CHAPTER-2

REVIEW

OF LITERATURE

2: REVIEW OF LITERATURE

2.1 Oral cancer registries in India.

GLOBOCAN is an international cancer registry, which focuses on various cancer incidences and mortality across the globe as reported by the International Agency for Research on Cancer (IARC). India contributes a major load to the world's oral cancer burden. For the World population, 377713 newly diagnosed oral cancer cases and mortality of 177757 individuals were observed as per GLOBOCAN 2020. Out of these approximately 36% of the world's newly diagnosed cases and 42.33% of deaths were from India.[1, 2] In India, 1,35929 new cases were diagnosed and 75290 people died due to oral cancer in the year 2020.[2] Male and Female age-standardized incidence rate for Indian population per 1 lakh is 14.8 and 4.6. Age-standardized (world) incidence rates for the Indian population for incidence and mortality were 9.8 and 5.4 per one lakh population.[1, 2]

Sharma et al. (2018) summarized the incidence of oral cancer as per the National cancer registry program (NCRP) from twenty-nine population-based cancer registries in India. Seven regions which included north, south, central, west, east, north-east, and rural west of India were reported for the year 2006 to 2011. They reported a higher incidence of oral cancer in the central region of India. The maximum value of age-adjusted incidence rate (AAIR) of mouth cancer was 64.8 % in the central region for both males and females. Males had a higher incidence than

females in all other regions while only females in the northeast had a higher incidence as compared to males. [27]

Zhang et al. (2022) in their paper reported the trend of oral cancer in the nine most populous countries as estimated by The Global Burden of Disease Study 2019 (GBD 2019). For India, the annual age-standardized incidence rate increased from 7.53 in 1990 to 8.82 in 2019. The incidence increased from 39,064 to 1,04838 cases in 1990 and 2019 respectively. While estimated annual percentage changes (EAPCs) was 0.23.[28]

2. Incidence of Tobacco use in the Indian population

Million-death study (MDS) was conducted from 1998 to 2014 analyzing data from 14 million individuals' premature death for causes that result in one million deaths. This study is one of its kind and the only one in the world, which takes such a large sample to observe various, causes of premature death in India. Tobacco use reported one million deaths annually and is one of the highest causes of premature death in India. [29]

A National Family and Health Survey (NFHS-4) was conducted in 2015-16 and reported that 6.8% of women and 44.5 % of men were consuming using tobacco as the national average. It also reported the national average for alcohol consumption among males as 29.2 % and females as 1.2 % .[30] Uttarakhand reported 43.7% and Uttar Pradesh reported 53 % of men with tobacco consumption, while for females it was 2.9% and 7.6% respectively. The northeast states had the highest incidence of tobacco use around ranging from 70 to 80%.[31, 32]

The Global adult tobacco survey (GATS) is a multi-national systematic survey to monitor and document tobacco use in adults with the participation of the world health organization (WHO). In India GATS -1 was conducted in 2009-10, followed by GATS-2 in 2016-17. Thirty states and two union territories were included for the population above 15 years of age. In GATS-2 28.6% of the population was using some form of tobacco, this was a six-point reduction from GATS -1. 42.4% of males and 14.2% of females of the surveyed population were using tobacco in GATS-2.[33, 34]

A National Non-communicable disease monitoring survey (NNMS) was conducted by ICMR-NCDIR (Indian Council of Medical Research -National Centre for Disease Informatics and Research) in 2017-2018. This survey included 11 reputed institutions across India with the intent to monitor national Non-communicable diseases targets. 32.8% of the total population was tobacco users. 51.1 % of men and 13% of women in the survey consumed some form of tobacco. [35]

2.3 Periodontitis and Oral cancer evidence-based interlink

Tenzel et al. (2007) in their paper on chronic periodontitis and risk of tongue reported that with each millimeter of alveolar bone loss due to periodontitis there was a 5.23 times risk of tongue cancer.[36] In another paper Tenzel et al (2009) reported a 4.3 times risk of tongue cancer with every millimeter loss of alveolar bone.[4]

