ANALISIS KARAKTERISTIK SIFAT FISIKOKIMIA (DERAJAT KEASAMAN, LAJU ALIR, KEKENTALAN) SALIVA PASIEN RADIOTERAPI KANKER KEPALA DAN LEHER

***Literature Review* dengan Pendekatan Sistematis**

Untuk memenuhi sebagian persyaratan

mencapai gelar Sarjana Kedokteran Gigi

Diajukan oleh:

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FAKULTAS KEDOKTERAN GIGI

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KARYA TULIS ILMIAH

Literature Review

CHARACTERISTIC ANALYSIS OF PHYSICAL CHEMISTRY PROPERTIES (ACIDITY, FLOW RATE, AND CONSISTENCY) SALIVA IN HEAD AND NECK CANCER RADIOTHERAPY PATIENT

Yang dipersembahkan dan disusun oleh
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Telah di pertahankan di depan Dewan Penguji
Pada tanggal 28 Juli 2021
Dan dinyatakan telah memenuhi syarat

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Semarang, 16 AUG 2021

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SURAT PERNYATAAN

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MOTTO DAN PERSEMBAHAN

Motto:

"*Allah SWT tidak membebani seseorang melainkan sesuai dengan kesanggupannya (QS. Al-Baqarah 286). Selalu bersyukur dan tetap melakukan yang terbaik."*

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Dosen Pembimbing dan Dosen Penguji
Orang Tua
Sahabat dan Teman-teman
Semua pihak yang telah membantu dalam terselesainya Literature Review ini

PRAKATA

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Muhammad Henri Indrawan

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DAFTAR SINGKATAN

- LET : *Linear Energy Transfer*
- TNF : *Tumor Necrosis Factor*
- PIP2 : *Phospatidyl Inositol Biphospate*
- PLC : *Phospolipase C*
- VIP : *Vasoactive Intestinal Peptide*
- Ach : *Acetilcholine*
- IP3 : *Inositol Triphosphate*
- IP3R : *Inositol Triphosphate Receptor*
- BMI : *Body Mass Index*
- AdC : *Adenylate Cyclase*
- PKA : Protein Kinase A
- PKC : Protein Kinase C
- CRA : *Caries Risk Assessment*
- GP : Protein G
- AQ5 : Aquaporin *5*
- EPIR : *Epithelial Polymeric Immunoglobulin Receptor*
- IMRT : *Intensity-Modulated Radiotherapy*
- OHI : *Oral Hygiene Index*
- RIOM : *Radiation-Induced Oral Mucositis*
- WHO : *World Oral Health*
- DNA : *Dexyribose-Nucleic Acid*
- RNA : *Ribose-Nucleic Acid*
- HPV : *Human Papilloma Virus*
- EBV : *Epstein Barr-Virus*
- aPRP : *Acidic Proline-Rich Protein*
- bPRP : *Basic Proline-Rich Protein*
- gPRP : *Basic Glycosylated Proline-Rich Protein*
- QoL : *Quality of Life*
- MUC5B : *Mucin 5B*
- MUC7 : *Mucin 7*
- RE : Retikulum Endoplasma
- PUMA : *p53 Upregulated Modulator of Apoptosis*
- BAX : *Bcl-2-associated X protein*
- VDAC : *Voltage-dependent anion channel*
- MAC : *mitochondrial apoptosis-induced channel*
- ATM : *Ataxia–Telangiectasia Mutated*
- ORAI : *Activated Calcium Channel Protein*
- TPRC1 : *Transient Receptor Potential Channel 1*

ABSTRAK

Penyakit Kanker Kepala dan Leher ditemukan pada oral, hidung, laring, dan faring. Kasus baru dunia mencapai 890.000 serta kematiannya 450.000 orang di tahun 2018. Salah satu perawatannya yaitu radioterapi memberikan pengaruh pada sifat fisikokimia saliva (laju alir, kekentalan, dan derajat keasaman). Analisis dilakukan pada sifat fisikokimia karena dapat menentukan kondisi kualitas produksi saliva. Analisis berikut bertujuan untuk mendapatkan analisis terbaru mengenai proses perubahan sifat fisikokimia saliva pasien radioterapi kanker kepala dan leher.

Pencarian artikel pada *Google Scholar, Academia,* dan *Microsoft Academy* sebanyak 39.972 artikel yang kemudian dilakukan skrining judul dan abstrak *free full text* sesuai kata kunci menjadi 52 artikel. Artikel tersebut diseleksi sesuai kriteria eksklusi yaitu 17 artikel dan inklusi 35 artikel. Sehingga terdapat 35 artikel yang akan dianalisis.

Hasil analisis mayoritas pasien radioterapi tersebut mengalami Xerostomia. Pada fase akut, laju alir saliva mulai menurun, kekentalan meningkat, dan derajat keasaman meningkat. Pada fase lanjut, kualitas sifat fisikokimia saliva semakin menurun karena kadar tinggi radiasi pengion merusak DNA dan membran sel asinar. Hasil produksi kelenjar saliva primer menjadi hipertonik karena kegagalan enzim protein kinase A dan kinase C melakukan fosforilasi membentuk material protein di sel asinar.

Kesimpulannya, radioterapi dapat menyebabkan Xerostomia sehingga terjadi penurunan kualitas sifat fisikokimia saliva pasien Radioterapi Kanker Kepala dan Leher. Edukasi menjadi hal utama untuk menangani komplikasi Xerostomia dengan menjaga OHI seperti sikat gigi, *chlorhexidine*, aplikasi *fluoride* atau stimulus saliva, dan lain-lain. Analisis dapat dikembangkan dengan mengamati *outcome* kekentalan secara kuantitatif.

Kata kunci: fisikokimia saliva; radioterapi; kanker kepala dan leher; sekresi saliva

ABSTRACT

Head and Neck Cancer (oral, nose, faring and laring area) are 890.000 new cases and 450.000 deaths in 2018. One of treatment's Radiotherapy affects saliva's quality in physicochemical properties (flow rate, consistency, and acidity). Physicochemical properties are analysed because they can influence saliva's quality. The aim of study is getting updated analysis about physicochemical properties' saliva in Radiotherapy of Head and Neck Cancer Patient.

There are 39.972 articles, searched in Google Scholar, Academia, and Microsoft Academy database. The articles that connected with keywords topic are 52 articles with abstract and title screening process. Next process is selecting articles and getting 17 excluding articles and 35 including articles. The total articles are 35 articles. Therefore, they're ready to be analysed.

Major result of analysis is radiotherapy affecting patient to Xerostomia. There's reducing flow rate, increasing consistency, and pH decrease in acute phase. In late phase, physicochemical properties' saliva quality is decreased because of high ionizing radiation damaging DNA and membrane of acinar cell. Primary saliva became hypertonic because protein kinase A enzyme and protein kinase C enzyme fail to do phosphorylation to build protein materials in acinar cell.

Conclusion is radiotherapy making Xerostomia impact decreasing physicochemical or physical chemistry properties' quality in head and neck cancer. Education is main thing to take Xerostomia's complication for maintaining OHI like teeth brushing, chlorhexidine, fluoride or salivary stimulant application, and others. Analysis can be developed for observation of consistency outcome based on quantity.

Keywords: *physicochemical saliva; radiotherapy; head and neck cancer; salivary secretion*

BAB I

PENDAHULUAN

1.1 Latar Belakang

Kanker kepala dan leher merupakan keganasan jaringan yang terjadi pada laring, faring, nasofaring, orofaring, rongga mulut, hidung, dan kelenjar mulut (Fernandes *et al.*, 2018). Menurut Riset Kesehatan Dasar (Riskedas) tahun 2018 didapatkan prevalensi kanker mencapai 1,79% yang berkisar 1.017.290 orang di Indonesia. Hasil studi *Global Burden of Disease* (GBD) didapatkan prevalensi kanker kepala dan leher di seluruh dunia mencapai lima persen penduduk dengan 650.000 kasus baru dan kematian 350.000 pertahun. Hasil studi didapatkan faktor predisposisi kanker kepala dan leher terdiri dari perokok, alkohol, usia pasien atau efek *aging*, pola diet makan, kebersihan mulut, infeksi EBV dan HPV (Ngan *et al.*, 2018).

Penatalaksanaan kanker kepala dan leher terdiri dari kemoterapi, radioterapi, maupun kombinasi antara kemoterapi dan radioterapi. Radioterapi adalah pengobatan kanker dengan transmisi partikel berupa cahaya atau gelombang yang dapat merusak dan menghambat perkembangan sel kanker (Nur Fitriatuzzakiyah et al., 2017). Molekul-molekul sel kanker akan pecah karena terionisasi oleh gelombang cahaya radioterapi yang dapat menangani penyakit kanker kepala dan leher. Efek samping yang didapat yaitu sel normal di dalam tubuh pun dapat mengalami kerusakan oleh radioterapi (Muhammad Tsalis F., 2012).

Radioterapi yang lama dilakukan di area kepala dan leher dapat menyebabkan efek samping hiposaliva karena radiasi ionisasi menghancurkan sel di area target pada kelenjar saliva (Surjadi and Amtha, 2013).

Profil saliva merupakan informasi karakteristik dan kandungan saliva yang dapat terukur terdiri dari pH, volume, zat komponen seperti zat anorganik maupun organik (Samad, 2013). Kandungan organik saliva berupa enzim maltase, enzim amilase, albumin, kreatinin, musin, beberapa hormone berupa testosterone dan kortisol, serta vitamin C (Riskayanty *et al*., 2014). Kandungan anorganik saliva berupa fosfat, natrium, kalium, kalsium, magnesium dan zat lainnya (Samad, 2013). Profil saliva dapat dipengaruhi radioterapi dari efek pajanan radiasi sinar X yang mengenai area target organ kelenjar saliva (Susanti *et al*., 2015).

Sifat fisikokimia adalah sifat yang menentukan suatu bentuk benda padat, cair, maupun udara yang memiliki materi baik terkait maupun tidak terkait dengan perubahan komposisi kimianya. Sifat tersebut merupakan kombinasi dari sifat fisik dan sifat kimia. Pengukuran yang dilakukan pada sifat fisik dapat diamati di saat materi sudah atau belum mengalami perubahan fisik seperti kepadatan, warna, titik beku, titik didih, dan lain-lain. Sifat kimia dapat diamati dari perubahan material kimia yang berbeda dari sebelumnya seperti toksisitas, keasaman, reaktivitas, dan lain-lain (Champeroux *et al*., 2013).

Karekteristik sifat fisikokimia saliva dapat terbagi sifat fisik maupun sifat kimia. Sifat fisik saliva didapat dengan apa yang dilihat bentuk secara kasat mata seperti volume atau laju alir, maupun kekentalan. Sifat kimia dapat diamati dari kapasitas buffer atau derajat keasaman dari cairan saliva yang berpengaruh terhadap kesehatan gigi dan mulut (Kubala *et al.*, 2018). Karakteristik saliva seperti derajat keasaman, kekentalan, dan laju alir saliva dapat mempengaruhi kualitas saliva sebagai pertahanan rongga mulut terhadap perkembangan patogen yang bersifat destruktif (Kasuma, 2015).

Saliva merupakan cairan biologis yang dapat berfungsi untuk memperkirakan prognosis, membantu menegakkan diagnosis klinis, pemantauan, dan menentukan rencana perawatan pasien yang memiliki penyakit sistemik maupun rongga mulut. Pemeriksaan saliva memiliki banyak keuntungan baik untuk pasien maupun operator. Proses pemeriksaannya meminimalisir efek invasif terhadap pasien, dan membutuhkan waktu yang lebih efisien. Prosedur pengambilan sampel saliva dilakukan dengan mudah karena tidak membutuhkan keahlian khusus dari operator. Sampel saliva yang didapatkan lebih mudah dan aman untuk disimpan dan dikirim ke laboratorium terkait. Kenyamanan didapatkan lebih baik pada pemeriksaan dan pengambilan sampel saliva dikarenakan pasien tidak mendapatkan trauma secara fisik maupun psikologis (Lacombe *et al.*, 2017).

Ajaran Islam juga menjelaskan bahwa setiap penyakit pasti ada obat atau perawatannya meskipun dalam pengembangannya belum memberikan kesembuhan secara utuh. Dari hadist riwayat Ibnu Mas'ud, bahwa Nabi Muhammad bersabda :

إِنَّ اللهَ لَمْ يَنْزِلْ دَاءً إِلاَّ وَأَنْزَل لَهُشِفَاءً، عَلِمَهُ مَنْ عَلِمَهُ و جَهِلَهُ مَنْ جَهِلَهُ

"Sesungguhnya Allah *Ta'ala* tidak menurunkan penyakit, kecuali Allah juga menurunkan obatnya (perawatan). Ada orang yang mengetahui ada pula yang tidak mengetahuinya." (HR. Ahmad, shahih)

Hadist tersebut menjelaskan Allah SWT tidak akan memberikan ujian kepada hamba-Nya di luar batas kemampuan hamba-Nya. Keyakinan bahwa setiap orang pasti bisa mendapat kesembuhan merupakan sifat yang harus dimiliki setiap umat untuk bisa mendapat ridha Allah SWT.

Dari uraian yang telah ditulis di atas, penulis ingin melakukan *literature review* dengan pendekatan sistematis tentang analisis karakteristik sifat fisikokimia saliva pada pasien radioterapi kanker kepala dan leher.

1.2 Rumusan Review

1. Bagaimana karakteristik (derajat keasaman, laju alir, dan kekentalan) sifat fisikokimia saliva pada pasien kanker kepala dan leher yang dapat dideteksi melalui saliva?
2. Bagaimana mekanisme perubahan karakteristik (derajat keasaman, laju alir, kekentalan) sifat fisikokimia saliva pada pasien kanker kepala dan leher yang melakukan perawatan radioterapi?
3. Mengapa perlu dilakukan pengukuran karakteristik (derajat keasaman, laju alir, kekentalan) sifat fisikokimia saliva pada pasien kanker kepala dan leher yang melakukan perawatan radioterapi?

1.3 Tujuan Review

1.3.1 Tujuan Umum

Tujuan umum tinjauan review ini adalah untuk menyediakan referensi publikasi yang relevan terkait dengan analisis karakteristik sifat fisikokimia (derajat keasaman, laju alir, dan kekentalan) saliva pasien radioterapi kanker kepala dan leher.

1.3.2 Tujuan Khusus

a. Untuk mengetahui karakteristik (derajat keasaman, laju alir, dan kekentalan) sifat fisikokimia saliva pada pasien kanker kepala dan leher.

b. Untuk mengetahui perubahan karakteristik (derajat keasaman, laju alir, dan kekentalan) sifat fisikokimia saliva pada pasien kanker kepala dan leher yang melakukan perawatan radioterapi.
c. Untuk mengetahui manfaat atau kegunaan dari deteksi karakteristik (derajat keasaman, laju alir, dan kekentalan) sifat fisikokimia saliva pada pasien kanker kepala dan leher yang melakukan perawatan radioterapi.

BAB II

METODE PENELITIAN

2.1 Pencarian Literatur

Dilakukan penelurusan literatur publikasi pada basis data elektronik *Academia*, *Microsoft Academy*, dan *Google Scholar* dengan menggunakan metode PICO (*Population*, *Intervention*, *Comparison and Outcome*) yaitu dengan kata kunci (*Salivary* AND *Mechanism* AND *Secretion* AND *Composition* AND *Physical Chemistry Properties* AND *Flow Rate* AND *Following Radiotherapy* AND *Head and Neck Cancer Patient*), (*Salivary* AND *Mechanism* AND *Secretion* AND *Composition* AND *Physical Chemistry Properties* AND *Consistency* AND *Following Radiotherapy* AND *Head and Neck Cancer Patient*), (*Salivary* AND *Mechanism* AND *Secretion* AND *Composition* AND *Physical Chemistry Properties* AND *Acidity* AND *Following Radiotherapy* AND *Head and Neck Cancer Patient*).

