days of treatment, include mucositis, trismus, infection and dysphagia. Late side effects include osteoradionecrosis, radiation caries and periodontal disease.

TABLE 1: The Radiation Therapy Oncology Group acute radiation morbidity scoring criteria.[27]

Mucous membranes (mucositis)		Salivary gland (salivary hypofunction/xerostomia)
Grade 0	No change over baseline	No change over baseline
Grade 1	Mild pain, may require analgesia	Mild mouth dryness, slightly thickened saliva, slightly altered taste, but changes are not reflected by altered feeding behaviour (e.g., increased use of liquids with meals)
Grade 2	Patchy mucositis that may produce serosanguinous discharge and/or moderate pain requiring analgesics	Moderate to complete dryness, thick, sticky saliva and markedly altered taste.
Grade 3	Confluent fibrinous mucositis that may include severe pain requiring narcotics	—
Grade 4	Ulceration, haemorrhage, necrosis	Acute salivary gland necrosis

Dental management of the oral cancer patient is multidisciplinary and includes oral-maxillofacial surgeons and specialist/consultant dentists who liaise with general dental practitioners (GDPs) and auxiliary dental team members (**Figure 3**). Dental management should begin pre treatment and continue during and after treatment.[6-8] In recent years, significant advancements have been made in the delivery of RT, particularly in the area of sparing tissues surrounding the tumour from radiation. Some of the more significant advances in RT and their effects on the dental care of patients are outlined in this paper.

Oral and dental complications of radiotherapy

Mucositis

Mucositis can range in severity from areas of erythema to ulcers exhibiting necrosis and bleeding.[9,10] It is a serious complication of radiotherapy occurring in almost 100% of irradiated patients.[9,11] The Radiation Therapy Oncology Group (RTOG) scale is often used to grade mucositis (**Table 1**). Mucositis causes pain, which affects and is aggravated by swallowing. This leads to reduced food intake, weight loss and, in severe cases, can necessitate nasogastric or percutaneous endoscopic gastrostomy (PEG) feeding and interruptions to RT treatment plans.[11-14] Areas that readily develop mucositis include the soft palate, tonsillar pillars, buccal mucosa, lateral border of the

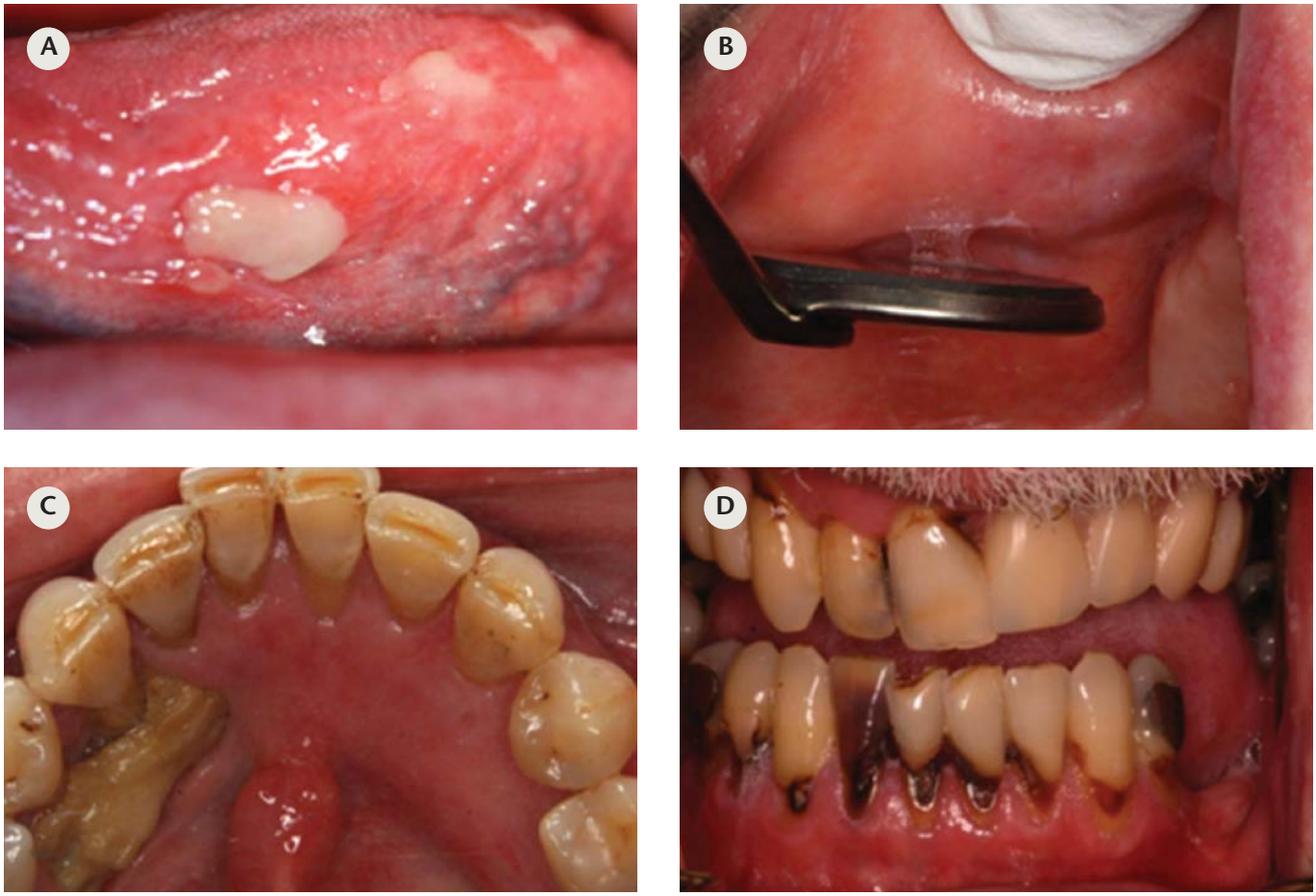

FIGURE 2: Side effects of radiotherapy, including mucositis (a), dry mouth (b), osteoradionecrosis (c) and radiation caries (d).