Moraes et al. (2016) in their case-control study compared cases with oral cancer and controls without any cancer. Cases reported severe chronic generalized

periodontitis and higher values of probing pocket depth and clinical attachment loss as compared to controls. They concluded that patients diagnosed with severe periodontitis are at a higher risk of oral cancer.[37]

In their systematic review, Javed et al. (2016) observed the relationship between periodontitis and oral cancer and included studies from 1984 to 2015. The study was conducted as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria. Twelve case-control studies were included which fulfilled all the criteria. Nine studies reported a two to five-fold increase in the risk of oral carcinoma in patients with periodontitis compared to those who do not have periodontitis after adjusting for all the risk factors the association between periodontitis and oral cancer was small but statistically significant.[7]

Gopinath et al. (2020) in their systematic review and meta-analysis studied periodontitis as a putative risk factor for head and neck carcinoma. They included seventeen case-control studies and four cohort studies across the globe as per PRISMA criteria. Nine studies qualified for meta-analysis and pooled odds ratio for them was 3.17, making periodontitis a three-fold risk factor for head and neck carcinoma.[8]

A meta-analysis by Vu H et al. (2021) reported an association of head and neck carcinoma with periodontitis while adjusting for smoking and alcohol. The study was conducted as per PRISMA criteria. Twenty-two studies from 1990 to 2020 were included for statistical analysis. Twenty studies were case-control while two were cohort studies. 19 studies reported a positive association of periodontitis with head and neck cancer with an odds ratio ranging widely from 1.15 to 9.33.[38]

Komlos et al. (2021) conducted a case-control study of 200 individuals; the incidence of oral cancer in periodontitis was 57.1% while 28.6% had no periodontitis. They concluded that periodontitis is an independent risk factor and individuals with severe periodontitis should be in close observation for the risk of developing oral cancer.[6]

2.4 Oral Quality of Life in cancer patients

Epstein et al. (1999) conducted a patient-based survey, six months after the completion of radiotherapy in oro-pharyngeal cancer patients. European Organization for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire QLQ-C30 was used. Dental decay was increased by 38.5% while 91.8% of participants reported xerostomia. Epstein et al (2001) reported that quality of life does not return to baseline even by 6 months. They concluded that patients had poor oral parameters for quality of life (QOL) and these worsened after receiving radiotherapy.[39, 40]

In another study, Duke et al. (2005) reported dental status and QOL amongst five-year cancer survivors of head and neck carcinoma. Post cancer loss of dentition, trismus, and higher DMFT scores were reported. This resulted in worsening chewing and recreational activity, pain, swallowing, and speech.[41]

Carranza et al. (2008) in their review on QOL in oral cancer emphasized that cross-sectional and longitudinal studies on quality of life reported poor scores in oral functions such as mastication, swallowing, and phonetics. Oral symptoms including

xerostomia, sticky saliva, mucositis, and altered taste were also deteriorated in patients receiving radiotherapy for oral carcinoma. [25]

In a prospective study of head and neck carcinoma, Kakoei et al. (2012) reported that the xerostomia and oral quality of life scores worsen with time. Participants' recall visits showed that with each milliliter reduction in saliva Quality of life decreased by 2.25 %. [42]

A systematic review by Moore et al. (2014) included thirty-one articles on oral quality of life scores. The quality of life for patients who have received cancer therapy for oral cancer had poor scores for functional aspects such as swallowing and mastication along with psychological aspects such as anxiety and depression.[43]

In a study, Barrios et al. (2014) reported that malnourishment is a significant factor in the worsening of oral health-related quality of life including oral health impact profile (OHIP) and oral impacts on daily performance (OIDP) in patients of oral carcinoma.[44] In another study Barrios et al. (2015) reported that odds of 11.6 and 21.2 fold for worsening of OHIP and OIDP scores in the cases as compared to controls for oral cancer.[45] Barrios et al. (2015) in yet another study reported a statistically significant association between long-term oral health-related quality of life scores and overall health-related scores in oral and oro-pharyngeal cancer after adjustment of all confounding factors.[26]