Selanjutnya jurnal tersebut diseleksi sesuai dengan kriteria inklusi dan ekslusi menurut peneliti. Data jurnal yang didapatkan akan dikumpulkan pada aplikasi *Mendeley*, yang merupakan perangkat lunak untuk membantu penulis memanajemen referensi.

2.2 Kriteria Inklusi dan Kriteria Eklsusi

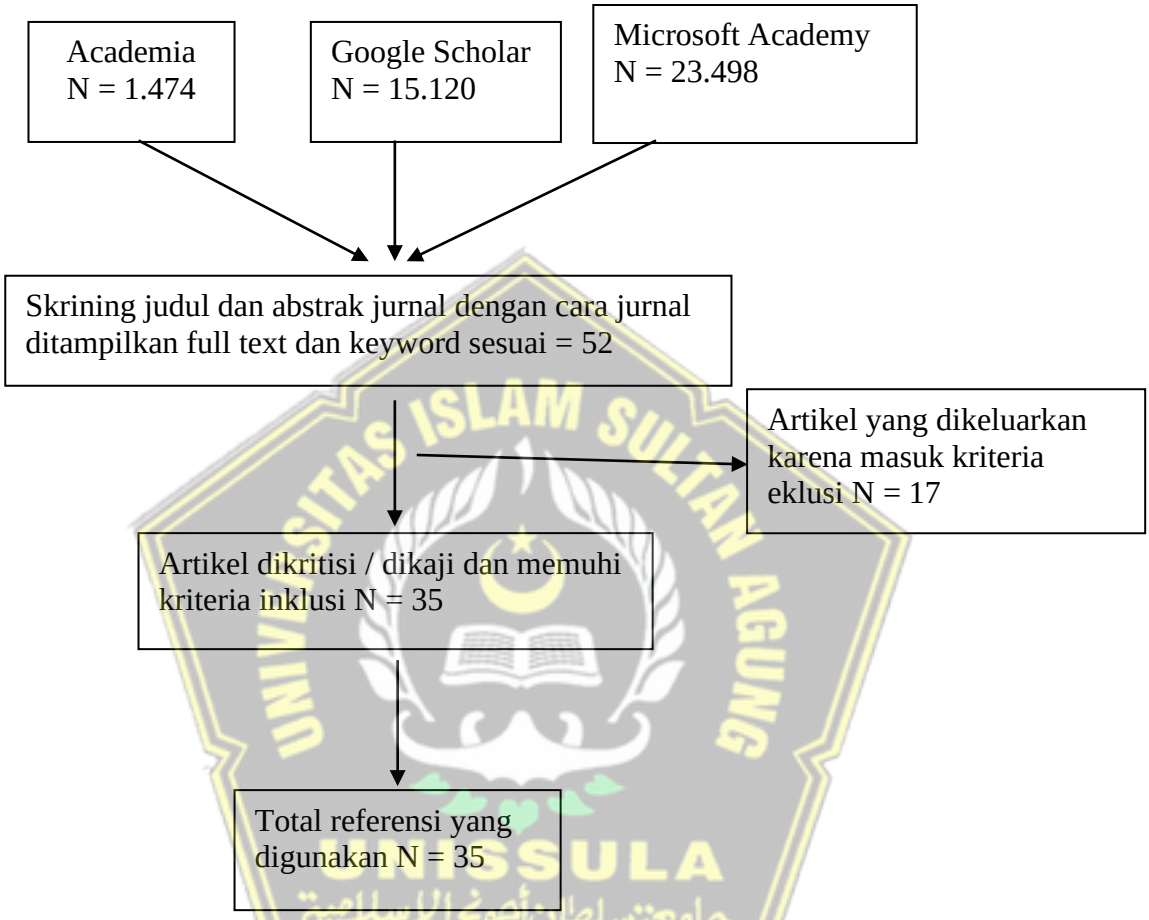
2.2.1 Kriteria Inklusi

- Jurnal yang dipublikasikan pada tahun 2013-2020.
- Jurnal berbahasa Inggris.
- Subjek penelitian manusia pada jurnal tertulis penelitian yang jelas.
- Jurnal yang dipublikasikan dapat diakses secara *free full text.*
- Tipe *outcome* yang bisa diamati adalah hal-hal terkait profil sifat fisikokimia saliva terdiri dari laju alir, vikositas atau kekentalan, dan derajat keasaman saliva pada pasien radioterapi kanker laring, faring, nasofaring, orofaring, rongga mulut, hidung, dan kelenjar mulut.

2.2.2 Kriteria Eklusi

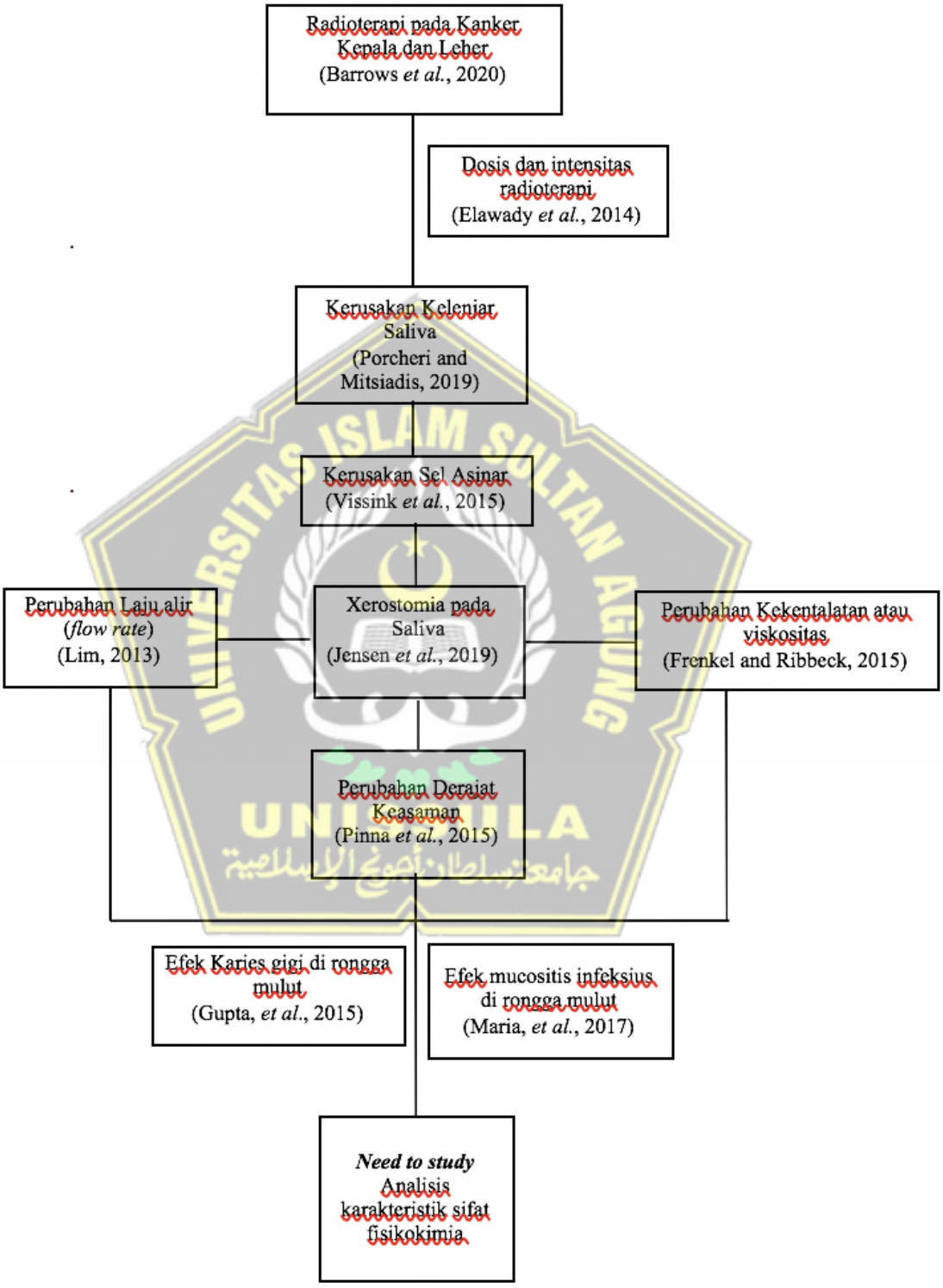
- Jurnal tidak didapat akses secara *free full text*.
- Jurnal yang memiliki referensi kurang dari 10 literatur.
- Subjek penelitian non-manusia pada jurnal tertulis penelitian yang jelas.
- Jurnal yang dipublikasikan pada tahun 2012 atau tahun sebelumnya.
- Tipe outcome yang diamati tidak terkait karakteristik (derajat keasaman, laju alir, dan kekentalan) sifat fisikokimia.

2.3 Alur Pencarian Literatur



Gambar 2. 1 Alur Pencarian Review

2.4 Peta Literature Review



Gambar 2. 2 Peta Literature Review

BAB III

HASIL KAJIAN LITERATUR DAN PEMBAHASAN

3. 1 Hasil Kajian *Literature Review*

Pencarian artikel dilakukan melalui pangkalan data elektronik seperti *Google scholar*, *Microsoft Academy*, dan *Academia*. Terdapat 39.972 artikel yang diperoleh sesuai dengan *keyword*. Seluruh artikel diskrining kesesuaian jurnal *fulltext* sehingga didapatkan 52 artikel, kemudian artikel tersebut disesuaikan dengan kriteria inklusi didapatkan yaitu sebanyak 35 artikel dan kriteria eksklusi didapatkan sebanyak 17 artikel. Hasil artikel yang digunakan yaitu berjumlah 35 artikel.

3.2 Pembahasan

3.2.1 Radioterapi pada Pasien Kanker Kepala dan Leher

3.2.1.1 Radioterapi

Radioterapi merupakan perawatan menangani sel abnormal atau sel kanker yang rusak dengan radiasi pengion berupa radionuklida, radioisotop yang dapat menghasilkan elektromagnetik berupa sinar gamma atau partikel ion radiasi berupa neutron, proton atau elektron. Zat radiasi pengion dapat ditemukan seperti sinar X dan radium. Zat ion radionuklida terdiri dari zat radium, caesium, kobalt, iridium, stronsium, dan lain-lain. Sinar gamma didapatkan dari radium, caesium, kobalt dan iridium. Sementara partikel ion bisa didapatkan seperti zat stronsium dan emas (Karthik and Mohan, 2017).

Proses radioterapi terjadi dengan induksi kerusakan pada bagian DNA sel yang dapat menghambat proses pertumbuhan, perkembangan serta profilerasi dari sel tubuh. Radiasi ion radioterapi dapat merusak ke bagian sel tubuh normal. Pemberian dosis efektif dari radioterapi dapat menjaga kesehatan sel tubuh normal disamping merusak sel kanker (Pinna *et al.*, 2015).

Pemberian radioterapi kanker kepala dan leher dapat dilakukan dengan tiga cara seperti brakiterapi, teleterapi, dan terapi sistemik. Brakiterapi menggunakan aplikator sumber radiasi yang ditanamkan di area sel kanker atau area dekat jaringan kanker. Metode tersebut memiliki kelebihan lebih efisien menangani jaringan kanker bermassa besar. Bentuk aplikatornya terdiri dari jarum, tabung, benih bola, kabel dan lain-lain. Jarum menjadi bentuk aplikator yang dapat menangani Kanker Kepala dan Leher. Teleterapi adalah radioterapi yang menggunakan alat *beam* atau tabung yang dapat diarahkan ke area tumor dengan jarak tertentu berkisar 80 – 100 cm. Metode teleterapi dapat dilakukan untuk perawatan kuratif seperti pembedahan maupun perawatan paliatif untuk rehabilitasi dampak buruk dari kanker. Metode terapi sistemik pada radioterapi dapat dilakukan dengan pemberian obat kandungan radioisotop yang dapat memicu efek kerusakan pada sel target. Pemberian dapat dilakukan secara oral maupun suntikan intravena (Karthik and Mohan, 2017). Prinsip ketiga kerja radioterapi tersebut yaitu memberikan kerusakan sel oleh radiasi pengion sehingga terjadi

kerusakan rantai tunggal maupun rantai ganda pada DNA sel supaya sel tidak bisa tumbuh dan berkembang dengan baik (Porcheri and Mitsiadis, 2019).

IMRT memiliki kelebihan yang tidak dimiliki radioterapi konvensional. IMRT menggunakan tehnik termonitor lewat teknologi komputer dan *fluence beam* yang menjadi tabung khusus dapat mengatur dosis radiasi yang minimal dengan efek yang efisien menangkal kanker. IMRT menjadi perawatan umum untuk kanker area tertentu yang memiliki akses radiasi cukup kompleks seperti kanker kepala dan leher, payudara, paru-paru, prostat, dan lain-lain (Karthik and Mohan, 2017)

3.2.1.2 Efek Radioterapi terhadap Kanker Kepala dan Leher

Dampak utama radioterapi kanker kepala dan leher yaitu hiposalivasi. Titik utama proses ini terjadi pada sel asinar yang sangat radiosensitif terhadap radiasi pengion. Tingkat keparahan hiposalivasi dipengaruhi oleh dosis radioterapi dan besar kerusakan jaringan saliva oleh radioterapi. Faktor lain seperti sistem imun berpengaruh terhadap regenerasi sel dan kerusakan sel oleh radioterapi. Dosis rendah radioterapi yang diberikan pada Pasien Kanker Kepala dan Leher dengan imun yang kurang baik, sudah dapat menyebabkan efek kerusakan tinggi pada kualitas saliva yang dihasilkan. Kerusakan kelenjar saliva secara ireversibel dapat terjadi dengan dosis melebihi lebih dari 30 Gy (Deng *et al.,* 2015). Menurut Saleh dan kawan-kawan dosis kerusakan ireversibel pada kelenjar saliva ditemukan dari 26 sampai 39 Gy. Laju alir saliva dapat berkurang 10% setelah radioterapi (Saleh *et al.,* 2014). Semakin tinggi dosis radioterapi, semakin besar hambatan fase

sel untuk proliferasi sel, sintesis protein dan penyimpanan energi untuk perkembangan sel baru. (Huang and Zhou, 2020).

Efek radioterapi sering rusak di sel asinar kelenjar saliva parotid. Sekitar seminggu setelah radioterapi dapat membuat kadar saliva berkurang 60% - 90% dengan dosis radioterapi konvensional 5 sampai 10 Gy. Masa pergantian sel didapat 60 – 120 hari. Proses induksi ion radioterapi ke sel jauh lebih cepat daripada proses pergantian sel. IMRT menjadi radioterapi alternatif lebih efektif menangkal kanker dengan dosis yang lebih terjangkau (Delli *et al.*, 2014). Dosis rata-rata IMRT dengan 1 tahun berjumlah 26 – 43 Gy dapat memberikan reduksi 50% komplikasi Xerostomia. Ion tersebut bekerja lebih signifikan ke area langsung target kanker yang dituju (Chen *et al.*, 2013).

Menurut Liang dan kawan-kawan untuk dosis rata -rata Radioterapi Kanker Kepala dan Leher dapat merusak rongga mulut dengan kisaran 30-60 Gy. Dosis tersebut dapat merusak sasaran utama yaitu area gigi premolar dengan perkembangan karies lebih cepat 12-200 kali dari perkembangan karies umumnya. Kerusakan pertama terjadi adanya fraktur di area enamel gigi. Lesi karies dapat terbentuk pertama kali dengan dosis rata-rata lebih dari 35,8 Gy. Hasil dosis rata-rata lebih dari 50-60 Gy dapat menyebabkan penurunan drastis dentin dan enamel dari daya sifat kekasaran, serta kekuatan tarik (tes kepatahan). Dosis rata-rata pada 25-32 Gy didapatkan kerusakan pada Kelenjar Parotid. Kerusakan Kelenjar Submandibular didapatkan kisaran dosis rata-rata 40 Gy karena kerusakan yang terjadi sudah mencapai

Kelenjar Parotid. Rata-rata dosis kerusakan mencapai gigi-geligi didapatkan kisaran 60 Gy (Liang *et al.*, 2016).