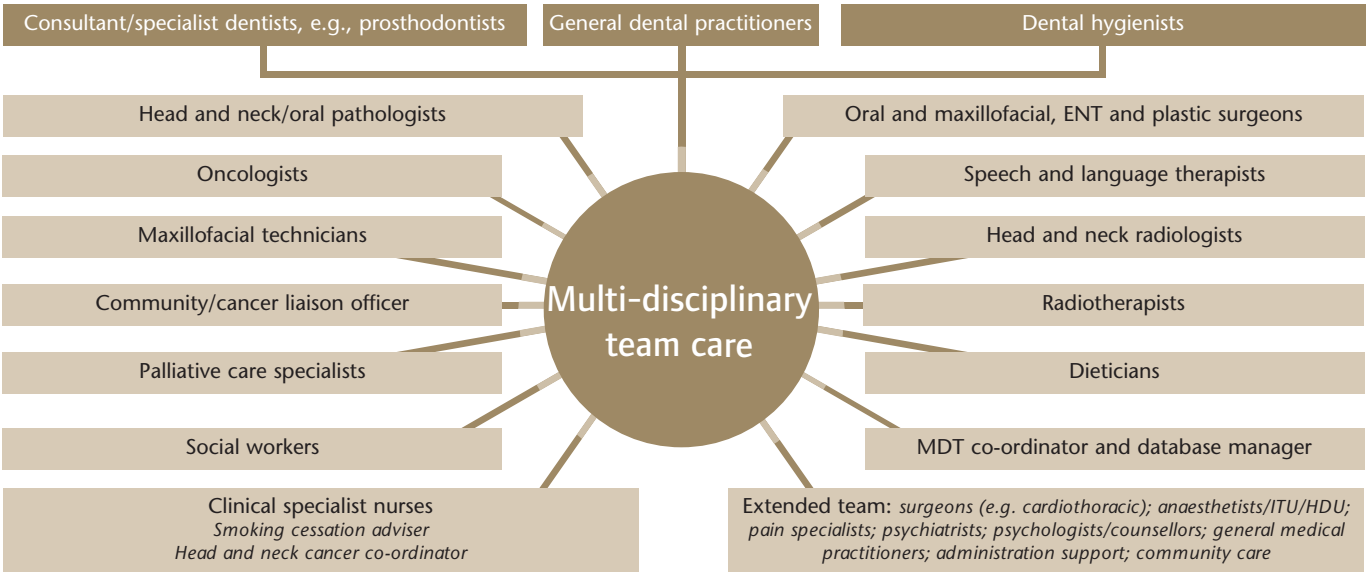

FIGURE 3: Care of the oral cancer patient is multidisciplinary.

tongue, pharyngeal walls and portions of the larynx.[15] It is estimated that 9-19% of RT interruptions are due to severe mucositis.[12] Mucositis commonly remains at peak levels for two weeks after RT; however, in some patients severe mucositis may persist for five to seven weeks.[16]

Xerostomia and xerostomia-related side effects

Xerostomia is the most frequent complaint following RT and its sequelae include: caries; infection; impaired masticatory function; nutritional deficiency; challenges with prosthetic rehabilitation; difficulty with speech; and, loss of taste.[6,8,17-21] Xerostomia may begin after the first week of RT.[8]

Persistent xerostomia can significantly impinge on the quality of life and psychological well-being of the RT patient.[21] Serous acini of the parotid gland are particularly sensitive to radiation.[22] The usual dose for oral cancer treatment is 60-70Gy delivered over six to seven weeks.[23] The mean dose of RT leading to permanent impairment of the parotid is 24Gy for unstimulated flow and 26Gy for stimulated salivary flow.[17] However, when parotid sparing techniques are employed and the dose to the sub-mandibular gland is below 39Gy xerostomia rarely occurs.[24,25] In some cases gland function can be recovered, particularly where only one parotid gland has been fully irradiated.[8,17] However, long-term retrospective analysis has shown that 65% of patients experience moderate to severe xerostomia, which requires support, following RT.[26] The RTOG scale is also used to grade xerostomia (**Table 1**).

Other oral side effects of RT

Other serious side effects of RT include osteoradionecrosis (ORN),[8] candidal infection,[28,29] periodontal disease[5] and muscle fibrosis[30] (**Figures 1** and **2**). The pathogenesis of ORN is not fully understood, although it is thought to occur as a result of irreversible damage to bone vascularisation and impairment of bone remodelling.[8] ORN more commonly affects mandibular bone[8] and can range from small asymptomatic bone exposures that remain stable or heal with conservative management, to severe necrosis requiring surgical intervention and reconstruction.[31]

Advancements in the delivery of radiotherapy

Advancements in radiotherapy generation

When initial studies on the delivery of RT to treat head and neck cancers began in 1896, neither the quantity nor the quality of radiation could be measured, and side effects included burning of the skin leading to necrosis and sloughing.[32] During the 1950s, cobalt-60 became a widely used source of RT. However, compared to modern RT techniques, cobalt-60 emits relatively low-energy photons so ionising radiation is deposited superficially, causing increased mucosal and cutaneous toxicity. Its use is now limited to palliative care and treatment of cancers in the developing world.[23] The development of linear accelerators to generate RT has facilitated increased tissue penetration and tissue sparing.[23] Using linear accelerator-derived RT, multi-leaf collimators and data derived from computed tomography (CT) scans, the RT beam may be shaped to match that of the tumours; this technique is known as three-dimensional conformal RT (CRT). Intensity-modulated RT (IMRT), a further technological advancement, allows the creation of dose gradients across the beam and the delivery of different doses to different targets simultaneously, further tailoring the delivery of RT to the specific tumour size and sparing surrounding tissues.[33] IMRT may allow further tissue sparing, leading to a reduction in RT-induced side effects.

However, studies comparing IMRT and CRT have shown mixed results. Chen *et al.* (2009)[34] studied 49 patients with oral cancer and found no significant difference in acute toxicity (mucositis) between patients treated with CRT and IMRT. Late toxicity could only be measured in 30 of the patients, and while it was shown that patients treated with IMRT had significantly less moderate to severe xerostomia and dysphagia, 100% of patients experienced some degree of both xerostomia and dysphagia. Patients in both groups experienced fibrosis and trismus, but the sample size was too small to derive statistical significance. In a similar study, Chao *et al.* (2001) showed that patients treated with IMRT had higher rates of stimulated salivary flow than those treated with CRT.[21] However, follow-up times (six months) were short; recovery of the glands can continue for up to 12 months post RT.[8]

Brachytherapy, a method of RT delivery whereby the radioactive source is placed inside or in close proximity to the area being treated, has been investigated for treatment of oral cancers; however, its use is limited to patients presenting with early T1 and T2 cancers.[23,35]

Advancements in radiotherapy treatment protocols and imaging techniques

Mean dose to the parotid gland is the best predictor of function following RT[36,37] and RT techniques aimed at sparing the parotid glands include inverse planning RT,[38] intra-operative RT,[39] RT boost techniques[33] and ipsilateral RT.[18,40,41] Ipsilateral delivery of RT has previously shown some success in the treatment of tonsilar and oropharyngeal cancers.[42,43] Vergeer *et al.* (2010) investigated ipsilateral RT in the treatment of well lateralised oral cancers.[18] Promisingly, only 5% of patients had grade 2 or greater xerostomia (RTOG scale) at two to three years post treatment. However, ipsilateral delivery is only suitable for well lateralised early stage cases where the risk of contralateral node metastasis is low.[40] In Vergeer's study 50% of the oral cancer patients in the study had cancer of the gingivae, which is not representative of the usual distribution of oral cancers.