In a study by Paglioni et al. (2020) Quality of life scores and DMFT scores were evaluated at one-year post-radiotherapy in head and neck cancer patients. Those who developed radiation caries were considered cases and those who did not were

controls. Quality of life scores for cases and DMFT scores were significantly higher for cases as compared to controls. They concluded that patients with head and neck cancer with radiation caries had poor quality of life scores.[46]

Yuwanati et al. (2021) in their meta-analysis evaluated twelve studies with pooled data. It was observed that oral health-related quality of life scores in patients who have received treatment for oral cancer was very poor and they deteriorated for combination therapy. Oral quality of life was significantly affected by oncology treatment and in turn, affects general quality of life irrespective of oral cancer type and treatment received. They concluded that preventive oral care should be considered while planning overall treatment for oral cancer patients.[47]

Choi et al. (2021) in their study reported that patients with the complaint of xerostomia have higher Oral Health Impact Profile-14 (OHIP-14) scores. Speaking difficulties and self-reported salivary flow affected the oral health-related quality of life scores significantly in patients with oral carcinoma.[48]

2.5 Oral disease burden and treatment needs

Wescott et al. (1975) reported that patients who did not follow oral hygiene and fluoride protocol had higher amputation of the crown, out of a total of fifteen patients, nine patients had fifty-seven crown amputations while six patients who adhered to the protocol had no amputation of crowns and only one decayed tooth surface.[49]

Classical papers by Garg et al. (1997), Dreizen et al. (1977), and Karmiol et al. (1975) on adverse effects of radiotherapy reported a high prevalence of radiation

caries, mucositis, and xerostomia, resulting in poor oral health. Radiation caries has a classical presentation with decay in the cervical region and proximal region near cemento-enamel and cemento-dentinal junction. They recommended the use of sialagogues; fluoride and strict oral care for reducing the oral disease burden.[50-52]

Lockhart et al. (1994) in their study reported a very high burden of oral disease before starting radiotherapy. 97% of the participants in the study needed some dental treatment before starting radiotherapy, 66% had periodontitis and 71% has one or more carious teeth and 91% had a failed restoration. They also reported that the majority of the patients did not get the recommended dental treatment before starting their oncology treatment.[53]

Jham et al. (2008) in their paper on pre radiotherapy oral disease burden status reported 41% of participants with periodontitis and 12% with dental decay.[54] Katsura et al. (2008) in their study reported an average probing periodontal pocket measurement of 4.82 mm for patients scheduled for radiotherapy at baseline.[55]

Sennhenn et al. (2009) studied separate sets of patients with oral cancer who have received radiotherapy at two-time points in the years 1993 and 2005. This was done to access the dental disease burden and improvement in dental treatment standards. They reported Quigley–Hein oral hygiene index (QHI) value for 1993 was > 3 while for 2005 it was < 2. The Community Periodontal Index of Treatment Needs (CPITN) of 3.4 was recorded for both time points. Over a period of a decade fluoride application via splints has become more popular. They recommended the need for coverage of dental care pre and post-radiotherapy needs to be intensified for better oral quality of life.[56]

Reviews by Chaudhari et al. (2013) and Jawad et al. (2015) focused on dental disease burden due to cancer therapies in head and neck carcinoma patients. Radiation caries, xerostomia, mucositis, candidiasis, trismus, and jaw necrosis are significant oral burdens after radiotherapy. A pre-assessment of dental status before starting radiotherapy is a must and the dentist needs to be an integral part of the multidisciplinary team for the care of head and neck cancer patients.[57, 58]

In their study, Critchlow et al. (2014) reported that patients with head and neck carcinoma at baseline had a high load of oral disease burden. 71% had periodontitis and 61% of individuals had at least one or more carious teeth. They reported the inclusion of dental restorative and preventive treatment as an essential part of oncology treatment for patients with head and neck carcinoma.[59]