3.2.2 Saliva pada Pasien Radioterapi Kanker Kepala dan Leher

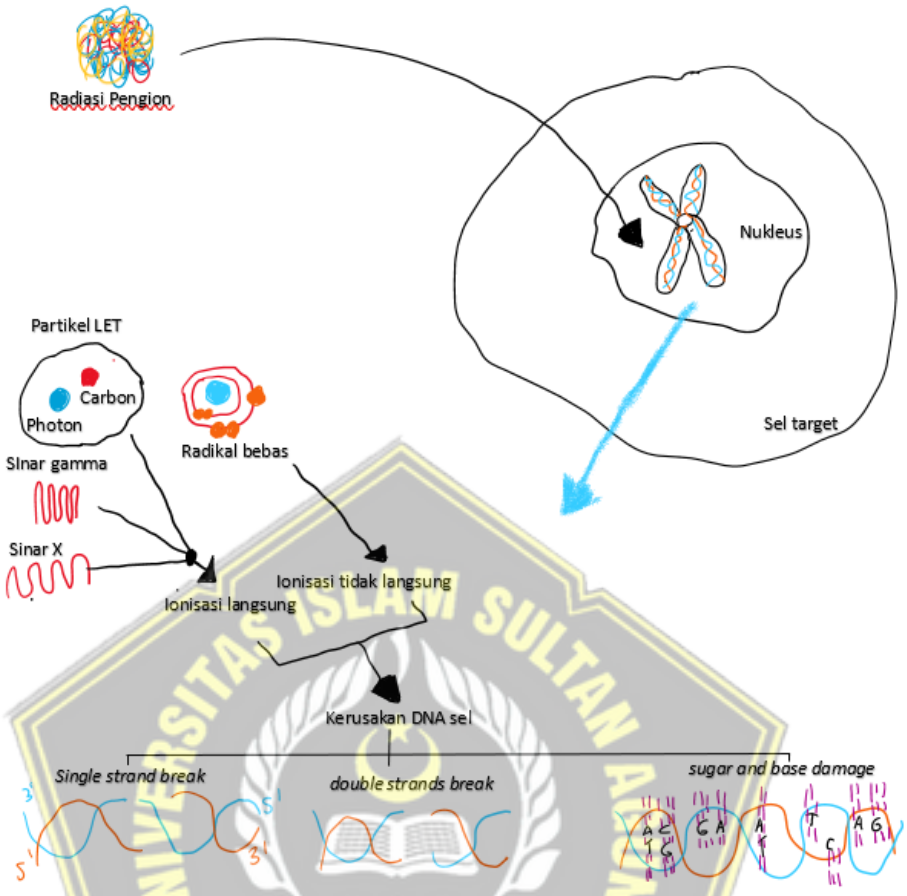
3.2.2.1 Kelenjar saliva Pasien Radioterapi Kanker Kepala dan Leher

Kelenjar saliva merupakan struktur esensial organ yang tersusun dari berbagai jaringan atau sel berguna untuk memproduksi saliva di rongga mulut (Porcheri and Mitsiadis, 2019). Kelenjar saliva teridiri dari bagian utama seperti tubul asinar, dan kelenjar eksokrin. Jaringan kelenjar saliva tersusun atas jaringan lunak yang memiliki banyak kadar sel epitel sebagai pelindung kelenjar saliva. Area rongga mulut memiliki dua jenis kelenjar saliva yaitu kelenjar saliva mayor (kelenjar parotid, submandibular, sublingual) dan minor. Kelenjar parotid menjadi kelenjar dengan ukuran terbesar disusul ukuran lebih kecil seperti submandibular, sublingual, dan kelenjar minor (Krishnamurthy, 2015).

Induksi ion radioterapi berawal memasuki area epitel di mukosa rongga mulut. Ion tresebut akan melakukan invasi cenderung ke area langsung di kelenjar saliva, terutama di sel asinar (Huang and Zhou, 2020). Induksi radiasi pengion dapat terjadi secara langsung dengan partikel LET seperti foton dan karbon, sinar gamma, atau sinar X dapat melakukan kerusakan DNA sel asinar. Induksi tidak langsung dapat terjadi dengan pembentukan radikal bebas dahulu yang dimana baru melakukan kerusakan DNA sel asinar. Hasil kerusakan sel berupa kerusakan untaian tunggal dan

ganda DNA, serta kehilangan basa nitrogen maupun fosfat pada DNA (Huang and Zhou, 2020).

Efek DNA yang rusak akan membuat sistem sel tidak dapat bekerja kembali. Efek kerusakan DNA sel paling dominan terjadi pada proses *double strand breaks*. Proses sel kerusakan DNA menyebabkan terjadinya gangguan metabolisme sel di dalam tubuh. Protein dari gen P53 dapat memicu proses reparasi DNA sel. Jika sel pada DNA gen P53 sudah rusak sangat banyak oleh radioterapi, dapat menyebabkan DNA sel sangat sulit melakukan reparasi. Protein p53 akan cenderung lebih memilih proses kematian sel terprogram (Huang and Zhou, 2020). Jika radioresisten sel tidak cukup menahan induksi ion dari radioterapi, maka sel terjadi *cycle arrest* (Huang and Zhou, 2020). Sel menjadi terhambat akan hal proliferasinya. Efek sel menjadi menyusut dan kemudian berhenti berkembang hingga akhirnya mengalami kematian sel terprogram seperti apoptosis, senesens, serta autofagi (Vissink *et al.*, 2015)



Gambar 3. 1 Proses Induksi Radioterapi ke Sel Target

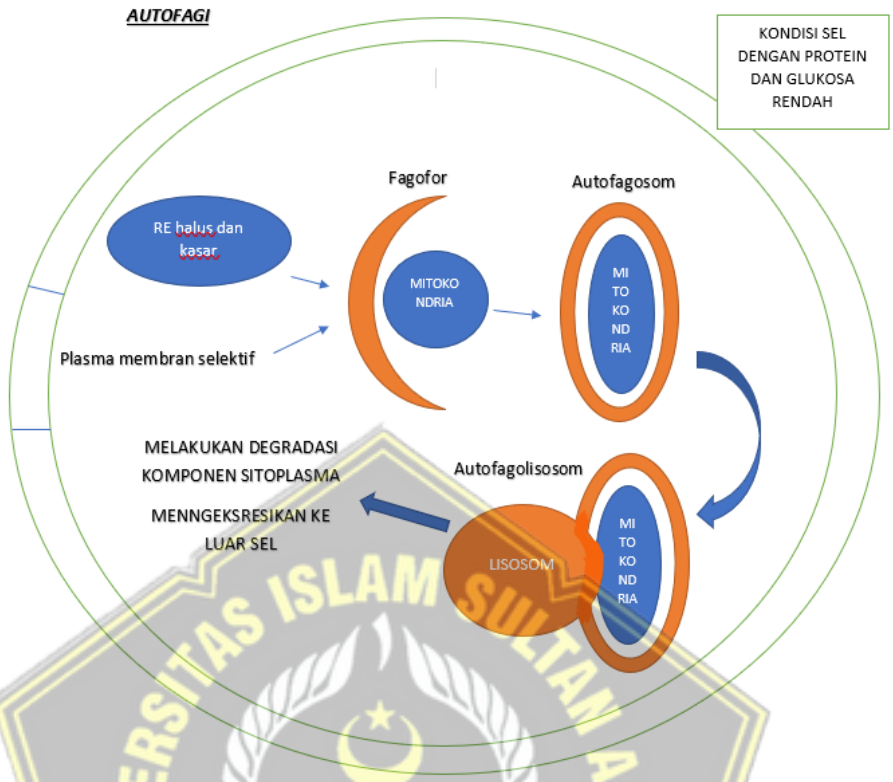
Sumber : (Huang and Zhou, 2020), (Sia *et al.*, 2020), (Delli *et al.*, 2014)

Gambar 3.1 Proses induksi ion radioterapi ke sel target. Induksi radiasi pengion dapat terjadi secara langsung yang terdiri dari partikel LET seperti foton dan karbon, sinar gamma, atau sinar X dapat melakukan kerusakan DNA sel. Induksi tidak langsung dari radiasi pengion perlu membentuk radikal bebas dahulu yang kemudian memasuki area inti sel baru melakukan kerusakan DNA sel. Kerusakan DNA sel yang dominan meliputi *single strand breaks, double strand breaks,* dan *sugar and base damage.* Kerusakan

yang sering terjadi dan sulit untuk dilakukan reparasi yaitu berada di proses *single strand breaks.*

Apoptosis dapat terjadi secara alur intrinsik dengan produksi Protein Sitokrom C yang disimpan di Mitokondria. Sitokrom C di sitoplasma mengaktifkan Protein Caspase 9 untuk inisiasi apoptosis terhadap sel sendiri. Alur ekstrinsik apoptosis diawali dengan membran sel teradiasi (reseptor mati) berikatan dengan ligan TNF-α1. TNF-α1 dari respon inflamasi dapat memicu sel mengaktifkan protein Caspase 8 untuk inisasi apoptosis. Protein Caspase 9 dan 8 menginisiasi apoptosis dengan cara megaktifkan protein Caspase 3 dan 7 yang melaksanakan degradasi komponen selular sel yang apoptosis. (Sia *et al.*, 2020)

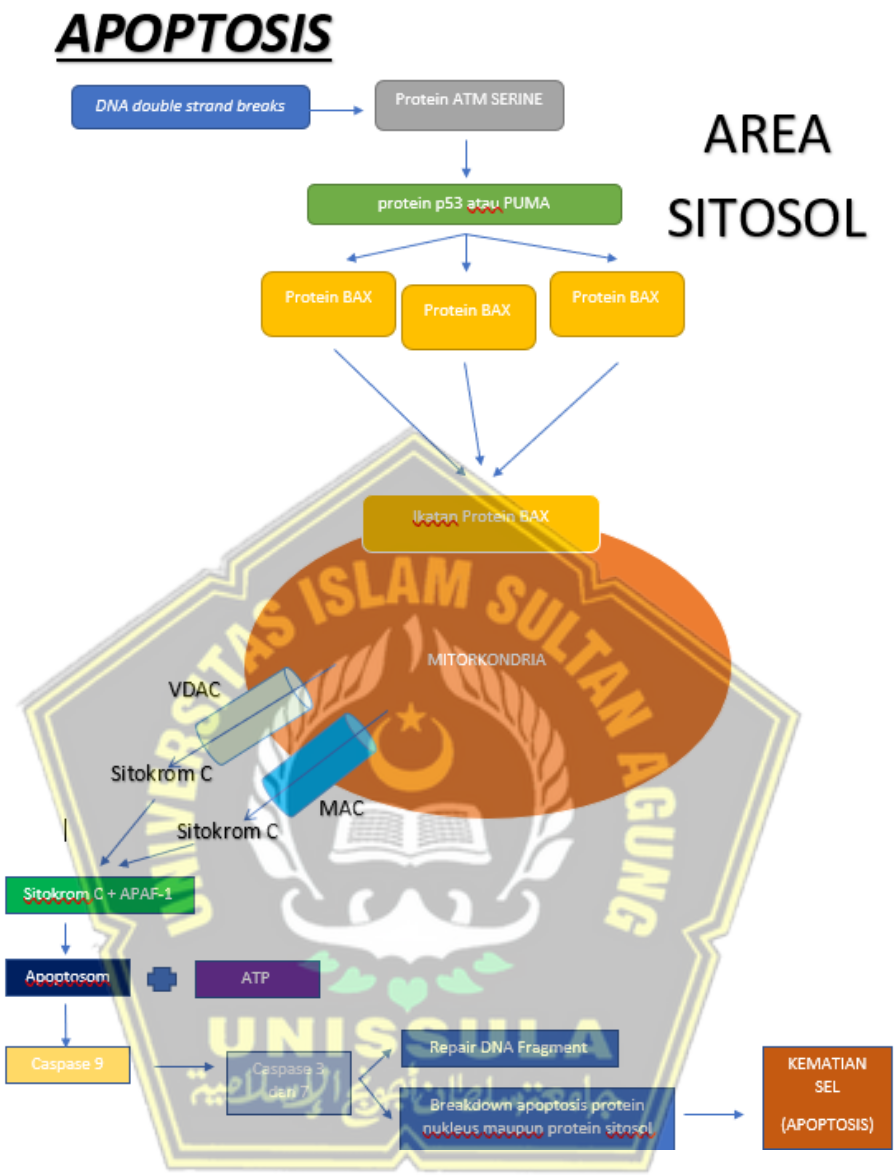
Proses senesens terjadi karena kerusakan DNA yang menyebabkan terjadinya *cycle arrest.* Siklus sel akan terhenti di proses proliferasi sel dipicu oleh protein gen p21. Nekrosis merupakan kerusakan sel karena infeksi atau inflamasi yang disebabkan sel mengalami perubahan esktrim dari pH, kehilangan energi, serta ion yang tidak stabil. Proses tersebut terjadi jika kerusakan DNA sudah mencapai titik sel tidak stabil dalam hal metabolismenya. Respon sel autofagi yaitu proses pembongkaran organel sitoplasma sel sendiri karena kekurangan energi dari sel. Proses dipicu oleh autofagolisosom. Autofagi dapat terjadi karena gagalnya respon apoptosis (Sia *et al.*, 2020).



Gambar 3. 2 Proses Autofagi Sel

Sumber : (Sia *et al.*, 2020)

Gambar 3.2 Kondisi sel kekurangan protein dan glukosa memicu proses autofagi. Proses awal terjadi pembentukan pelepasan material bagian RE halus dan kasar serta plasma membran selektif yang membentuk fagofor. Fagofor merekrut mitokondria membentuk autofagosom. Autofagosom bergabung bersama lisosom membentuk autofagolisosom untuk melakukan degradasi komponen sitoplasma yang dihancurkan untuk bisa disekresi ke luar sel.



Gambar 3. 3 Proses Apoptosis Jalur Intrinsik

Sumber : (Sia *et al.*, 2020)

Gambar 3.3 Apoptosis jalur intrinsik terjadi karena DSBs, memicu protein ATM serine mengaktifkan PUMA menghasilkan protein BAX. Protein BAX menuju membran plasma mitokondria dan membentuk ikatan protein BAX. Protein BAX memberi sinyal mitokondria mengeluarkan Sitokrom C melalui dua kanal yaitu VDAC dan MAC. Sitokrom C memanggil APAF-1 untuk

membentuk apoptosom. Apoptosom memerlukan ATP sebagai energi bekerja mengaktifkan Caspase 9. Caspase 9 berfungsi mengaktivasi Caspase 3 dan 7 yang bisa berfungsi untuk reparasi DNA atau memecah protein di sitosol maupun nukleus. Jika kerusakan p53 sudah cukup besar, tidak memungkinkan lagi untuk reparasi karena kerusakan kanker maupun radiasi pengion, maka fungsi lebih mengarah pemecahan protein menyebabkan kematian sel (apoptosis).

Gambar 3. 4 Apoptosis Jalur Ekstrinsik

Sumber : (Sia *et al.*, 2020)

Gambar 3.4 Apoptosis Jalur Ekstrinsik melalui TNF-α1 berikatan ligan yang memberi sinyal aktivasi Caspase 8. Caspase 8 dapat berfungsi untuk memicu aktivasi Caspase 3 dan 7 supaya melakukan degradasi protein di dalam sel.