Inverse planning and RT boost techniques are alternative RT delivery techniques, which aim to spare radiosensitive tissues by delivering higher doses of radiation to the tumour site and conventional fractions to secondary sites.[33] Neither technique has been successful at eliminating RT-associated toxicities. Butler *et al.* (1999) investigated simultaneous modulated accelerated RT boost: 80% of patients reported grade 3 mucositis (RTOG scale) and 45% had grade 2 or higher xerostomia.[33] Parliament *et al.* (2004) showed more promising results using inverse planning; however, 80% of patients in the study were suitable for bilateral parotid sparing.[38] Intra-operative RT facilitates treatment of the margins of tumours at the time of excision;

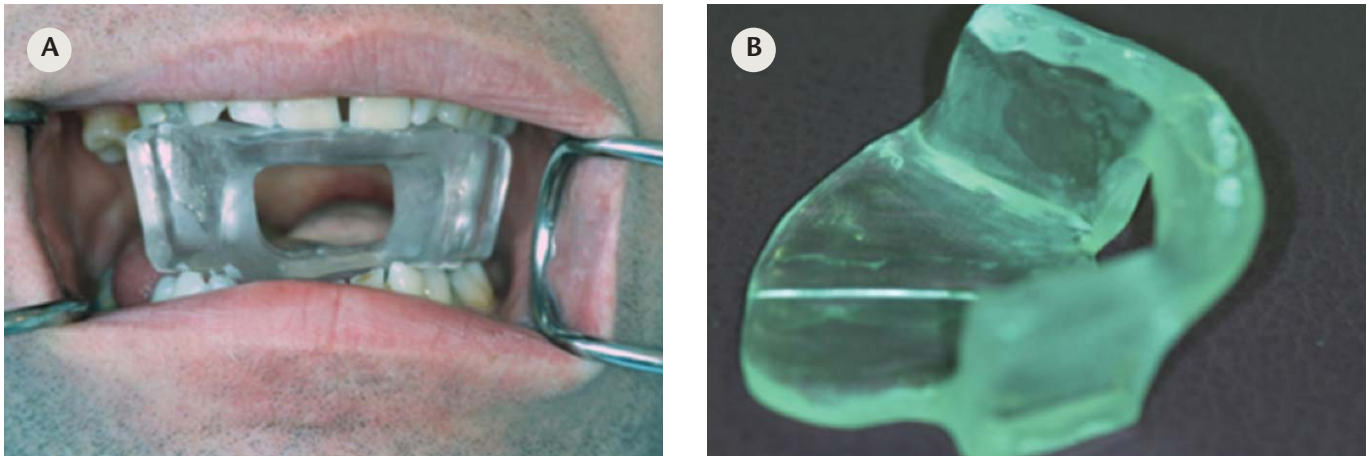

FIGURE 4: Pre radiation therapy radiation, a stent may be made.

however, a high-dose single fraction delivered to normal tissues creates a high risk of late complications and surgery must take place in a dedicated RT suite.[39]

As techniques for the generation and delivery of RT have advanced, so too have the techniques available for imaging the tumour tissues prior to and during RT.[44] Sharp dose gradients used with IMRT require accurate tumour imaging.[44] CT is the standard imaging modality used in RT treatment planning. However, when used in conjunction with magnetic resonance imaging (MRI), detailed definition of soft tissues, representing microscopic tumour extension, can be generated, and artefacts (e.g., amalgam) cause less interference.[23] Recently, the use of positron emission tomography (PET) has made staging and subsequent follow-up more accurate and facilitates improved detection of occult contra-lateral lymph node metastases.[40] In the future more radio-resistant hypoxic areas of tumours could be identified by PET imaging and targeted with higher doses of radiation; however, investigations regarding acute toxicity would also be required.[3]

Deriving meaningful results from the many RT delivery studies is difficult due to insufficient follow-up times,[45] lack of placebo or blinded assessment,[4,46] failure/inability to take baseline measurements[40,47] and small study populations.[11,48] Few studies are limited to oral cancers and therefore results presented are not specific to oral cancer.[49] In addition to the adjunctive treatment under investigation, subjects are often given concomitant chemotherapy; however, effects of how this additional variable may influence study outcomes are rarely considered.[28,38,50]

A wide range of grading schemes is used, in particular to grade quality of life (QoL) and xerostomia.[22,38,45,51] Graff *et al.* (2007) reported higher QoL scores for patients treated with IMRT; however, a statistically significant number of patients treated with CRT were unemployed and a higher number of CRT patients had co-morbidities and lymphatic involvement.[51] Henson *et al.*[52] (2001) and Parliament *et al.*[38] (2004) used different questionnaire instruments to assess patient-reported xerostomia. In contrast to the results of Parliament *et al.*, Henson *et al.* found that patients did not re-establish pre-treatment saliva levels, raising the question of whether Henson's questionnaire showed greater responsiveness or whether subjects in Parliament's study had, on average, better salivary function preservation.

Correlations between salivary flow measurements and patient-reported xerostomia are often weak. Cerezo *et al.* (2009) using the CTCAE (Common Terminology Criteria for Adverse Events) tool for measuring xerostomia, found that subjective measurements tend to underestimate salivary flow.[40] Jensen *et al.*[53] (2007) also found little correlation between patient-assessed symptoms according to the EORTC (European Organisation for Research and Treatment of Cancer) questionnaires (C30 and H&N35) and objective salivary flow measurements. Eisbruch *et al.*[24] (2001) described a low correlation between symptoms and salivary measurements, and concluded that both subjective questionnaires and measurement of the saliva should be included in xerostomia evaluation. The main objective of minimising side effects is to improve QoL; therefore, in clinical practice subjective symptoms may be more relevant.[40]

New methods of RT delivery, volumetric intensity modulated arc therapy[54,55] and particle therapy,[56,57] aim to further minimise side effects; however, it is anticipated that the dentist's role will remain critical and that the field of dental oncology will continue to gain more recognition.