Gupta et al. (2015) in their paper reported that radiation caries has a fast onset and known complication of radiotherapy due to xerostomia. Comprehensive dental care before during and after radiotherapy is essential to improve the quality of life in head and neck cancer patients. Recommendations of using fluoride, radiation sparing techniques, and salivary substitutes were proposed to manage the long-term oral toxicities of radiotherapy.[60]

Bhandari et al. (2020) and Moore et al (2020) in their paper focused on the role of the Dental expert as a part of the multi-disciplinary team for management of oral and head and neck carcinoma patients. They emphasized on oro-dental toxicities of cancer treatment and an increase in the load of dental disease as a side effect of chemo-radiotherapy. Both recommended including dental expectations for improving quality of life in head and neck carcinoma patients.[61,62]

In another cross-sectional study on head and neck cancer patients, Bhandari et al. (2021) reported a high incidence of radiation caries after completion of radiotherapy. 85% of participants developed radiation caries after one-year post-radiotherapy. While all patients developed radiation caries in 3-5 years after radiotherapy. The DMFT and DMFT scores were also very high. They reported that the oral disease burden is very high for head and neck carcinoma patients receiving radiotherapy.[63]

2.6. Oral care protocol

Hashim et al. (2016) analyzed 8,925 head and neck cancer cases and around 12,527 healthy controls from thirteen studies from the international head and neck cancer epidemiology consortium (INHANCE). They reported participants who had less than five missing teeth, went for annual dental visits, had healthy periodontium, and habit of brushing daily was at lower risk of head and neck cancer. After adjusting for all know variables and confounders good oral hygiene was inversely associated with the risk of head and neck cancer.[9]

Aguilar et al. (2018) in their quasi-experimental case-control study evaluated patients who got in-hospital supervised treatment and controls that got outpatient non-regulated treatment. Cases reported lower plaque index, carious teeth, and need for extractions as compared to the control group. Good oral hygiene and a decreased oral burden were found in patients who received supervised oral care protocol. They recommended using oral care protocol for better oral outcomes in oral cancer patients.[64]

Kumar et al. (2019) prepared clinical guidelines for oral care in cancer patients in association with The Royal College of Surgeons of England and The British Society for Disability and Oral Health. The guideline recommended in detail how the Dentist is integrated as an integral part of the cancer care team. Pre, Intra, and post-treatment dental interventions were advised, and focus on oral care agents such as analgesics, mouthrinses, and salivary substitutes were emphasized. Fluoride was recommended as an important part of the management of radiation caries. Involvement of the Dentist in treatment planning from the start of the patient care was recommended to provide good oral quality of life in these patients.[65]

National comprehensive cancer network (2020) Guidelines mentions a section on dental rehabilitation and care. The principle of dental evaluation and management (DENT-A) was introduced in 2014 by NCCN. It recommends strict oral care, Pre, Intra, and post-radiotherapy/cancer treatment.[23]

British Association of Head and Neck Oncologists (2020) published their recommendation as BAHNO Standards. They recommended all patients with head and neck should see a qualified dental expert before starting cancer therapy. They recommended a restorative Dentist to be part of the Multidisciplinary team for head and neck cancer. Pre-treatment dental assessment and treatment along with Fluoride were recommended for all dentate subjects. Counseling should include oral hygiene, dental rehabilitation, and a restoration plan before any oncology treatment.[66]

Kawashita et al. (2020) in their paper, emphasized detailed oral care for head and neck cancer patients. They recommended including dental intervention pre, Intra, and post-cancer treatment to ensure good oral health. The need for Prosthetic

rehabilitation, fluoride use, necessary pre radiotherapy extraction, and rehabilitation were addressed.[67]

Lee et al. (2021) in their quasi-experimental study used fluoride varnish and mouth wash in head and neck cancer patients. They documented decreased caries scores, Plaque scores, bleeding on probing, and swallowing problems in the experimental group as compared to the control group. They reported that there was an improvement in oral quality of life and health in head and neck cancer patients who received comprehensive oral care including fluoride and oral care training.[17]