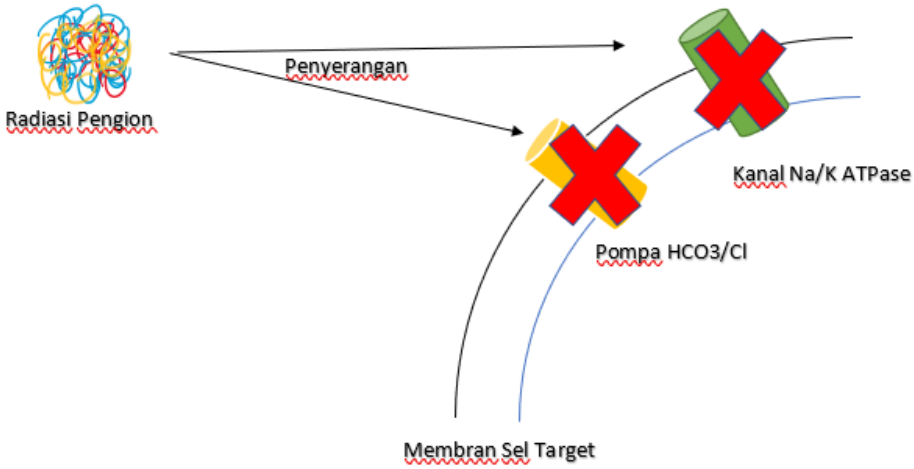
Gambar 3. 5 Proses Senesens Sel

Sumber : (Sia *et al.*, 2020)

Gambar 3.5 Proses Senesens terjadi pada fase siklus sel. Kerusakan p53 yang cukup parah akan beresiko untuk memicu p21 dalam melakukan proses *cycle arrest* yaitu berhenti dalam melakukan replikasi sel kembali. Sel menjadi

senesens di fase Mitosis atau fase M karena fase tersebut yang melakukan replikasi sel. Senesens tidak terjadi pada fase Sintesis atau fase S, fase Gap 1 atau fase G1, dan fase G2 atau fase Gap 2 karena fase tersebut cenderung berproses sintesis komponen sel dari organel, DNA, RNA dan protein. Hasil sel senesens akan ditindaklanjuti dengan program kematian sel tersendiri seperti apoptosis, nekrosis maupun autofagi supaya mencegah peredaran sel abnormal atau sel rusak.

Radioterapi merusak membran sel di Kanal Na/K ATPase dan pompa HCO3/Cl (Lan *et al.*, 2020). Mengakibatkan produksi saliva terbentuk kekurangan H20 dari Kanal Na/K ATPase, serta kapasitas buffer yang berkurang di HCO3/Cl (Proctor, 2016). Hasil saliva didapatkan laju alir menurun, kapasitas buffer seperti potassium, iodin, dan kalsium menurun. Kapasitas buffer utama yaitu bikarbonat mengalami penurunan drastis yang memicu pH saliva menjadi rendah (Lan *et al.*, 2020).



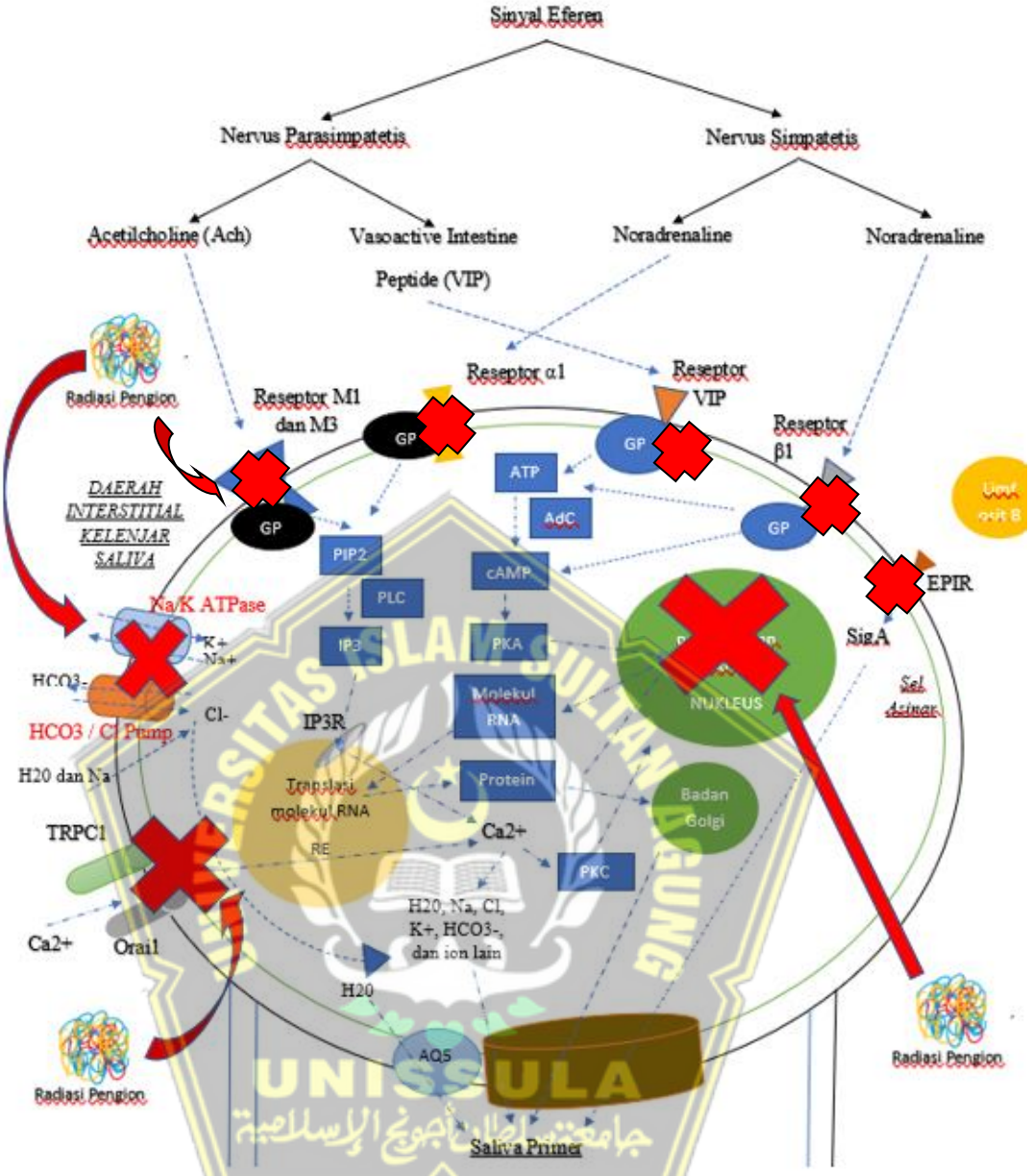
Gambar 3. 6 Proses Kerusakan Membran Sel oleh Radioterapi

Sumber : (Porcheri and Mitsiadis, 2019), (Proctor, 2016), (Lan *et al.*, 2020)

Gambar 3.6 Radioterapi menginduksi kerusakan di membran sel membuat Kanal Na/K ATPase dan pompa HCO3/Cl menjadi rusak. Mengakibatkan produksi saliva primer terbentuk menjadi saliva hipertonik karena akumulasi H20 kurang didapatkan dari Kanal Na/K ATPase, serta kapasitas buffer yang berkurang di saliva primer.

Proses pembentukan saliva primer dimulai dari sinyal impuls eferen yang disalurkan dari sistem saraf pusat menuju system saraf eferen otonom. Penyaluran pertama dapat melewai nervus parasimpatetis yang akan dibawa oleh dua neurotransmitter yaitu Ach dan VIP. Ach berikatan dengan reseptor musarinik 1 dan 3 serta VIP berikatan dengan reseptor VIP. Impuls nervus simpatetis disalurkan oleh neurotransmiter seperti noradrenaline menuju reseptor α1 dan β1. Reseptor α1, M1, dan M3 bekerja Bersama Protein G dari RE untuk memicu proses enzim PLC memecah Fosfolipid PIP2 menjadi Glikoprotein IP3 yang berfungsi sebagai *second messenger* berikatan dengan

reseptor IP3R pada RE. Informasi tersebut berupa perintah sekresi Ca2+ dari RE yang didapat dari difusi Ca2+ ke delam sel melalui pompa ORAI dan TRPC1. Ca2+ berfungsi untuk induksi sinyal pengaturan akumulasi ion, air, dan protein untuk dieksresikan ke luar sel asinar (Ekström *et al.*, 2017). Reseptor β1 dan VIP berikatan dengan Protein G untuk memicu Enzim AdC mengkonversi ATP menjadi cAMP. Molekul cAMP sebagai *second messenger* akan berfungsi untuk memberi induksi sinyal mengaktifkan Enzim PKA. PKA berfungsi untuk fosforilasi faktor pengaktif transkripsi DNA yang akan membantu mengaktifkan pembentukan material protein di nukleus. Ca2+ dapat meningkatkan produksi protein dengan mengaktifkan PKC yang berfungsi mengatur proses transkripsi di nukleus. Hasil transkripsi material protein nukleus berupa molekul RNA yang akan menuju RE untuk dilakukan proses translasi pembentukan berbagai macam protein. Protein kemudian disimpan di badan golgi untuk siap dieksresikan ke luar sel asinar. IgA dihasilkan oleh limfosit B yang berada di area insterstisial dan berikatan dengan EPIR (Proctor, 2016). IgA transitosis menuju area sitoplasma menjadi SigA yang kemudian dieksresikan bersama protein, air, serta ion lain. Air dapat keluar juga melalui pompa AQ5 tanpa energi. Hasil eksresi protein, ion, air, SigA akan membentuk saliva primer. Saliva primer normal didapatkan isotonik yang akan diproses menjadi saliva sekunder normal yang hipotonik (Porcheri and Mitsiadis, 2019).



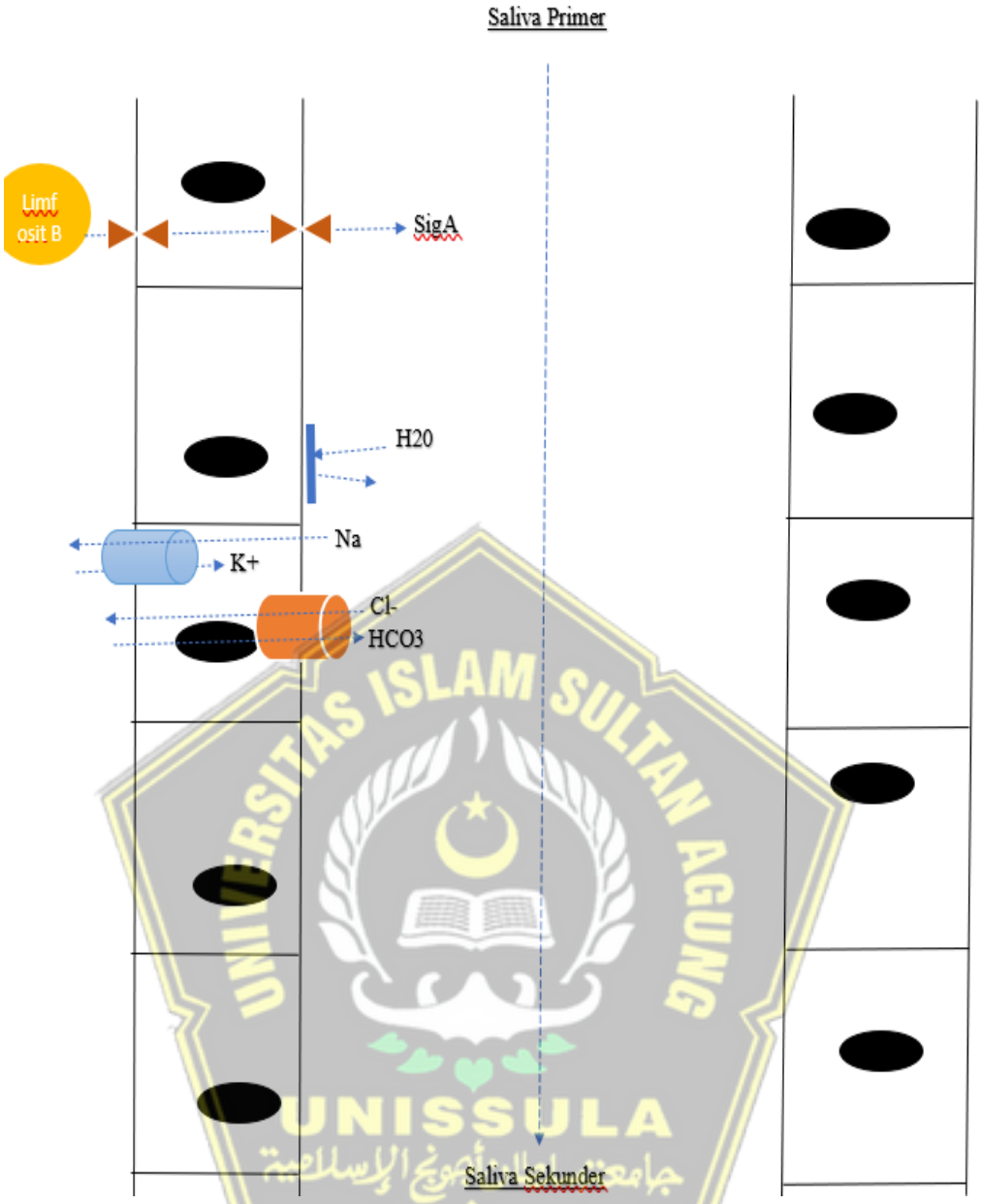
Gambar 3. 7 Proses Kerusakan Produksi Saliva Primer oleh Radioterapi

Sumber : (Ekström *et al.*, 2017) (Porcheri and Mitsiadis, 2019)(Proctor and Carpenter, 2014)(Proctor, 2016)(Vissink *et al.*, 2015), (Huang and Zhou, 2020)

Gambar 3.7. Radioterapi akan merusak proses pembentukan saliva primer. Proses kerusakan terjadi pada bagian nukleus serta membran sel seperti kanal ion dan reseptor. Kerusakan membran sel di kanal Na/K ATPase dan pompa

HCO3/Cl Radiasi menyebabkan kurangnya sekresi H20 dan HCO3 di sel asinar. Kerusakan nukleus yaitu DNA sel dapat menyebabkan hambatan produksi energi serta protein untuk sekresi saliva primer. PKC dan PKA gagal untuk fosforilasi produksi material protein yaitu molekul RNA. Molekul RNA yang gagal proses fosforilasi akan tidak aktif untuk melakukan proses translasi menjadi berbagai macam jenis protein di RE. Kerusakan membran sel di berbagai reseptor akan menghambat aktivitas Ca2+, pembentukan protein, serta sekresi saliva dengan H2O dan ion-ion lain. Kerusakan utama sel asinar serus yang sangat radiosensitif menyebabkan produksi saliva primer menjadi abormal yaitu hipertonik.

Proses normal perubahan saliva primer menjadi sekunder terjadi dari duktus interkalasi sampai duktus striata (Vissink *et al.*, 2015). Proses terjadi dengan penyerapan Na dan penambahan HCO3 di duktus melalui Na/K ATPase dan pompa HCO3/Cl karena area duktus terdapat banyak ATP dari sekresi saliva primer (Ekström *et al.*, 2017). Namun H20 tidak ikut masuk ke area dinding duktus karena terdapat sambungan sel *tight junction* yang banyak (Proctor and Carpenter, 2014). Proses saliva sekunder normal untuk semua kelenjar saliva didapatkan bersifat hipotonis dengan 99% air, 0,3% protein, 0,2% komponen organik anorganik (Kaczor-Urbanowicz *et al.*, 2017).