Adjunctive treatments used in the delivery of radiotherapy

To minimise side effects, many research groups have investigated the administration of adjunctive therapies concomitantly with RT. Such therapies include laser therapy,[11] anti-fungals,[28,48] pilocarpine,[22] zinc supplementation,[58] amifostine[4,46] and chemotherapeutic agents.[47,49] Surgical repositioning of the sub-mandibular gland has also been investigated, although not in the treatment of oral cancer patients.[59-61] Some success has been shown by the use of adjunctive therapies. Patients on amifostine showed significantly less grade 2 or higher xerostomia and higher unstimulated salivary flow rates.[46] The

administration of antifungals has been shown to significantly reduce the severity of mucositis and the number of interruptions to the delivery of RT.[28] However, to date, no adjunctive treatment has successfully managed to eliminate the side effects of xerostomia, mucositis and ORN.

Dental management of patients receiving radiotherapy

Despite the many advances in the delivery of RT, side effects remain unavoidable, particularly in patients who continue to smoke and/or consume alcohol, and in patients who require concomitant chemotherapy and RT delivery to nodal sites.[62] Fundamental dental care of oral cancer patients has not changed significantly.[63] Thorough oral hygiene (OH) practice, regular fluoride use, conservative treatment plans and management of xerostomia remain the cornerstones of treatment. A flow chart outlining ideal management of the dental patient is shown in **Figure 5**. Reports published by the National Institute for Clinical Excellence (NICE) (2004) and the Scottish Intercollegiate Guidelines Network (SIGN) (2006) have emphasised the importance of the dentist within the multidisciplinary team (MDT) and have recommended roles for specific members of the dental team.[64,65] For example, the NICE report suggests that although specialist dentists may form part of the MDT, long-term dental care should be provided by the primary care dental team.[64] Recent changes in dental management are mainly focused on standardisation of dental care, and defining roles and responsibilities within the dental team.

Dental management pre RT

The most important risk factors for complications following RT for oral cancer are pre-existing oral and dental disease, and poor oral care during and after cancer therapy.[7] The pre-RT dental visit therefore remains critical; patients are more likely to have their teeth now than in the past[66] and studies have shown that between 58% and 97% of patients examined prior to RT needed immediate dental care.[67-69] Treatment must be carried out promptly to maximise healing time and 'ideal' treatment plans often need to be adapted.[7] Pre-RT patients must be educated regarding the side effects of RT; trays are made for delivery of fluoride and/or chlorhexidine, and the importance of meticulous OH and long-term regular dental visits is emphasised (**Figures 4** and **5**).

Patient assessment requires decision making and clinical skills, and is best carried out by experienced dentists who can design treatment plans using information provided by other members of the MDT, e.g., tumour size and location, radiation dose and field of therapy.[6] Such information may influence the decision to extract teeth and the design of radiation stents.

Radiation stents are custom-made devices that displace or shield tissues, and which are used to position patients in repeatable positions, increasing the consistency of RT delivery to the tumour site (**Figure 4**).[5,70] The stents are usually fabricated by the dental team, and while they do not prevent RT-related side effects, they can reduce the incidence and severity of mucositis and xerostomia.[5,45] Intra-oral lead shields, used in the treatment of lip cancers, and positioning masks, for patient immobilisation during RT delivery, are also used as aids for the protection of healthy tissues.[5,38,71]

A current lack of evidence-based clinical guidelines means that decision making regarding extractions relies heavily on the clinician's experience.[72] Bruins *et al.* (1999) surveyed hospital-based dentists and oral-maxillofacial surgeons and found a high level of similarity in their decisions on which teeth to extract, despite the lack of guidelines,[72] contrary to the findings of Hong *et al.*[73] (2010). However, there is no evidence for prophylactic dental clearance before RT.[45,66] In addition to design and fabrication of radiation stents, consultant/specialist maxillofacial prosthodontists are often required to liaise with surgeons in planning dento-facial prosthesis.[8]

Dental management during RT

Treatments available for the management of mucositis are limited. Current management of mucositis is mainly palliative; however, research and development of targeted therapeutic interventions is ongoing.[62] In mild cases some relief is provided by mucosal coating solutions and anaesthetic agents such as lidocaine lollipops and benzydiamine hydrochloride rinses. More severe cases can be managed with analgesics and systemic antifungals if there is a risk of candidiasis.[8] Patients should be advised to use a soft toothbrush, gauze or mouth sponges, and chlorhexidine mouth rinses, and to leave dentures out. Jaw stretching exercises should also be encouraged during RT to maintain maximal mouth opening and prevent muscle fibrosis.[74] Routine dental treatment should be postponed until after RT, and patients requiring emergency dental treatment during RT should be managed in specialist centres.

Dental management post RT

Following RT oral cancer patients remain at high risk of caries, oral infection and oral functional impairment, which can seriously compromise QoL and necessitate life-long regular prophylaxis.[75] If complex restorative work, including intermediate and definitive prosthesis, are required after surgery, care should continue with a consultant/specialist maxillofacial prosthodontist.[5] Dental implants can be considered; however, implants placed in irradiated bone have an increased risk of failure compared to those placed in non-irradiated bone.[76]

Existing treatments for xerostomia offer some relief from the symptoms of dry mouth, but fail to restore gland function.[77] Management of xerostomia may include saliva substitutes, and frequent intake of fluids, and systemic cholinergics (e.g., pilocarpine) can also be prescribed where residual gland function remains.

ORN is a late complication of RT and the risk of developing it increases over time.[66] Advances in RT have decreased incidence rates from 11.8% pre 1968 to approximately 3% currently.[13,66,78] Risk of ORN needs to be evaluated by the clinician, but it is now recommended that patients requiring extraction should be managed in a specialist centre.[66,79-81] Endodontic treatment should be favoured over extraction and, when necessary, extractions should be as atraumatic