Jiang et al. (2021) in their randomized controlled trial, evaluated the effect of an integrated oral care program, which included detailed oral care instructions, xerostomia & oral care coaching, and counseling along with regular reinforcement. They reported that patients who received integrated oral care reported good oral health indicators as compared to controls. Xerostomia also improved in these patients and hence improving quality of life scores in head and neck cancer patients.[68]

A study was conducted by Sohn et al. (2021) on head and neck cancer patients with dental disease burden. Periodontally compromised patients and those with dental caries were enrolled in oral care for a period of one year. It was observed that regular dental visit and oral care program enrollment, oral prophylaxis; fluoride application improves oral hygiene, and periodontal parameters such as plaque index, gingival index, and clinical attachment loss. They recommended integrated oral care for head and neck cancer patients.[69]

2.7 Fluoride and dental caries

Dreizen et al. (1977) in their landmark study evaluated three oral care regimes which compared oral hygiene alone, oral hygiene with topical fluoride and oral hygiene, topical fluoride, and diet control. They recommended that 1% neutral sodium fluoride in a customized applicator tray was significantly effective in controlling radiation-induced decay in head and neck cancer.[70]

Horiot et al. (1983) documented 935 head and neck cancer patients for a duration of 10 years and reported that 4 % developed dental caries while 1% developed osteoradionecrosis (ORN) when fluoride incorporated oral care was given. In another randomized trial comparing fluoride gel and fluoride dentifrice. They reported that 3% developed dental caries in the fluoride gel group while 11% developed caries in the fluoride dentifrice group. They concluded that 5 min application of fluoride gel is effective in controlling dental decay in head and neck patients after completion of radiotherapy.[71]

Meyerowitz et al. (1991) evaluated twice daily 0.05% sodium fluoride mouth rinses on the mineralization status of enamel. They reported that twice-daily fluoride mouthrinses prevent demineralization in head and neck cancer patients who have received radiotherapy and developed xerostomia.[72]

A randomized double-blind clinical trial double parallel group was conducted by Sohn et al. (2021). They compared 0.42% sodium fluoride gel and 1.23% APF gel and found that customized tray application of 1.23 APF gel is more effective in preventing dental caries in head and neck cancer patients who have to receive radiotherapy.[73]

A systematic review and Meta-analysis by Marinho et al. (2004) was conducted on various types of fluoride gel, varnish, toothpaste, and mouth rinses. Studies from COCHRANE and MEDLINE databases among children and adolescents were included. Seventeen studies were included in this fifteen studies that were qualified for meta-analysis. They found that the toothpaste, gel, and mouth rinses do not differ significantly among themselves. It was found that more clinical data are needed to compare fluoride varnish and gel and their comparison was reported inconclusive.[74]

Bonan et al. (2006) in their study found poor oral hygiene at baseline for head and neck cancer patients scheduled to receive radiotherapy. 11.1% developed dental caries and 21.3% developed ORN in this low socioeconomic population group. They recommended the use of daily 1.23% fluoride gel along with a brush technique to increase application.[75]

American dental association (2006) recommended fluoride varnish and gel use in patients more than 18 years of age in a high-risk group such as xerostomia due to radiotherapy. Fluoride varnish and gel were recommended for three to six months in high-risk caries patients. This recommendation was based on the projection of adolescent data, as there is limited data on the adult population. The level of evidence was 'IV' and the strength of evidence was 'D' for these recommendation.[76]

Chambers et al. (2006) in their paper explained how radiotherapy results in radiation decay by increasing cariogenic organisms including streptococcus mutants and lactobacillus species. Xerostomia further increases the risk of radiation decay. Various topical fluorides at varied concentrations are used to prevent dental decay.