Gambar 3. 8 Proses Produksi Saliva Sekunder

Sumber : (Ekström *et al.*, 2017) (Porcheri and Mitsiadis, 2019), (Proctor and Carpenter, 2014), (Proctor, 2016), (Vissink *et al.*, 2015), (Roblegg, Coughran and Sirjani, 2019)

Gambar 3.8 Proses saliva primer (saliva normal yaitu isotonik) menjadi saliva sekunder (normal hipotonik). Terjadi penyerapan zat utama natrium. H20 tidak diserap oleh sel duktus. ATP terkandung cukup tinggi di area sel duktus

mengakibatkan jalur transport kanal Na/K dan kanal Cl/HCO3 menjadi lebih tinggi sehingga terjadi penyerapan besar pada natrium dan sekresi bikarbonat. Namun karena efek radioterapi menyebabkan saliva sekunder menjadi

Produksi di setiap kelenjar saliva berbeda-beda. Kelenjar Parotid memproduksi saliva dengan serus tertinggi (Krishnamurthy, 2015). Jumlah produksi tertinggi didapatkan oleh kelenjar protid di saat terstimulasi. Saat tanpa stimulasi didapatkan tertinggi yaitu produksi saliva dari kelenjar submandibular dan sublingual. Produksi paling rendah ditemukan oleh kelenjar saliva minor. Jenis produksi, dan presentase volume saliva di setiap kelenjar didapatkan pada Tabel 3.1 (Proctor, 2016).

Tabel 3. 1 Produksi Kadar Saliva di Setiap Tipe Kelenjar Saliva

Produksi Saliva	Jenis produksi	Tanpa Stimulus (%)	Betstimulus (%)
Seluruh saliva	Serumukus (*mixed*)	100	100
Kelenjar Parotid	*Pure* serus	28	53
Kelenjar Sub Mandibular dan Sublingual	Serumukus (*mixed*)	68	46
Kelenjar Minor	*Pure* mucus (Von Ebner *pure* serus)	4	1

Kelenjar parotid menjadi hal utama kerusakan oleh ionisasi radioterapi karena kadar sel asinar serus yang tinggi di kelenjar tersebut. Sel asinar serus bersifat paling radiosensitif sehingga menyebabkan mudah terkena kerusakan oleh ion radioterapi. Kerusakan awal terjadi dengan kadar cairan saliva yang menurun drastis sehingga berpengaruh terhadap kualitas laju alir maupun kekentalan saliva (Delli *et al.*, 2014). Efek akut Xerostomia

membuat produksi laju alir saliva menurun drastis serta tingginya kekentalan saliva (Pinna *et al.,* 2015). Hasil kondisi saliva menjadi lengket pada Xerostomia akut di pasien Radioterapi Kanker Kepala dan Leher (Chen *et al.*, 2013).

Faktor yang mempengaruhi kerusakan sel mukosa di area rongga mulut oleh radioterapi terdiri dari gender, usia, OHI, merokok, alkohol, gagal ginjal dan lain-lain. Usia memicu terhadap penurunan fungsi imun terutama produksi antibodi yang dialami usia dewasa. Gender terjadi respon stress yang sering dialami perempuan memicu penurunan imun serta perbedaan kadar anitoksidan yang tinggi di pria. Merokok dengan zat nikotin dan alkohol dengan etanol memicu kerusakan kanker yang lebih besar. Gagal ginjal menyebabkan fungsi metabolisme terganggu dalam penghantaran nutrisi ke area rongga mulut serta ditemukan zat kreatinin tinggi yang memicu terjadi pembentukan urea di oral (Maria *et al.*,, 2017). OHI buruk menyebabkan kerusakan berbagai reseptor pemicu impuls produksi saliva di mukosa oral seperti nosiseptor, reseptor gustatori, serta reseptor mekanis. Penggunaan obat seperti antihipertensi menyebabkan penghambatan ikatan reseptor adrenergik α1 dan β1. Obat antiaritmia sebagai penekan denyut jantung tidak normal dapat menyebabkan hambatan impuls reseptor adrenergik β1. Pengobatan antipsikotis dapat menyebabkan hambatan impuls di reseptor musarinik M1 dan M3 serta adrenergik α1 (Ekström *et al.*, 2017).

3.2.2.2 Sifat Fisikomia Saliva Pasien Radioterapi Kanker Kepala dan Leher

Radioterapi menyebabkan Xerostomia, kondisi rongga mulut yang mengalami kekeringan karena hiposalivasi (Barrows *et al.,* 2020). Radioterapi menyebabkan laju alir saliva berkurang karena rusaknya sel asinar yang terutama memproduksi kandungan air (H20) di saliva (Lan *et al.*, 2020). Laju alir saliva normal didapatkan rerata 1 ml/menit dengan terstimulus (Deng *et al.,* 2015). Kondisi tanpa stimulus didapatkan laju alir saliva dengan rata-rata 0,3-0,4 ml/menit (Proctor, 2016). Kualitas saliva mengalami penurunan laju alir setelah radioterapi dengan standar hiposalivasi yaitu di saat terstimulus produksi saliva didapatkan kurang dari 0,7 ml/menit serta tanpa stimulus berlaju kurang dari 0,1 ml/menit (Ekström *et al.*, 2017). Rerata hasil laju alir saliva pada Pasien Radioterapi Kanker Kepala dan Leher juga ditemukan sekitar kurang dari 0,5 ml/menit setelah 2 minggu perawatan. (Deng *et al.*, 2015).

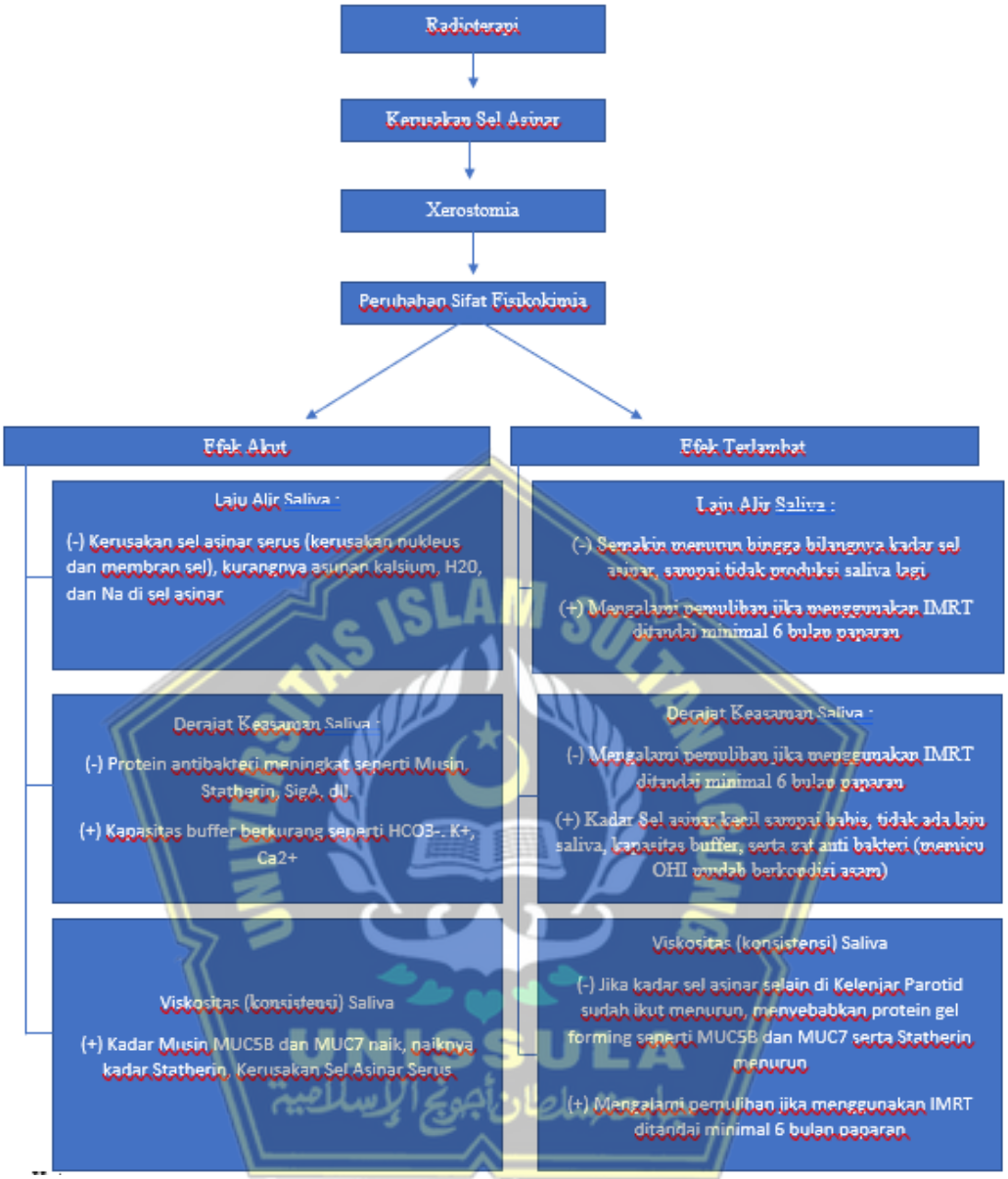
Kualitas saliva yang baik memiliki berbagai fungsi yang baik seperti larutan buffer yang dapat menetralkan keasaman lingkungan rongga mulut (Deng *et al.*, 2015). Kondisi normal pada sifat fisikokimia saliva memiliki berbagai standart yang pasti. Derajat keasaman saliva yang normal didapatkan pH 6,5 – 7,5. Derajat keasaman yang memicu kerusakan gigi geligi terjadi dengan pH 5,5 atau lebih rendah (Ekström *et al.,* 2017). Perubahan disebabkan rusak nya sel asinar menyebabkan konsentrasi larutan buffer yang menurun yaitu bikarbonat (Laheij *et al.,* 2015). Zat buffer lain ditemukan menurun seperti sodium, potasium, kalsium, magnesium, klorida,

dan fosfat. Kerusakan berakibat pada kanal ion yang tidak bisa memberikan akses transport ion (Lan *et al.*, 2020). Menurut Liang dan kawan-kawan induksi radiasi pengion dapat menyebabkan penurunan pH mencapai secara bertahap. Setelah 1 tahun radioterapi, proses penurunan pH dapat mencapai 6,9. Penurunan kapasitas buffer memberikan kandungannya menjadi 70.6% (Liang *et al.*, 2016). Menurut gupta, terjadi perubahan pH saliva setelah radioterapi dari kisaran pH 7 menjadi pH 5 (Gupta, *et al*., 2015).

Kondisi kekentalan saliva dapat diamati dari pemeriksaan visual serta kadar musin yang ada pada kondisi gejala awal Xerostomia (Deng *et al.*, 2015). Kondisi standart kekentalan densitas saliva biasanya terukur secara normal didapatkan kisaran 1 gram / ml (Ekström *et al.*, 2017). Kandungan musin menjadi hal utama yang bersifat viskoelastik yaitu dapat membentuk komponen lapisan jel (*gel forming*) untuk pelindung sel dari patogen. Komponen jsel berfungsi untuk melindungai traktus pencernaan, reproduksi, serta respiratorius. Musin yang paling besar peran dalam pembentukan jel (pelikel mukosa) yaitu MUC5B dan MUC7 (Frenkel and Ribbeck, 2015). Gel forming dapat dibentuk oleh protein lain seperti MUC1, Cystatin, Hystatin, dan Statherin (Roblegg, *et al*., 2019). Proses Xerostomia akut menyebabkan saliva lengket karena kerusakan oleh radioterapi sel asinar serus yang sangat sensitif. Produksi musin menjadi tinggi dan bekerja untuk merespon kadar tinggi bakteri di oral karena jumlah produksi saliva yang berkurang pesat (Delli *et al.*, 2014). Musin berperan dalam hal perlindungan imun di area mukosa oral dengan perlindungan mekanis melalui *gel forming* (mukosa

pelikel) atau *tissue coating*. Produksi musin dapat dipicu dari kondisi rongga mulut yang memiliki banyak patogen yang sudah menginvasi (Frenkel and Ribbeck, 2015). Konsistensi akan menurun ketika memasuki fase lanjut Xerostomia karena kerusakan *massive* sel asinar serus dan mukus (Jensen *et al.*, 2019).

PERUBAHAN SIFAT FISIKOKIMIA SALIVA PADA RADIOTERAPI KANKER KEPALA DAN LEHER



Keterangan :
(-) : Berkurang atau jumlah kadar suatu sifat berkurang
(+) : Bertambah atau jumlah kadar suatu sifat bertambah

Gambar 3. 9 Skema Perubahan Sifat Fisikokimia Saliva oleh Radioterapi

Sumber : (Vissink *et al.*, 2015), (Jensen *et al.*, 2019), (Lacombe *et al.*, 2017), (Gupta, *et al.*, 2015), (Lan *et al.*, 2020), (Pinna *et al.*, 2015), (Roblegg, *et al.*, 2019)

Gambar 3.9 Proses radioterapi menginduksi kerusakan terutama di sel asinar kelenjar saliva. Kerusakan sel asinar serus yang paling radiosensitif menyebabkan efek akut Xerostomia seperti laju alir menurun, kekentalan naik, serta derajat keasaman naik karena kurangnya beberapa kapasitas buffer. Fase lanjut pada Xerostomia dengan fase radioterapi dengan dosis radiasi tinggi menyebabkan laju alir, dan kekentalan semakin menurun, namun derajat keasaman semakin naik karena semakin rusaknya fungsi kelenjar saliva. Hasil IMRT ditemukan mengalami pemulihan di kelenjar saliva menyebabkan fase terlambat mengalami perbaikan sifat fisikokimia saliva karena IMRT menggunakan dosis yang jauh lebih minimalis daripada radioterapi konvensional. Dosis diberikan lebih tepat terarah pada area target dan meminimalisir merusak area jaringan lain sehingga memberikan peluang regenerasi kelenjar saliva.

3.2.3 Manfaat Analisis Kualitas Sifat Fisikokimia Saliva pada Pasien radioterapi Kanker Kepala dan Leher

Analisis sifat fisikokimia saliva menjadi cerminan kondisi tubuh pasien. Pemeriksaan sifat fisikokimia saliva dapat menentukan diagnosa, *monitoring*, dan rencana perawatan. Kelebihan pemeriksaan sifat fisikokimia saliva tidak dibutuhkan keahlian khusus, tidak menimbulkan trauma fisik maupun psikologis sehingga mudah menganalisis hasil sifat fisikokimia saliva pasien radioterapi kanker kepala dan leher (Motamayel *et al.*, 2018).

Penentuan diagnosa dengan sifat fisikokimia saliva dapat menentukan kondisi Xerostomia oleh radioterapi. Poin biomarker utama didapatkan dari

laju alir menurun serta kekentalan tinggi menunjukkan Xerostomia akut. Xerostomia fase lanjut menunujukkan dengan kadar produksi saliva yang sangat rendah (Motamayel *et al.*, 2018). Sifat dari laju alir, kekentalan, dan derajat keasaman saliva dapat menjadi tolak ukur utama dalam hal kualitas fungsi saliva menjaga rongga mulut (Hosseini-Yekani *et al.*, 2018). Kualitas laju alir, kekentalan, dan derajat keasaman dapat menyebabkan perubahan buruk kondisi oral yang sangat cepat oleh radioterapi (Gupta *et al*., 2015).

Prospek *monitoring* dapat berfokus pada fase akut Xerostomia di saat radioterapi kanker kepala dan leher. Kerusakan kelenjar saliva di fase tersebut menjadi cukup tinggi karena sel asinar serus yang radiosensitif. Mengamati proses perubahan sifat fisikokimia selama radioterapi kanker kepala dan leher akan memberikan prognosis yang lebih tepat untuk proses pemulihan penyakit kanker dan Xerostomia. (Jensen *et al.*, 2019). *Monitoring* dan pemilihan rencana perawatan yang tepat akan menangani QoL pasien radioterapi kanker kepala dan leher seperti susah menelan, makan, minum, bicara, nyeri infeksi mukosa oral yang detruktif dan sebagainya. Pengawasan OHI serta psikologis menjadi hal penting untuk pasien dalam menjaga rongga mulut dari infeksi oportunistik (Maria, *et al*, 2017).