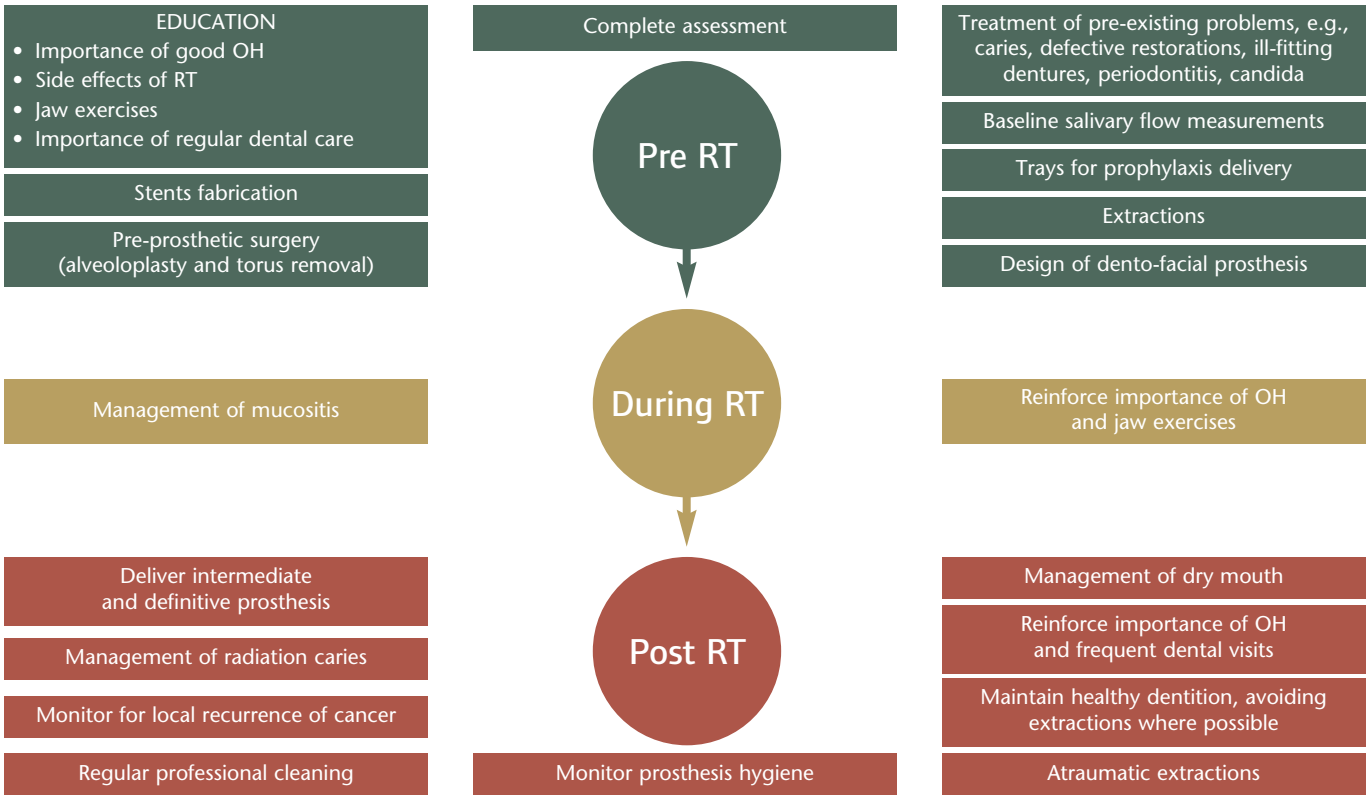

FIGURE 5: Dental management of the oral cancer patient before during and after radiotherapy.

as possible. Chlorhexidine mouthwash and antibiotic cover should be administered prior to extraction, and placement of a splint to prevent trauma during healing should also be considered. There is currently no evidence that hyperbaric oxygen therapy reduces the incidence of ORN.[82]

The role of the GDP

Compliance with OH routines is often difficult for oral cancer patients.[83] However, the importance of basic dental care, including good OH and regular dental assessment, should be emphasised. The GDP is often best placed to provide regular care to the patient.[5,8]Aspects of oral care that can be carried out by the GDP, in conjunction with the dental hygienist where appropriate, include:[5,8,64]

- evaluation and reinforcement compliance with OH measures and fluoride use;
- diet analysis and advice;
- advice on prosthesis maintenance;
- reinforcement of advice on lifestyle changes;
- regular professional cleaning;
- Monitoring for signs of second primaries;
- reassurance for patients fearful of recurrence;
- simple/routine restorative procedures; and,
- referral of patients to specialised centres for extractions and complex restorative procedures.

Monitoring for second primaries is particularly important; the recurrence rate for oral cavity squamous cell carcinoma is approximately 30%.[84]

Discussion and conclusions

New methods of RT delivery have reduced the side effects of RT for oral cancers; however, long-term irreversible damage to the salivary glands, connective tissues, vasculature and bone is still induced, leading to unavoidable side effects. Recent publications have attempted to define roles within the dental team and standardise care of the oral cancer patient, in particular the importance of long-term regular support within the community and specialised care where necessary. However, current recommendations for the dental management of the oral cancer patient tend to be based on expert opinion rather than evidence-based studies.

Many challenges still face the dental team, including the lack of an effective treatment to relieve the symptoms and sequelae of xerostomia,[77] the high number of patients lost to follow-up,[85] poor patient compliance[83] and the prevention of ORN.[45] In addition, many oral cancer patients are not provided with specialist dental care; some are referred to their GDPs prior to RT, while others receive no dental care prior to RT.[86-89] Scientific evidence has shown that good oral health is directly related to a patient's quality of life and therefore the role of the dental team in the management of the oral cancer patient before, during and after RT remains critical.

It is hoped that in the future these challenges will be addressed by

increased communication between all members of the cancer team, including dentists, and with the formulation of evidence-based guidelines, in particular focusing on highlighting the role of the GDP. It is also hoped that dental care will continue to evolve concurrently with new methods of RT delivery, thereby maximising the inevitably reduced QoL of the oral cancer patient.