Fluoridated gel, varnish, tooth dentifrices, mouthrinses and sustain release fluoride are used to prevent radiation caries.[77]

Chambers et al. (2007) compared daily 0.4% stannous fluoride application in a custom tray with an intraoral fluoride-releasing system (IFRS) bonded to the maxillary molar buccal surface. The follow-up was done for four years, it was seen that IFRS had significantly lower radiation caries. IFRS was well tolerated with minimal side effects compared to daily fluoride gel application.[78]

Papas et al. (2008) conducted their study on re-mineralizing tooth dentifrices in head and neck cancer patients. It was reported that individuals who were prescribed re-mineralizing dentifrice had a significantly lower rate of root caries as compared to those using conventional fluorinated dentifrices. The root caries increment per year was 0.04 ± 0.052 and 1.65 ± 0.051 respectively for the aforementioned groups.[79]

Aguiar et al. (2009) in their review on radiation caries and their clinical and biological expression. They classified radiation decay into three types. Type one; is in the cervical area involving cement enamel junction, Type two; affects occlusal aspects of teeth, and Type three; is seen as a change in dentine color due to demineralization. They found that diet and oral microflora changes due to radiation causing favorable factors for the progression of decay. Topical fluoride in form of varnish, gel, dentifrices, and mouth rinses is recommended to prevent or slow the progression of radiation caries. Uses of fluorinated restorative material are also encouraged for this lesion. A dentist with expertise in oncology restorative care is required for the management of these conditions in head and neck cancer patients.[80]

Lopes C et al. (2018) in their in vitro study evaluated the effect of the topical application of fluoride during irradiation on tooth enamel demineralization. They Irradiated tooth surfaces at 70 Grays and evaluated the effect of fluoride on micro-hardness and elasticity modulus of enamel. It was seen that fluoride was reported significantly effective in reducing enamel demineralization and maintaining tooth enamel integrity on microscopic examination. While the enamel mineral composition and elastic modules were altered by radiation.[81]

In a systematic review by Mickenautsch et al. (2018) they included ten clinical studies and concluded that fluoride in form of glass ionomer or resin-modified glass ionomer restoration had more caries prevention compared to composite and amalgam restoration. Similarly, the use of topical fluoride and sustained release fluoride varnish is effective for dental caries prevention and progression in patients with xerostomia.[82]

Wu et al (2019) conducted an in-vitro study on irradiated tooth dentine with 68.25 Gy. Fluoride, Casein phosphate polypeptide-amorphous calcium phosphate (CPP-ACP) and infiltration resin as a separate application or as a combination of the above was studied. Vickers diamond indenter evaluated Micro-hardness. All the above applications reported increases in micro-hardness of dentine. Infiltration resin with CPP-ACP, CPP-ACP with fluoride, and infiltration resin alone had the highest protective effect on irradiated dentine tissue.[83]

Lopes M et al. (2021) conducted their in vitro study on an irradiated primary tooth with 30.6 Gy. They evaluated the effect of fluoridated toothpaste, Acidulated phosphate fluoride (APF) gel, and their combination on these irradiated teeth. Micro-

hardness and polarized light microscopy were used for analyzing the demineralization of enamel. They reported that fluoride toothpaste and APF gel do not affect the enamel demineralization by radiation.[84]

Palmier et al. (2020) in their review documented that radiation caries affects the cervical and occlusal area of teeth and progresses six to one year after radiotherapy. They also cautioned that radiation caries if not treated increased the risk of ORN after extraction. Fluoride application is essential and effective in controlling radiation caries. The use of fluorinated restoration was also recommended along with a close follow-up for prevention and restorative treatment.[21]

A randomized controlled clinical trial was conducted by Agnol et al. (2021) on 68 healthy participants. They compared 1.23 APF gel and fluoride varnish and its penetration in dental biofilm. To achieve a similar concentration of fluoride ions, fluoride varnish needs four hours while APF gel needs just four-minute of application.[85]

Akbari et al. (2021) conducted an in vitro study for evaluating micro-hardness in the enamel of permanent teeth. Vickers micro-hardness technique was used to see micro-hardness at demineralization and re-mineralization stages. It was reported that CPP-ACP, Fluoride varnish, and fluoride gel all resulted in improved micro-hardness of enamel as compared to controls. Fluoride varnish and gel were better than CPP-ACP.[86]