Aspek rencana perawatan dapat dipahami oleh dokter gigi maupun pasien karena mengacu akan hal sifat fisikokimia saliva. Dokter gigi menjadi tahu mengenai edukasi utama yang perlu diberikan kepada pasien radioterapi kanker kepala dan leher untuk meningkatkan produksi kualitas sifat fisikokimia saliva (Gupta *et al*., 2015). Edukasi bisa diberikan seperti kondisi

oral yang diperbolehkan untuk radioterapi kanker kepala dan leher berdasarkan keilmuan konservasi, prosthodonsi, periodonsi, biologi oral, orthodonsi, maupun bedah mulut (Beech *et al.*, 2014). Sebelum radioterapi, dokter gigi perlu mengedukasi mengenai perawatan dan manifestasi oral pada radioterapi. Perawatan utama yang bisa dilakukan oleh pasien meliputi menjaga OHI seperti *dental flossing* setiap hari dan sikat gigi 2-4 kali sehari, mengontrol plak dengan cairan kumur *chlorhexidine* setelah sikat gigi, pemberian *fluoride* dengan konsentrasi 5000ppm, obat stimulan produksi saliva seperti *pilocarpine* dengan dosis aman berkisar 2,5 mg dalam waktu 3 kali sehari selama 8-12 minggu atau sesuai dosis yang ada (Gupta, *et al.*, 2015). *Pilocarpine* dapat memberikan induksi situmulus reseptor M1 dan M3 untuk mangaktifkan Ca2+ supaya bisa melakukan sekresi saliva primer (Hu *et al.*, 2020).

3.3 Keterbatasan

Keterbatasan *literature review* ini yaitu keterbatasan jurnal atau artikel terkait *outcome* kekentalan dengan besaran yang sesuai. Pengamatan analisis dapat dilakukan untuk pengukuran *outcome* khusus pada kekentalan saliva yang disebabkan oleh radioterapi kanker kepala dan leher dengan besaran yang pasti.

BAB IV

KESIMPULAN DAN REKOMENDASI

4.1 Kesimpulan

Radioterapi kanker kepala dan leher dapat menyebabkan kerusakan kualitas sifat fisikokimia saliva melalui Xerostomia. Proses Xerostomia terjadi pada fase akut yaitu sifat fisikokimia laju alir saliva dan derajat keasaman menurun serta kekentalannya meningkat. Terjadi penurunan kualitas sifat fisikokimia (laju alir, kekentalan, dan derajat keasaman) yang merusak jaringan rongga mulut di fase lanjut. Pengaruh utama kerusakan tersebut yaitu akibat dosis radioterapi. Semakin tinggi dosis radioterapi, maka semakin tinggi efek kerusakan sifat fisikokimia saliva. Kerusakan utama terjadi pada sel asinar yang mengalami kerusakan DNA dalam proses *double strand breaks* serta kerusakan pompa ion dan reseptor membran sel asinar.

Penanganan kesehatan oral pasien radioterapi kanker kepala dan leher dapat dilakukan dengan mengamati hasil sifat fisikokimia saliva. Edukasi menjadi hal utama persiapan menjaga kesehatan oral untuk menghadapi komplikasi radioterapi kanker kepala dan leher dengan mengamati sifat fisikokimia saliva. Edukasi utama yang diberikan meliputi *maintaining* OHI dan memberikan stimulasi saliva sehingga kualitas sifat fisikokimia saliva meningkat.

4.2 Rekomendasi

1. Untuk analisis lebih lanjut mengenai pengamatan atau penelitian besaran satuan kekentalan saliva sehingga didapatkan hasil yang lebih akurat secara kuantitatif.

2. Untuk analisis lebih lanjut mengenai pengamatan atau penelitian sifat fisikokimia saliva yang berkaitan dengan pengelompokan sampel berdasarkan faktor predisposisi spesifik seperti penggunaan alkohol, rokok, dan lain-lain.

3. Untuk penelitian lebih lanjut mengenai perubahan sifat fisikokimia saliva sebelum dan setelah radioterapi pasien kanker dan leher.

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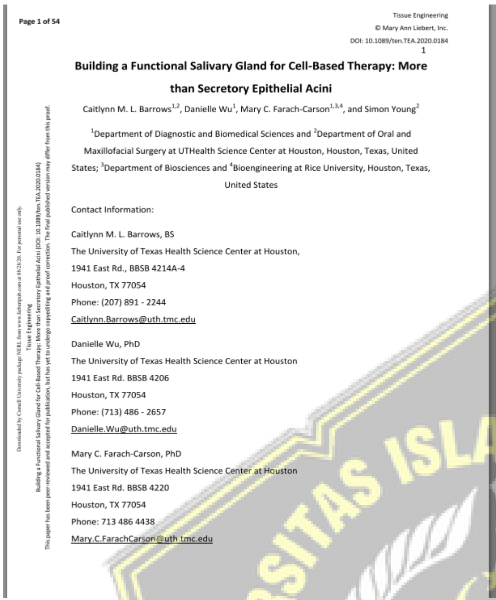

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Building a Functional Salivary Gland for Cell-Based Therapy: More than Secretory Epithelial Acini

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Dental management of patients irradiated for head and neck cancer

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ABSTRACT

Patients undergoing radiation therapy as either primary, adjuvant, combination therapy or palliative management of head and neck malignancies are prone to a range of dental complications. Strategies for prevention and management of such complications may be controversial. This article aims to highlight the current understanding and management of the dental needs for patients before, during and after radiation therapy.

Keywords: Head and neck oncology, management, prevention, radiation, restoration.

Abbreviations and acronyms: GIC = glass ionomer cement; HNC = head and neck cancer; HPV = Human Papilloma Virus; IMRT = intensity-modulated radiotherapy; ISOO = International Society of Oral Oncology; MASCC = Multinational Association of Supportive Care in Cancer; MDT = multidisciplinary team; MMP = matrix metalloproteinases; OPC = oropharyngeal candidiasis; ORN = osteoradionecrosis of the jaw; PRP = platelet-rich plasma; RMGIC = resin modified glass ionomer cement; RT = radiation therapy.

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INTRODUCTION

Head and neck cancers (HNC) are often treated with radiation therapy (RT), a technique that utilizes ionizing radiation and exerts therapeutic effect by semi-selectively damaging the genetic material of vulnerable malignant cells, either directly or through the production of free radicals, resulting in cell death.

Adverse effects of RT arise by the same mechanism damaging normal cells, especially those that are rapidly dividing, or otherwise less capable of repairing radiation induced damage.[1] In the oral cavity these can be cells of the mucous membrane, underlying soft tissue, tooth, periosteum, bone, glands and vasculature resulting in specific radiation syndromes. Such syndromes include xerostomia and dysgeusia from salivary gland damage, mucositis from epithelial damage, pathological alterations in the normal flora alterations, radiation caries, reduced mouth opening from changes in collagen structure and osteoradionecrosis of the jaw (ORN) from reduced bone healing capacity.[2–6]

Management of oral health is especially important for the HNC patient as oral complications are common both during and after radiation. For example, xerostomia may affect up to 90% of patients undergoing radiotherapy; mucositis more than 60%; candidiasis more than 40%; post-radiotherapy dental decay more than 50%[7] and osteoradionecrosis up to 15%.[3,4,8,9]

While the majority of oral complications are unavoidable consequences of ionizing radiation (deterministic), some are preventable.[10] The incidence of some complications is associated with treatment factors, such as in the case of osteoradionecrosis and dental extractions.[8,11,14] As oral complications are common, potentially preventable and have iatrogenic factors, it is essential that those working with HNC patients be aware of the prevention and management of radiotherapy-related oral complications.

In this article we aim to highlight the current understanding and management of the dental needs for patients who have or will undergo radiation therapy.

Pre-radiotherapy dental assessment

The benefit of a multidisciplinary team (MDT) approach to assessing, diagnosing and managing head and neck cancer patients is widely acknowledged and as such, every patient with head and neck cancer should be managed in this environment.[15] Given the oral and dental implications related to treatment, a dental practitioner with experience in HNC should be included at the minimum. An expanded dental team

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Scintigraphic assessment of salivary function after intensity-modulated radiotherapy for head and neck cancer: Correlations with parotid dose and quality of life

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SUMMARY

Objective: We investigated salivary function using quantitative scintigraphy and sought to identify functional correlations between parotid dose and quality of life (QoL) for head and neck cancer (HNC) patients receiving intensity-modulated radiotherapy (IMRT).
Materials and methods: Between August, 2007 and June, 2008, 31 patients treated IMRT for HNC were enrolled in this prospective study. Salivary excretion function (SEF) was previously measured by salivary scintigraphy at annual intervals for 2 years after IMRT. A dose-volume histogram of each parotid gland was calculated, and the normal tissue complication probability (NTCP) was used to determine the tolerance dose. QoL was longitudinally assessed by the EORTC QLQ-C30 and H&N35 questionnaires prior to RT, and at one, three, 12 and 24 months after RT.
Results: A significant correlation was found between the reduction of SEF and the mean parotid dose measured at 1 year (correlation coefficient, $R^2 = 0.651$) and 2 years ($R^2 = 0.310$) after IMRT ($p < 0.001$). The TD_{50} of the parotid gland at 1 year after IMRT is 43.6 Gy, comparable to results from western countries. We further found that contralateral parotid and submandibular gland function preservation was correlated with reduced sticky saliva and a better QoL compared to the functional preservation of both parotid glands, as determined by the EORTC QLQ-H&N35 questionnaire.
Conclusion: A significant correlation was found between the reduction of SEF and the mean parotid dose. Preservation of contralateral parotid and submandibular gland function predicts a better QoL compared to preservation of the function of both parotid glands.

Introduction

Xerostomia is a common side-effect that occurs after radiotherapy (RT) in patients with head and neck cancer (HNC). Modern RT techniques, such as three-dimensional conformal RT, or intensity-modulated RT (IMRT), can spare salivary glands, thus preserving salivary flow rates and improving observer-accessed xerostomia compared to conventional RT.[1–3] The parotid gland dose-volume response following RT has been investigated in several large prospective studies.[4–8] A wide range (26–43 Gy) of threshold mean dose (TD_{50}), the dose resulting in a 50% probability of a complication for the whole organ irradiated uniformly, for parotid gland-stimulated salivary flow, has been reported. The mean dose reported to preserve parotid gland function in Asian studies varies from 31 to 43.9 Gy[9–11]; yet, none reported the TD_{50}.

Although the apparent improvement in objective salivary function and observed xerostomia was achieved by 3-D conformal or IMRT, the result does not necessarily improve the patient-reported xerostomia.[12] Since xerostomia is mainly a quality of life issue, a patient-reported quality of life questionnaire is more useful in assessing salivary function. Therefore, in the present prospective

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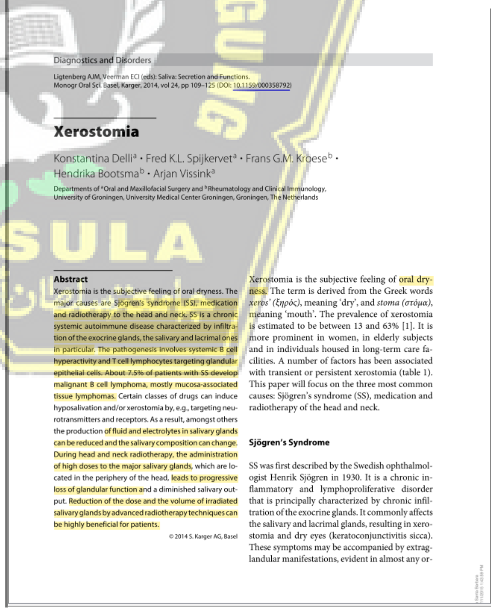

Diagnostics and Disorders

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Xerostomia

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Abstract

Xerostomia is the subjective feeling of oral dryness. The major causes are Sjögren's syndrome (SS), medication and radiotherapy to the head and neck. SS is a chronic systemic autoimmune disease characterized by infiltration of the exocrine glands, the salivary and lacrimal ones in particular. The pathogenesis involves systemic B cell hyperactivity and T cell lymphocytes targeting glandular epithelial cells. About 7.5% of patients with SS develop malignant B cell lymphoma, mostly mucosa-associated tissue lymphomas. Certain classes of drugs can induce hyposalivation and/or xerostomia by, e.g., targeting neurotransmitters and receptors. As a result, amongst others the production of fluid and electrolytes in salivary glands can be reduced and the salivary composition can change. During head and neck radiotherapy, the administration of high doses to the major salivary glands, which are located in the periphery of the head, leads to progressive loss of glandular function and a diminished salivary output. Reduction of the dose and the volume of irradiated salivary glands by advanced radiotherapy techniques can be highly beneficial for patients.

Xerostomia is the subjective feeling of oral dryness. The term is derived from the Greek words *xeros' (ξηρός)*, meaning 'dry', and *stoma (στόμα)*, meaning 'mouth'. The prevalence of xerostomia is estimated to be between 13 and 63% [1]. It is more prominent in women, in elderly subjects and in individuals housed in long-term care facilities. A number of factors has been associated with transient or persistent xerostomia (table 1). This paper will focus on the three most common causes: Sjögren's syndrome (SS), medication and radiotherapy of the head and neck.

Sjögren's Syndrome

SS was first described by the Swedish ophthalmologist Henrik Sjögren in 1930. It is a chronic inflammatory and lymphoproliferative disorder that is principally characterized by chronic infiltration of the exocrine glands. It commonly affects the salivary and lacrimal glands, resulting in xerostomia and dry eyes (keratoconjunctivitis sicca). These symptoms may be accompanied by extraglandular manifestations, evident in almost any or-

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Review

Dental demineralization and caries in patients with head and neck cancer

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SUMMARY

Concurrent chemoradiation (CCR) therapy is a standard treatment for patients with locally advanced head and neck cancer (HNC). It is well documented that CCR causes profound acute and late toxicities. Xerostomia (the symptom of dry mouth) and hyposalivation (decreased salivary flow) are among the most common treatment side effects in this cohort of patients during and following treatment. They are the result of radiation-induced damage to the salivary glands. Patients with chronic hyposalivation are at risk for demineralization and dental cavitation (dental caries), often presenting as a severe form of rapidly developing decay that results in loss of dentition. Usual post-radiation oral care which includes the use of fluoride, may decrease, but does not eliminate dental caries associated with radiation-induced hyposalivation. The authors conducted a narrative literature review regarding dental caries in HNC population based on MEDLINE, PubMed, CINAHL, Cochrane database, EMBASE, and PsycINFO from 1985 to 2014. Primary search terms included *head and/or neck cancer, dental caries, dental decay, risk factor, physical symptom, physical sequelles, body image, quality of life, measurement, assessment, cost, prevention, and treatment*. The authors also reviewed information from National Institute of Dental and Craniofacial Research (NIDCR), American Dental Association (ADA), and other related healthcare professional association web sites. This literature review focuses on critical issues related to dental caries in patients with HNC: potential mechanisms and contributing factors, clinical assessment, physical sequelea, negative impact on body image and quality of life, potential preventative strategies, and recommendations for practice and research in this area.

Introduction

Treatment paradigms for head and neck cancer (HNC) have shifted dramatically over the past two decades. Increased use of chemoradiation for patients with locally advanced HNC has improved local disease control and overall survival [1]. Unfortunately, chemoradiation is associated with increased acute and late effects that result in substantial symptom burden and decrements in quality of life (QoL) [2–5]. A second major paradigm shift results from the epidemic of human papillomavirus (HPV)-associated HNCs [6,7]. These tumors are biologically and epidemiologically distinct. Of note, the literature provides evidence of improved survival in patients with HPV-positive HNC [8]. Patients with HPV-associated HNC are younger, thus long-term functional outcomes are of critical importance as these patients are likely to live for protracted periods with the late effects of therapy. The treatment and epidemiologic shifts noted above have resulted in an increased number of HNC survivors. There are more than half a million HNC survivors in the United States [9]. Prevention and treatment of long-term effects of HNC therapy have therefore become a priority issue. Among common but under-addressed long-term effects of radiation therapy are oral complications such as, xerostomia and hyposalivation, dental demineralization and caries, trismus, and osteonecrosis [10] (see Figs. 1 and 2).