References

1. **National Cancer Registry.** Cancer Trends – Cancers of the head and neck. Dublin, Ireland; 2011 [updated 2011; cited 2012 September 24]. Available from: www.ncri.ie.
2. **McCartan, B., Flint, S.** Intra-oral cancer. Part 1: epidemiology, aetiology and diagnosis. *Cancerwise* 2005; 4 (4): 3-7.
3. **Bhide, S.A., Nutting, C.M.** Advances in radiotherapy for head and neck cancer. *Oral Oncol* 2010; 46 (6): 439-441.
4. **Brizel, D.M., Wasserman, T.H., Henke, M., *et al.*** Phase III randomised trial of amifostine as a radioprotector in head and neck cancer. *J Clin Oncol* 2000; 18 (19): 3339-3345.
5. **MacCarthy, D., Omer, O., Nunn, J., Cotter, E.** Oral health needs of the head and neck radiotherapy patient: 1. Epidemiology, effects of radiotherapy and role of the GDP in diagnosis. *Dental Update* 2005; 32 (9): 512-514, 6-8, 21-22.
6. **Omer, O., MacCarthy, D., Nunn, J., Cotter, E.** Oral health needs of the head and neck radiotherapy patient: 2. Oral and dental care before, during and after radiotherapy. *Dental Update* 2005; 32 (10): 575-576, 8-80, 82.
7. **Joshi, V.K.** Dental treatment planning and management for the mouth cancer patient. *Oral Oncol* 2010; 46 (6): 475-479.
8. **Barclay, S.C., Turani, D.** Current practice in dental oncology in the UK. *Dental Update* 2010; 37: 555-561.
9. **Simoes, A., Eduardo, F.P., Luiz, A.C, *et al.*** Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers. *Lasers Surg Med* 2009; 41 (4): 264-270.
10. **World Health Organisation**. Handbook for reporting results of cancer treatment. Geneva: WHO; 1979.
11. **Arora, H., Pai, K.M., Maiya, A., Vidyasagar, M.S., Rajeev, A.** Efficacy of He-Ne laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; 105 (2): 180-186, 6 e1.
12. **Trotti, A., Bell, L.A., Epstein, J.B., *et al.*** Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. *Radiother Oncol* 2003; 66 (3): 253-262.
13. **Chambers, M., Garden, A., Lemon, J., Kies, M., Martin, J.** Oral complications of cancer treatment. In: **Davies, A., Finlay, I., (eds.).** *Oral Care in Advanced Disease*. Oxford: Oxford University Press; 2005: 171-184.
14. **Nicolatou-Galitis, O., Dardoufas, K., Markoulatos, P., *et al.*** Oral pseudomembranous candidiasis, herpes simplex virus-1 infection, and oral mucositis in head and neck cancer patients receiving radiotherapy and granulocyte-macrophage colony-stimulating factor (GM-CSF) mouthwash. *J Oral Pathol Med* 2001; 30 (8): 471-480.
15. **Parsons, J.T.** The effect of radiation on normal tissues of the head and neck. In: **Millon, R.R., Cassisi, N.J., (eds.).** *Management of Head and Neck Cancer: A Multidisciplinary Approach (2nd ed.).* Philadelphia: J.B. Lippincott Company; 1994: 245-289.
16. **Scully, C., Sonis, S., Diz, P.D.** Oral mucositis. *Oral Dis* 2006; 12 (3): 229-241.
17. **Eisbruch, A., Ten Haken, R.K., Kim, H.M., Marsh, L.H., Ship, J.A.** Dose, volume, and function relationships in parotid salivary glands following conformal and intensity-modulated irradiation of head and neck cancer. *Int J Radiat Oncol Biol Phys* 1999; 45 (3): 577-587.
18. **Vergeer, M.R., Doornaert, P.A., Jonkman, A., *et al.*** Ipsilateral irradiation for oral and oropharyngeal carcinoma treated with primary surgery and postoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 2010; 78 (3): 682-688.
19. **Gerlach, N.L., Barkhuysen, R., Kaanders, J.H., *et al.*** The effect of hyperbaric oxygen therapy on quality of life in oral and oropharyngeal cancer patients treated with radiotherapy. *Int J Oral Maxillofac Surg* 2008; 37 (3): 255-259.
20. **Anand, A.K., Jain, J., Negi, P.S., *et al.*** Can dose reduction to one parotid gland prevent xerostomia? A feasibility study for locally advanced head and neck cancer patients treated with intensity-modulated radiotherapy. *Clin Oncol (R Coll Radiol)* 2006; 18 (6): 497-504.
21. **Chao, K.S., Deasy, J.O., Markman, J., *et al.*** A prospective study of salivary function sparing in patients with head-and-neck cancers receiving intensity-modulated or three-dimensional radiation therapy: initial results. *Int J Radiat Oncol Biol Phys* 2001; 49 (4): 907-916.
22. **Warde, P., O'Sullivan, B., Aslanidis, J., *et al.*** A Phase III placebo-controlled trial of oral pilocarpine in patients undergoing radiotherapy for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2002; 54 (1): 9-13.
23. **McArdle, O., O'Mahony, D.** *Oncology, An Illustrated Colour Text*. Philadelphia: Elsevier Ltd; 2008.
24. **Eisbruch, A., Kim, H.M., Terrell, J.E., *et al.*** Xerostomia and its predictors following parotid-sparing irradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001; 50 (3): 695-704.
25. **Murdoch-Kinch, C.A., Kim, H.M., Vineberg, K.A., Ship, J.A., Eisbruch, A.** Dose-effect relationships for the submandibular salivary glands and implications for their sparing by intensity modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 2008; 72 (2): 373-382.
26. **Wijers, O.B., Levendag, P.C., Braaksma, M.M., *et al.*** Patients with head and neck cancer cured by radiation therapy: a survey of the dry mouth syndrome in long-term survivors. *Head Neck* 2002; 24 (8): 737-747.
27. **Radiation Therapy Oncology Group.** Acute radiation morbidity scoring criteria. Philadelphia, 2011 [updated 2011; cited 2011 November 28]. Available from: www.rtog.org/researchassociates/adverseeventreporting/acuteradiationmorbidityscoringcriteria.aspx.
28. **Nicolatou-Galitis, O., Velegraki, A., Sotiropoulou-Lontou, A., *et al.*** Effect of fluconazole antifungal prophylaxis on oral mucositis in head and neck cancer patients receiving radiotherapy. *Support Care Cancer* 2006; 14 (1): 44-51.
29. **Grotz, K.A., Genitsariotis, S., Vehling, D., Al-Nawas, B.** Long-term oral candida colonisation, mucositis and salivary function after head and neck radiotherapy. *Support Care Cancer* 2003; 11 (11): 717-721.
30. **Garnett, M.J., Nohl, F.S., Barclay, S.C.** Management of patients with reduced oral aperture and mandibular hypomobility (trismus) and implications for operative dentistry. *Br Dent J* 2008; 204 (3): 125-131.