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Methods

The authors conducted a narrative literature review regarding dental caries in HNC population based on MEDLINE, PubMed,

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REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Head and Neck Cancer

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ALTHOUGH HEAD AND NECK CANCER IS ASSOCIATED WITH PAIN, DISFIGURation, dysfunction, psychosocial distress, and death, recent advances have brought substantial improvements in outcomes. The introduction of immune-checkpoint inhibitors for treatment of recurrent or metastatic head and neck cancer led to a remarkable benefit for some patients. In parallel, improvements in standard therapy, such as minimally invasive, organ-sparing surgical techniques; advances in radiotherapy, and curative multimodal approaches, have enhanced preservation of function and reduced morbidity and mortality. Increased awareness and diagnosis of human papillomavirus (HPV)–associated oropharyngeal carcinoma, alongside decreases in tobacco-related head and neck cancers, are similarly changing the understanding of this disease, its treatment, and the prognosis for affected patients.

DEFINITION

The prognosis and multimodal therapeutic options for patients with head and neck cancer vary depending on epidemiologic factors, anatomical location, and stage. There is marked heterogeneity of tumors arising in the head and neck region (Fig. 1). The focus here is on squamous-cell carcinomas arising from mucosal surfaces of four major anatomical sites: the oral cavity, sinonasal cavity, pharynx, and larynx. (Nasopharyngeal cancer is not discussed because of differences in epidemiology, pathology, natural history, and treatments that are beyond the scope of this review.)

EPIDEMIOLOGY

Head and neck cancer was the seventh most common cancer worldwide in 2018 (890,000 new cases and 450,000 deaths),[1] accounting for 3% of all cancers (51,540 new cases) and just over 1.5% of all cancer deaths (10,030 deaths) in the United States.[2] Typically diagnosed in older patients in association with heavy use of tobacco and alcohol, head and neck cancers are slowly declining globally, in part because of decreased use of tobacco.[3,4]

Conversely, cases of HPV-associated oropharyngeal cancer, induced primarily by HPV type 16, are increasing, predominantly among younger people in North America and northern Europe, reflecting a latency of 10 to 30 years after oral-sex exposure.[4,5] The fraction of head and neck cancers diagnosed as HPV-positive oropharyngeal cancers in the United States rose from 16.3% in the 1980s to more than 72.7% in the 2000s as a result of increased awareness, identification of the association between HPV and cancers of the head and neck, and enhanced diagnostic evaluation for HPV.[3] The effectiveness of prophylactic HPV vaccination is less well defined for oropharyngeal cancer than for anogenital and cervical can-

Saliva and the Control of Its Secretion

Jörgen Ekström, Nina Khosravani, Massimo Castagnola, and Irene Messana

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Journal of Oral Microbiology

REVIEW ARTICLE

Salivary mucins in host defense and disease prevention

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Mucus forms a protective coating on wet epithelial surfaces throughout the body that houses the microbiota and plays a key role in host defense. Mucins, the primary structural components of mucus that creates its viscoelastic properties are critical components of the gel layer that protect against invading pathogens. Altered mucin production has been implicated in diseases such as ulcerative colitis, asthma, and cystic fibrosis, which highlights the importance of mucins in maintaining homeostasis. Different types of mucins exist throughout the body in various locations such as the gastrointestinal tract, lungs, and female genital tract, but this review will focus on mucins in the oral cavity. Salivary mucin structure, localization within the oral cavity, and defense mechanisms will be discussed. These concepts will then be applied to present what is known about the protective function of mucins in oral diseases such as HIV/AIDS, oral candidiasis, and dental caries.

Keywords: saliva; mucin; oral health; MUC5B; MUC7

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Mucins, the primary gel-forming components of mucus, provide a critical layer of protection on wet epithelial surfaces in the body including the gastrointestinal tract, female genital tract, and respiratory tract. Unregulated mucin production can greatly affect the health of the host. For example, mice spontaneously develop ulcerative colitis when intestinal mucin is artificially downregulated (1). In a separate study where lung mucin was downregulated in mice, there were significantly more bacteria in their lungs, which greatly reduced long-term survival (2). In the oral cavity, decreased salivary flow is linked to the increased incidence of candidiasis and dental caries, which could be caused by reduced levels of salivary mucins (3–6). These findings highlight the importance of regulated mucin production, but our understanding of the precise mechanisms by which mucins provide protection in the oral cavity is continually being revised. One of the primary questions that still remains unanswered is how the mucus layer protects the oral cavity from pathogenic microbes and harmful substances while also providing a home for the beneficial oral microbiota. This review will provide an overview of what is known about the structural features of salivary mucins, potential mechanisms by which salivary mucins protect the oral cavity without widespread bacterial killing, and how they play a role in the prevention of specific oral diseases.

Introduction to salivary mucins

There are at least 20 identified mucins throughout the human body that cover wet epithelial surfaces such as the gastrointestinal tract, respiratory tract, and eyes. A summary of areas where mucins can be found in the body is given in Fig. 1a. Each of these mucins has a unique structure that can influence its localization and function. This section will address structural aspects of the mucins found in the oral cavity, MUC5B, MUC7, MUC19, MUC1, and MUC4 (7).

Mucins in the oral cavity

Each of the salivary mucins MUC5B, MUC7, MUC19, MUC1, and MUC4 are composed of a unique domain structure that influences the mucins' physical properties and localization in the oral cavity (Fig. 1b). MUC5B is the primary gel-forming mucin in the mouth that is secreted by mucous cells in the submandibular, sublingual, palatine, and labial salivary glands (8, 9). Transcripts and glycoproteins of MUC19, another gel-forming salivary mucin, have been identified, but MUC5B is still thought to be the predominate gel-forming mucin in the oral cavity (10–12).

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Radiation-induced dental caries, prevention and treatment - A systematic review

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Abstract

Go to:

Introduction

Head and neck squamous cell carcinoma is the sixth most common form of cancer worldwide and represents approximately 5% of all cancers diagnosed annually in the United States.[1] India continues to report the highest prevalence of oral cancers with 75,000–80,000 new cases of such cancers reported every year. There are about 700,000 new cases of cancers every year in India out of which tobacco-related cancers are 300,000. According to WHO 8.2 million people worldwide died from cancer in 2012, 60% of world's total new annual cases occur in Africa, Asia, and Central and South America.

Head and neck cancers (HNCs) are often treated with radiation therapy (RT), a technique that utilizes ionizing radiation and semi-selectively damages the genetic material of vulnerable malignant cells, directly or through the production of free radicals, leading to cell death. Beech *et al.*, mentioned in a study that RT damages normal cells also,

Hadley *et al. Medical Gas Research* 2013, **3**:15
http://www.medicalgasresearch.com/content/3/1/15

MEDICAL GAS RESEARCH

STUDY PROTOCOL Open Access

Does hyperbaric oxygen therapy have the potential to improve salivary gland function in irradiated head and neck cancer patients?

Tiffany Hadley[1], Cassaundra Song[2], Lauren Wells[3], Jennifer Lehnhardt[3], Marcy Wells Rogers[3], Jeffery Anderson[4], Michael Terry[5], Brian Novy[6] and Takkin Lo[7*]

Abstract

Following radiotherapy, many patients with osteoradionecrosis suffer from xerostomia, thereby decreasing their quality of life. Patients can develop problems with speech, eating, increased dental caries, dysphagia, fractured dentition, chronic refractory osteomyelitis and osteoradionecrosis. Symptoms associated with salivary gland dysfunction can be severe enough that patients terminate the course of their radiotherapy prematurely due to the decrease in their quality of life. Currently, the only treatments available to patients are palliative. A definitive treatment has yet to be discovered. Head and neck cancers, which comprise 5% of overall cancer treatments, rank 8th most expensive to treat in the United States today. Hyperbaric oxygen is being considered for the therapy of radiated salivary glands because it has been shown to stimulate capillary angiogenesis and fibroplasia in radiation treated tissues. It has been hypothesized that salivary acinar cells undergo apoptosis following radiation therapy. The purpose of this paper is to discuss the mechanisms of salivary gland injury and evaluate whether hyperbaric oxygen therapy improves salivary gland function in patients who develop xerostomia and osteoradionecrosis following head and neck radiation.

Keywords: Osteoradionecrosis, Xerostomia, Saliva, Hyperbaric Oxygen Therapy

Background

Head and neck cancers account for approximately 5% of the overall cancers treated in the United States and ranked the 8th most expensive cancer in the United States today [1]. There are five primary sites that make up this group of cancers: larynx, pharynx, oral cavity, salivary glands, and paranasal sinuses [2]. Of these patients who undergo standard head and neck radiotherapy, significant damage to the salivary glands can occur and result in hyposalivation and xerostomia, which is the condition of dry mouth caused by decreased salivation. In addition, hyposalivation is among the most widely recognized causes of dental caries, and oral discomfort, which includes oral sores, changes in taste, difficulty chewing, swallowing, and difficulty with speech [3]. This condition place patients at risk for dental caries and tooth decay because saliva normally bathes the oral cavity and acts as a clearing agent [4]. Xerostomia is one of the most common complications of head and neck irradiation, and essentially all patients that undergo radiotherapy will develop some form of xerostomia as a result of damage to their major and minor salivary glands [5]. End-stage complications of hyposalivation include fractured dentition, osteonecrosis, and chronic refractory osteomyelitis. Patients affected by salivary gland dysfunction often terminate their radiotherapy course prematurely because they become malnourished and experience a significant decrease in their quality of life [5]. Intensity-modulated radiation therapy as opposed to traditional radiation therapy, acupuncture, other masticatory or gustatory stimulatory therapies, administration of cytoprotective agents (i.e. amifostine), stimulation of residual tissue with cholinergic muscarinic agents (i.e. pilocarpine and bethanecol), and various lubricating agents are some options to aid with symptom control

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Original Article

Relationship between Physicochemical Properties of Saliva and Dental Caries and Periodontal Status among Female Teachers Living in Central Iran

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ABSTRACT

Objectives: There are inconsistent data about the association between saliva properties, dental caries, and periodontal status. In this study, we tried to examine the association between dental caries and periodontal status with salivary viscosity, flow rate, pH, and buffering capacity in adults.

Methods: In the present cross-sectional study, 450 female teachers were randomly selected from schools located in Yazd, Iran. Oral examinations were conducted, and unstimulated saliva samples were collected. Salivary viscosity, flow rate, pH, and buffering capacity were assessed. The salivary physicochemical properties were compared among teachers with different types of oral health. Analyses were done using the Statistical Package for the Social Sciences version 16.

Results: In total, 431 female teachers aged 40.45 ± 8.18 years were included in the study. Salivary flow rate, buffering capacity, pH, and viscosity, community periodontal index status were not significantly different in participants with and without tooth caries. There was a reverse linear association between salivary pH and flow rate with the decayed, missed, and filled teeth index ($P < 0.05$). The saliva buffering capacity was not significantly related to dental properties. Those with bleeding on probing had lower salivary pH, and buffering capacity compared to those with healthy gum. However, the salivary resting flow rate was not different in participants with bleeding on probing and healthy participants.

Conclusion: Based on our results, saliva properties might be important predictors in oral health status. This means that any change in saliva combination might affect periodontal and dental diseases. Future prospective studies are recommended to confirm these results.

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KEYWORDS: *Dental caries, periodontal index, physicochemical properties, saliva*

Introduction

Saliva is a body fluid secreted by salivary glands which essentially contains water, proteins, glycoproteins, electrolytes, small organic molecules, and compounds that is transported from the bloodstream.[1-3] It plays an important role in maintaining oral health due to its biological functions such as food swallowing, lubrication of oral tissues, and washing off food debris.[1] Saliva also helps maintaining the integrity of dental tissues and especially helps in prevention of dental caries.[2] Furthermore, it has three specific roles in the oral cavity. First, it protects the enamel against demineralization caused by the acids. Second, it facilitates the remineralization of incipient caries and then the last one it has some antimicrobial functions.[1,4]

Saliva can be assessed by some characteristics, such as flow rate, buffering capacity, hydrogen-ion

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Accepted Article

Dry mouth diagnosis and saliva substitutes — A review from a textural perspective

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Signal Transduction and Targeted Therapy www.nature.com/sigtrans

REVIEW ARTICLE OPEN

DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer

Rui-Xue Huang[1] and Ping-Kun Zhou[2,3]

Radiotherapy is one of the most common countermeasures for treating a wide range of tumors. However, the radioresistance of cancer cells is still a major limitation for radiotherapy applications. Efforts are continuously ongoing to explore sensitizing targets and develop radiosensitizers for improving the outcomes of radiotherapy. DNA double-strand breaks are the most lethal lesions induced by ionizing radiation and can trigger a series of cellular DNA damage responses (DDRs), including those helping cells recover from radiation injuries, such as the activation of DNA damage sensing and early transduction pathways, cell cycle arrest, and DNA repair. Obviously, these protective DDRs confer tumor radioresistance. Targeting DDR signaling pathways has become an attractive strategy for overcoming tumor radioresistance, and some important advances and breakthroughs have already been achieved in recent years. On the basis of comprehensively reviewing the DDR signal pathways, we provide an update on the novel and promising druggable targets emerging from DDR pathways that can be exploited for radiosensitization. We further discuss recent advances identified from preclinical studies, current clinical trials, and clinical application of chemical inhibitors targeting key DDR proteins, including DNA-PKcs (DNA-dependent protein kinase, catalytic subunit), ATM/ATR (ataxia–telangiectasia mutated and Rad3-related), the MRN (MRE11-RAD50-NBS1) complex, the PARP (poly(ADP-ribose) polymerase) family, MDC1, Wee1, LIG4 (ligase IV), CDK1, BRCA1 (BRCA1 C terminal), CHK1, and HIF-1 (hypoxia-inducible factor-1). Challenges for ionizing radiation-induced signal transduction and targeted therapy are also discussed based on recent achievements in the biological field of radiotherapy.

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INTRODUCTION

The increasing prevalence of cancer worldwide is a major challenge to the improvement of quality and length of life. According to reports, 975,396 patients were newly diagnosed with cancer in 2012, and there were 358,392 deaths due to cancer in youth globally[1]. In 2015, the number of identified cancer cases increased to ~17.5 million, and the deaths from cancers increased to 8.7 million globally. Notably, from 2005 to 2015 (an 11-year span), the number of patients with cancer increased by 33%[2]. In 2016, ~9 million deaths were attributed to cancer, an increase of almost 18% over one decade[3]. Moreover, in the United States in 2017, there were 1,688,780 newly diagnosed cancer patients and almost 600,920 deaths due to cancer[4]. These numbers have increased rapidly annually, and in 2018, ~18.1 million newly diagnosed cancer patients and 9.6 million cancer deaths were reported worldwide[5]. In China, in 2014, there were 3.804 million newly diagnosed cancer patients and 2.296 million cancer deaths, and the statistical results showed that the crude incidence rate and the crude mortality rate were 278.07 per 100,000 people and 167.89 per 100,000 people, respectively[6]. Furthermore, it is estimated that by 2035, the number of annual cancer deaths will reach 14.5 million because worldwide cancer cases are expected to dramatically increase from 15 million at present to 24 million in the next 20 years[7]. Moreover, in parallel with the increasing rates of cancer diagnosis and death, the global burden of cancer has gradually increased over the past decade. Based on the Global Burden of Disease Cancer Collaboration announcement, 208.3 million disability-adjusted life-years (DALYs) were attributed to cancer globally in 2015. Lung cancer was the top cause of death among males, accounting for 25.9 million DALYs, while in females, breast cancer-attributable deaths were the top cause, accounting for 15.1 million DALYs[8]. Significant advances in the war against cancer have been achieved over the past decade. For instance, deaths from Hodgkin lymphoma declined significantly between 2005 and 2015 (−6.1%; 95% uncertainty interval: −10.6% to −1.3%), and other cancer deaths, such as deaths from esophageal cancer and stomach cancer, have also significantly decreased over the past decade[8]. Additionally, through large-action control of tobacco use and human papillomavirus vaccination in females, the burden of cancer in the female population has been substantially decreased in both economically developed and economically developing areas[7]. Although large-scale implementation of prevention and treatment methods has made these improvements possible, there is still a long way to go in the fight against cancer.