31. **Mendenhall, W.M.** Mandibular osteoradionecrosis. *J Clin Oncol* 2004; 22 (24): 4867-4868.
32. **McCarty, P.J., Millon, R.R.** History of diagnosis and treatment of cancer in the head and neck. In: **Millon, R.R., Cassisi, N.J., (eds.).** *Management of Head and Neck Cancer: A Multidisciplinary Approach (2nd ed.).* Philadelphia; J. B. Lippincott, 1994: 1-29.
33. **Butler, E.B., The, B.S., Grant, W.H. 3rd, *et al.*** Smart (simultaneous modulated accelerated radiation therapy) boost: a new accelerated fractionation schedule for the treatment of head and neck cancer with intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys* 1999; 45 (1): 21-32.
34. **Chen, W.C., Hwang, T.Z., Wang, W.H., *et al.*** Comparison between conventional and intensity-modulated post-operative radiotherapy for stage III and IV oral cavity cancer in terms of treatment results and toxicity. *Oral Oncol* 2009; 45 (6): 505-510.
35. **Podd, T.J., Carton, A.T., Barrie, R, *et al.*** Treatment of oral cancers using iridium-192 interstitial irradiation. *Br J Oral Maxillofac Surg* 1994; 32 (4): 207-213.
36. **Braam, P.M., Terhaard, C.H., Roesink, J.M., Raaijmakers, C.P.** Intensity-modulated radiotherapy significantly reduces xerostomia compared with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; 66 (4): 975-980.
37. **Jellema, A.P., Doornaert, P., Slotman, B.J., Leemans, C.R., Langendijk, J.A.** Does radiation dose to the salivary glands and oral cavity predict patient-rated xerostomia and sticky saliva in head and neck cancer patients treated with curative radiotherapy? *Radiother Oncol* 2005; 77 (2): 164-171.
38. **Parliament, M.B., Scrimger, R.A., Anderson, S.G., *et al.*** Preservation of oral health-related quality of life and salivary flow rates after inverse-planned intensity-modulated radiotherapy (IMRT) for head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2004; 58 (3): 663-673.
39. **Rutkowski, T., Wygoda, A., Hutnik, M., *et al.*** Intra-operative radiotherapy (IORT) with low-energy photons as a boost in patients with early-stage oral cancer with the indications for postoperative radiotherapy: treatment feasibility and preliminary results. *Strahlenther Onkol* 2010; 186 (9): 496-501.
40. **Cerezo, L., Martin, M., Lopez, M., Marin, A., Gomez, A.** Ipsilateral irradiation for well lateralised carcinomas of the oral cavity and oropharynx: results on tumour control and xerostomia. *Radiat Oncol* 2009; 4: 33.
41. **Jellema, A.P., Slotman, B.J., Doornaert, P., Leemans, C.R., Langendijk, J.A.** Unilateral versus bilateral irradiation in squamous cell head and neck cancer in relation to patient-rated xerostomia and sticky saliva. *Radiother Oncol* 2007; 85 (1): 83-89.
42. **O'Sullivan, B., Warde, P., Grice, B., *et al.*** The benefits and pitfalls of ipsilateral radiotherapy in carcinoma of the tonsillar region. *Int J Radiat Oncol Biol Phys* 2001; 51 (2): 332-343.
43. **Eisbruch, A., Ship, J.A., Martel, M.K., *et al.*** Parotid gland sparing in patients undergoing bilateral head and neck irradiation: techniques and early results. *Int J Radiat Oncol Biol Phys* 1996; 36 (2): 469-480.
44. **Bhide, S.A., Nutting, C.M.** Recent advances in radiotherapy. *BMC Med* 2010; 8: 25.
45. **Ben-David, M.A., Diamante, M., Radawski, J.D., *et al*.** Lack of osteoradionecrosis of the mandible after intensity-modulated radiotherapy for head and neck cancer: likely contributions of both dental care and improved dose distributions. *Int J Radiat Oncol Biol Phys* 2007; 68 (2): 396-402.
46. **Wasserman, T.H., Brizel, D.M., Henke, M., *et al.*** Influence of intravenous amifostine on xerostomia, tumour control, and survival after radiotherapy for head-and- neck cancer: 2-year follow-up of a prospective, randomised, phase III trial. *Int J Radiat Oncol Biol Phys* 2005; 63 (4): 985-990.
47. **Lazarus, C., Logemann, J.A., Pauloski, B.R., *et al.*** Effects of radiotherapy with or without chemotherapy on tongue strength and swallowing in patients with oral cancer. *Head Neck* 2007; 29 (7): 632-637.
48. **Stokman, M.A., Spijkervet, F.K., Burlage, F.R., *et al.*** Oral mucositis and selective elimination of oral flora in head and neck cancer patients receiving radiotherapy: a double-blind randomised clinical trial. *Br J Cancer* 2003; 88 (7): 1012-1016.
49. **Elting, L.S., Keefe, D.M., Sonis, S.T., *et al.*** Patient-reported measurements of oral mucositis in head and neck cancer patients treated with radiotherapy with or without chemotherapy: demonstration of increased frequency, severity, resistance to palliation, and impact on quality of life. *Cancer* 2008; 113 (10): 2704-2713.
50. **Pauloski, B.R., Rademaker, A.W., Logemann, J.A., *et al.*** Relationship between swallow motility disorders on videofluorography and oral intake in patients treated for head and neck cancer with radiotherapy with or without chemotherapy. *Head Neck* 2006; 28 (12): 1069-1076.
51. **Graff, P., Lapeyre, M., Desandes, E., *et al.*** Impact of intensity-modulated radiotherapy on health-related quality of life for head and neck cancer patients: matched-pair comparison with conventional radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; 67 (5): 1309-1317.
52. **Henson, B.S., Inglehart, M.R., Eisbruch, A., Ship, J.A.** Preserved salivary output and xerostomia-related quality of life in head and neck cancer patients receiving parotid-sparing radiotherapy. *Oral Oncol* 2001; 37 (1): 84-93.
53. **Jensen, K., Lambertsen, K., Torkov, P., *et al.*** Patient-assessed symptoms are poor predictors of objective findings. Results from a cross-sectional study in patients treated with radiotherapy for pharyngeal cancer. *Acta Oncol* 2007; 46 (8): 1159-1168.
54. **Vanetti, E., Clivio, A., Nicolini, G., *et al.*** Volumetric modulated arc radiotherapy for carcinomas of the oro-pharynx, hypo-pharynx and larynx: a treatment planning comparison with fixed field IMRT. *Radiother Oncol* 2009; 92 (1): 111-117.
55. **Verbakel, W.F., Cuijpers, J.P., Hoffmans, D., *et al.*** Volumetric intensity-modulated arc therapy vs. conventional IMRT in head-and-neck cancer: a comparative planning and dosimetric study. *Int J Radiat Oncol Biol Phys* 2009; 74 (1): 252-259.
56. **Chan, A.W., Liebsch, N.J.** Proton radiation therapy for head and neck cancer. *J Surg Oncol* 2008; 97 (8): 697-700.
57. **Weber, D.C., Chan, A.W., Lessell, S., *et al.*** Visual outcome of accelerated fractionated radiation for advanced sinonasal malignancies employing photons/protons. *Radiother Oncol* 2006; 81 (3): 243-249.
58. **Ertekin, M.V., Uslu, H., Karslioglu, I., Ozbek, E., Ozbek, A.** Effect of oral zinc supplementation on agents of oropharyngeal infection in patients receiving radiotherapy for head and neck cancer. *J Int Med Res* 2003; 31 (4): 253-266.
59. **Rieger, J., Seikaly, H., Jha, N., *et al.*** Submandibular gland transfer for prevention of xerostomia after radiation therapy: swallowing outcomes. *Arch Otolaryngol Head Neck Surg* 2005; 131 (2): 140-145.

60. **Jha, N., Seikaly, H., McGaw, T., Coulter, L.** Submandibular salivary gland transfer prevents radiation-induced xerostomia. *Int J Radiat Oncol Biol Phys* 2000; 46 (1): 7-11.
61. **Jha, N., Seikaly, H., Harris, J., *et al.*** Phase III randomised study: oral pilocarpine versus submandibular salivary gland transfer protocol for the management of radiation-induced xerostomia. *Head Neck* 2009; 31 (2): 234-243.
62. **Lalla, R.V., Sonis, S.T., Peterson, D.E.** Management of oral mucositis in patients with cancer. *Dent Clin North Am* 2008; 52 (1): 61-68.
63. **Dreizen, S., Brown, L.R., Daly, T.E., Drane, J.B.** Prevention of xerostomia-related dental caries in irradiated cancer patients. *J Dent Res* 1977; 56 (2): 99-104.
64. **National Institute for Clinical Excellence.** Improving outcomes in head and neck cancers. London, 2004.
65. **Scottish Intercollegiate Guidelines Network.** Diagnosis and management of head and neck cancer. A national clinical guideline. Edinburgh, 2006.
66. **Kanatas, A.N., Rogers, S.N., Martin, M.V.** A practical guide for patients undergoing exodontia following radiotherapy to the oral cavity. *Dent Update* 2002; 29 (10): 498-503.
67. **Jham, B.C., Reis, P.M., Miranda, E.L., *et al.*** Oral health status of 207 head and neck cancer patients before, during and after radiotherapy. *Clin Oral Investig* 2008; 12 (1): 19-24.
68. **Lizi, E.C.** A case for a dental surgeon at regional radiotherapy centres. *Br Dent J* 1992; 173 (1): 24-26.
69. **Lockhart, P.B., Clark, J.** Pre-therapy dental status of patients with malignant conditions of the head and neck. *Oral Surg Oral Med Oral Pathol* 1994; 77 (3): 236-241.
70. **Turner, G.E.** Maxillofacial prosthetics. In: **Million, R.R., Cassisi, N.J, (eds.).** *Management of Head and Neck Cancer: A Multidisciplinary Approach (2nd ed.).* Philadelphia: J.B. Lippincott Company; 1994: 169-183.
71. **Bova, F.J.** Treatment planning for irradiation of head and neck cancer. In: **Million, R.R., Cassisi, N.J., (eds.).** *Management of Head and Neck Cancer: A Multidisciplinary Approach (2nd ed.).* Philadelphia: J.B. Lippincott Company; 1994: 291-309.
72. **Bruins, H.H., Jolly, D.E., Koole, R.** Preradiation dental extraction decisions in patients with head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; 88 (4): 406-412.
73. **Hong, C.H., Napenas, J.J., Hodgson, B.D., *et al.*** A systematic review of dental disease in patients undergoing cancer therapy. *Support Care Cancer* 2010; 18 (8): 1007-1021.
74. **MacCarthy, D., Omer, O., Nunn, J.** Intra-oral cancer. Part 2: oral and dental care for head and neck cancer patients. *Cancerwise* 2006; 5 (2): 3-11.
75. **Meurman, J.H., Gronroos, L.** Oral and dental health care of oral cancer patients: hyposalivation, caries and infections. *Oral Oncol* 2010; 46 (6): 464-467.
76. **Ihde, S., Kopp, S., Gundlach, K., Konstanyinovic, V.S.** Effects of radiation therapy on craniofacial and dental implants: a review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 107: 56-65.
77. **Brosky, M.E.** The role of saliva in oral health: strategies for prevention and management of xerostomia. *J Support Oncol* 2007; 5 (5): 215-225.
78. **Wahl, M.J.** Osteoradionecrosis prevention myths. *Int J Radiat Oncol Biol Phys* 2006; 64 (3): 661-669.
79. **Koga, D.H., Salvajoli, J.V., Alves, F.A.** Dental extractions and radiotherapy in head and neck oncology: review of the literature. *Oral Dis* 2008; 14 (1): 40-44.
80. **McLeod, N.M., Bater, M.C., Brennan, P.A.** Management of patients at risk of osteoradionecrosis: results of survey of dentists and oral and maxillofacial surgery units in the United Kingdom, and suggestions for best practice. *Br J Oral Maxillofac Surg* 2010; 48 (4): 301-304.
81. **Koga, D.H., Salvajoli, J.V., Kowalski, L.P., Nishimoto, I.N., Alves, F.A.** Dental extractions related to head and neck radiotherapy: ten-year experience of a single institution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2008; 105 (5): e1-6.
82. **Fritz, G.W., Gunsolley, J.C., Abubaker, O., Laskin, D.M.** Efficacy of pre- and post-irradiation hyperbaric oxygen therapy in the prevention of post-extraction osteoradionecrosis: a systematic review. *J Oral Maxillofac Surg* 2010; 68 (11): 2653-2660.
83. **Epstein, J.B., van der Meij, E.H., Lunn, R., Stevenson-Moore, P.** Effects of compliance with fluoride gel application on caries and caries risk in patients after radiation therapy for head and neck cancer. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1996; 82 (3): 268-275.
84. **Liu, S.A., Wong, Y.K., Lin, J.C., *et al.*** Impact of recurrence interval on survival of oral cavity squamous cell carcinoma patients after local relapse. *Otolaryngol Head Neck Surg* 2007; 136 (1): 112-118.
85. **Toljanic, J.A., Heshmati, R.H., Bedard, J.F.** Dental follow-up compliance in a population of irradiated head and neck cancer patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; 93 (1): 35-38.
86. **Schiodt, M., Hermund, N.U.** Management of oral disease prior to radiation therapy. *Support Care Cancer* 2002; 10 (1): 40-43.
87. **Epstein, J.B., Parker, I.R., Epstein, M.S., Stevenson-Moore, P.** Cancer-related oral health care services and resources: a survey of oral and dental care in Canadian cancer centres. *J Can Dent Assoc* 2004; 70 (5): 302-304.
88. **Epstein, J.B., Parker, I.R., Epstein, M.S., *et al.*** A survey of National Cancer Institute-designated comprehensive cancer centers' oral health supportive care practices and resources in the USA. *Support Care Cancer* 2007; 15 (4): 357-362.
89. **Barker, G.J., Epstein, J.B., Williams, K.B., Gorsky, M., Raber-Durlacher, J.E.** Current practice and knowledge of oral care for cancer patients: a survey of supportive health care providers. *Support Care Cancer* 2005; 13 (1): 32-41.