The management of cancer mainly involves surgery, radiotherapy, chemotherapy, and the rapidly evolving field immunotherapy[9]. The most commonly used cancer therapies over the past century include chemotherapy and radiotherapy methods[10–12]; among these, radiotherapy is widely and predominantly used prior to surgery and other treatment methods[13–15]. Radiotherapy is

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Article

ARTICLE

Salivary Gland Hypofunction and Xerostomia in Head and Neck Radiation Patients

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Abstract

Background: The most manifest long-term consequences of radiation therapy in the head and neck cancer patient are salivary gland hypofunction and a sensation of oral dryness (xerostomia).
Methods: This critical review addresses the consequences of radiation injury to salivary gland tissue, the clinical management of salivary gland hypofunction and xerostomia, and current and potential strategies to prevent or reduce radiation injury to salivary gland tissue or restore the function of radiation-injured salivary gland tissue.
Results: Salivary gland hypofunction and xerostomia have severe implications for oral functioning, maintenance of oral and general health, and quality of life. Significant progress has been made to spare salivary gland function chiefly due to advances in radiation techniques. Other strategies have also been developed, e.g., radioprotectors, identification and preservation/expansion of salivary stem cells by stimulation with cholinergic muscarinic agonists, and application of new lubricating or stimulatory agents, surgical transfer of submandibular glands, and acupuncture.
Conclusion: Many advances to manage salivary gland hypofunction and xerostomia induced by radiation therapy still only offer partial protection since they are often of short duration, lack the protective effects of saliva, or potentially have significant adverse effects. Intensity-modulated radiation therapy (IMRT), and its next step, proton therapy, have the greatest potential as a management strategy for permanently preserving salivary gland function in head and neck cancer patients. Presently, gene transfer to supplement fluid formation and stem cell transfer to increase the regenerative potential in radiation-damaged salivary glands are promising approaches for regaining function and/or regeneration of radiation-damaged salivary gland tissue.

It is well documented that head and neck radiotherapy, in addition to its antitumor effects, inevitably induces severe adverse effects to normal oral tissues surrounding the tumor tissue. Adverse effects include mucositis, pain, salivary gland hypofunction (objectively decreased saliva secretion), and xerostomia (subjective feeling of dry mouth), fungal infection, taste disturbances and muscular fibrosis. Depending on the cumulative radiation dose to the gland tissue, permanent salivary gland hypofunction may occur, impeding oral functioning, compromising oral and general health, and diminishing the quality of life following radiation therapy in head and neck cancer patients (1–4). In addition, the head and neck cancer patient may also experience a heavy economic burden due to the extensive need for oral preventive measures and dental treatment after radiation therapy. It should be noted that salivary gland hypofunction and xerostomia may also be sequelae of other radiation regimes, although to a much lesser extent, that is, radioiodine treatment of thyroid cancer and preconditioning total body irradiation in hematopoietic stem cell transplantation for the treatment of hematologic malignancies (4–6).

The National Institutes of Health (NIH) Consensus Conference

In 1989, the NIH sponsored the first Development Consensus Conference on Oral Complications of Cancer Therapies (7). No

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Minireview

Saliva diagnostics – Current views and directions

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Impact statement

The purpose of this mini-review is to make an update about the present and future applications of saliva as a diagnostic biofluid in many fields of science such as dentistry, medicine and pharmacotherapy. Using saliva as a fluid for diagnostic purposes would be a huge breakthrough for both patients and healthcare providers since saliva collection is easy, non-invasive and inexpensive. We will go through the current main diagnostic applications of saliva, and provide a highlight on the emerging, newly developing technologies and tools for cancer screening, detection and monitoring.

Abstract

In this review, we provide an update on the current and future applications of saliva for diagnostic purposes. There are many advantages of using saliva as a biofluid. Its collection is fast, easy, inexpensive, and non-invasive. In addition, saliva, as a "mirror of the body," can reflect the physiological and pathological state of the body. Therefore, it serves as a diagnostic and monitoring tool in many fields of science such as medicine, dentistry, and pharmacotherapy. Introduced in 2008, the term "Salivaomics" aimed to highlight the rapid development of knowledge about various "omics" constituents of saliva, including: proteome, transcriptome, micro-RNA, metabolome, and microbiome. In the last few years, researchers have developed new technologies and validated a wide range of salivary biomarkers that will soon make the use of saliva a clinical reality. However, a great need still exists for convenient and accurate point-of-care devices that can serve as a non-invasive diagnostic tool. In addition, there is an urgent need to decipher the scientific rationale and mechanisms at convey systemic diseases to saliva. Another promising technology called liquid biopsy enables detection of circulating tumor cells (CTCs) and fragments of tumor DNA in saliva, thus enabling non-invasive early detection of various cancers. The newly developed technology – electric field-induced release and measurement (EFIRM) provides near perfect detection of actionable mutations in lung cancer patients. These recent advances widened the salivary diagnostic approach from the oral cavity to the whole physiological system, and thus point towards a promising future of salivary diagnostics for personalized individual medicine applications including clinical decisions and post-treatment outcome predictions.

Keywords: Saliva, diagnostics, trancriptomics, point-of-care, liquid biopsy, biomarkers

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Introduction

Saliva (whole saliva [WS], oral fluids [OFs]) is an acidic (pH = 6–7) biological fluid composed of secretions from the three major salivary glands (parotid, submandibular, sublingual) and from minor glands (i.e. labial, buccal, lingual, and palatal tissues), gingival crevicular fluid, cell debris, plaque, bacteria, nasal and bronchial secretions, lining cells, blood and exogenous substances.[1,2] It contains 99% water, 0.3% proteins and both 0.2% inorganic and organic substances.[3] The most prevalent inorganic components include: sodium, potassium, calcium, magnesium, chloride, and carbonates, while the organic components comprise amylases, peroxidase, lipase, mucins, lysozyme, lactoferrins, kallikreins, cystatins, hormones, and growth factors.[4] In a healthy individual, the daily salivary secretion is estimated to be between 0.5 and 1.5 L.[3]

Saliva plays an important role in many biological functions such as perception of oral sensations (i.e. taste, temperature and touch), lubrication, chewing, swallowing, and digestion. In addition, it enhances remineralization of tooth enamel and prevents demineralization due to its buffering capacity.[4–7]

Saliva also protects oral mucosa against biological, mechanical, and chemical factors, as well as against bacterial, viral, and fungal infections, thus maintaining the oral cavity ecosystem remain in balance.[8,9]

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Radiotherapy for Head and Neck cancers-a review

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Abstract

Radiotherapy still remains an enigma in the treatment of Head and Neck cancers. Radiotherapy treatment planning of Head and Neck cancers pose a challenge due to its proximity to critical adjacent organs. This article briefs the various types, uses, techniques of Radiotherapy.

Keywords: Radiotherapy, Van de Graff Generator, Linearaccelerator, Brachytherapy, Teletherapy.
Key Messages: Radiotherapy still remains an enigma in the treatment of Head and Neck cancers. Radiotherapy treatment planning of Head and Neck cancers pose a challenge due to its proximity to critical adjacent organs. This article briefs the evolution, various types, uses, techniques of Radiotherapy.

Introduction

The invention of xray by Wilhelm Conrad Roentgen and radioactivity by Henry Becquerel marked a history in the evolution of radiotherapy.[1,2] The various rays used in radiotherapy consists of electromagnetic (x rays and Gamma rays) and Particulate radiation (Electrons, Protons, Neutrons).

The first application of Radiotherapy in the field of Medicine was done by Emile Grubbe on 29th January, 1896[3] in Chicago for the treatment of breast carcinoma.[4,5] The evolution of radiotherapy machines is shown in Table 1.

Table 1: Evolution of radiotherapy machines

Year	Evolution of radiotherapy machines
1900	Low voltage Teletherapy <150 KV
1919	Radium Teletherapy Machines
1920	Orthovoltage Xray Machines 200-500 KV
1922	Radium Howitzer
1939	Megavoltage Xray Machines > 1MV
1956	First Cobalt therapy machine (Eldorado A) at W.I.A cancer Institute, Chennai
1953	Linear Accelerator (LINAC) 8MV
1968	Gamma Knife
1976	First Linear Accelerator at Cancer Institute, Chennai
1980	Linac Based- Stereotactic Radiotherapy(SRT)
1993	Tomotherapy
1994	MiMIC Tomotherapy
1995	MLC Dynamic
1997	MLC Step and Shoot or MSF(Multi static field) First LINAC based Stereotactic Radiotherapy started in AIIMS(All India Institute of Medical sciences)
2002	Helical Tomotherapy
2013	Hybrid Linac MRI (linac-MR)

Radiotherapy has a wide range of applications in the treatment of tumors like Lymphoma, seminoma, Myeloma, Ewings sarcoma, Wilms tumor, Medulloblastoma-an exquisitely radiosensitive tumor and Kaposi Sarcoma occurring in AIDS, to palliate disease symptoms of bone pain from metastatic tumors, to prevent the development of leptomeningeal disease and brain metastases in acute leukemia and lung cancer, control of Brain metastases, reversal of spinal cord compression, superior vena cava obstruction, shrinkage of Painful masses.

Radiation therapy or Radiotherapy is the use of electromagnetic radiation like x-rays or gamma rays or particulate radiation like neutrons, protons, electrons to destroy or damage cancer cells.

The initially developed Co-60 teletherapy units that produce gamma rays failed to treat deep seated cancers. Hence to increase the depth of penetration of the charged Particle Accelerators are used.

An accelerator is a device that accelerate charged particles using electromagnetic fields. There are two types of Particle accelerators-Electrostatic accelerators –those that require electric fields that do not change with time E.g. Linear accelerator invented by Rolf Wideroe (1927), Van De Graaff Accelerator by Robert Van De Graaff (1929), Cockcroft-Walton accelerator by John cockroft and Ernest Walton (1932) and oscillating field accelerators- those that require electric fields that change with time e.g., Cyclotron by Ernest Lawrence (1928), Betatron by Donald Kerst (1940), Microtron by Vladimir Veksler (1945), Synchrotron by Frank Goward and D Barnes.

Linear Accelerator: A linear Accelerator is a device that increases or accelerates the velocity of charged particle like Electron, Neutron, Proton when subjected to combined electric and magnetic field thereby

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REVIEW

Salivary gland disorders: A comprehensive review

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Abstract

Salivary glands are complex in nature. They could be either tubulo acinar, merocrine or exocrine glands secreting mainly saliva. Salivary gland is one of the main soft tissue structures in the maxillofacial area. Saliva is a clear, slightly acidic muco serous fluid that coats the teeth, mucosa and thereby helps to create and maintain a healthy environment in the oral cavity. Salivary glands may be affected by a number of diseases, local and systemic and the prevalence of salivary gland diseases depend on various etiological factors. The glands may be infected by viral, bacterial, rarely fungal or its ductal obstruction which may cause painful swelling or obstruction, affecting their functions. The salivary gland may also be affected by a various benign and malignant tumours. This review article briefly describes about the various salivary gland disorders, diagnostic techniques and their management including the recent advances and the future perspective.

Key words: Salivary gland disorders; Xerostomia; Salivary biomarker; Salivary diagnostics; Exocrine glands

Core tip: The aim of this article was to analyse detailed aspects of various salivary gland disorders, their diagnostic and therapeutic advances in the prevention and management of salivary gland diseases of the oral cavity, including the recent developments and their future perspective.

Krishnamurthy S, Vasudeva SB, Vijayasarathy S. Salivary gland disorders: A comprehensive review. *World J Stomatol* 2015; 4(2): 56-71 Available from: URL: http://www.wjgnet.com/2218-6263/full/v4/i2/56.htm DOI: http://dx.doi.org/10.5321/wjs.v4.i2.56

INTRODUCTION

A gland consists of specialized type of cells, wherein they produce products which are used elsewhere in the body. Salivary glands are complex, tubulo acinar, exocrine or merocrine glands secreting mainly saliva. Saliva is the product of the major and minor salivary gland dispersed throughout the oral cavity. It is a complex mixture of organic, inorganic components and water, carrying out several functions. There are three pairs of major salivary glands namely parotid, sub mandibular and sublingual glands in addtion to numerous minor salivary glands in the oral cavity[1].

Saliva Electrolyte Analysis and Xerostomia-related Quality of Life in Nasopharyngeal Carcinoma Patients Following Intensity-Modulated Radiation Therapy

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BMC Research Notes

RESEARCH ARTICLE Open Access

Proteins and peptides in parotid saliva of irradiated patients compared to that of healthy controls using SELDI-TOF-MS

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Abstract

Background: Radiotherapy to the head and neck area damages the salivary glands. As a consequence hyposalivation may occur, but also the protein composition of saliva may be affected possibly compromising oral health. The aim of our study was to compare the relative abundance of proteins and peptides in parotid saliva of irradiated patients to that of healthy controls.

Methods: Using Lashley cups and citric acid, saliva from the parotid glands was collected from nine irradiated patients and ten healthy controls. The samples were analyzed with SELDI-TOF-MS using a NP20 and IMAC-30 chip in the molecular weight range of 1–30 kDa.

Results: On the NP20 chip 61 (out of 217) and on the IMAC-30 chip 32 (out of 218) peaks differed significantly in intensity between the saliva of the irradiated patients and healthy controls. 55 % of the significant peaks showed higher intensity and 45 % showed lower intensity in the saliva of irradiated patients. The peaks may represent, amongst others, the salivary proteins lysozyme, histatins, cystatin, protein S100 and PRP's.

Conclusions: Large differences were found in the relative abundance of a wide range of proteins and peptides in the parotid saliva of irradiated patients compared to healthy controls.

Keywords: Head and neck cancer, Saliva, Proteomics, Parotid gland, SELDI-TOF-MS

Background

Radiotherapy is often needed for the management of a tumor in the head and neck area. Usually radiotherapy involves the primary treatment of a tumor, but it can also be used additionally to surgery or as part of palliative care. The radiation-induced consequences for the healthy oral tissues can be divided into early and late effects. The early effects consist of damage to the oral mucosa, salivary glands and taste. Late effects comprise damage to the salivary glands, dentition, periodontium, bone, muscles and the joints [1, 2].

Damage to the salivary glands leads to a rapid decrease in salivary flow after the start of radiotherapy [3]. Weeks after the start of radiotherapy, the flow rate gradually starts to recover and only after 5 years the mean parotid flow rate may return to baseline levels [4, 5]. However, 21 % of patients still suffered from a significantly lowered salivary flow 5 years after radiotherapy [5].

There are secondary effects related to changes in salivary flow and to changes in composition. Saliva is an important host defense mechanism helping to keep the oral cavity free of diseases like caries, gingivitis, periodontitis and infections as a result of antimicrobial, buffering and remineralizing capacities [6, 7]. There is a risk for radiation caries, a form of caries that develops very rapidly when salivary functions are disturbed and affects tooth surfaces that are normally resistant to the development of caries [8].

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ORIGINAL ARTICLE

Radiation caries in nasopharyngeal carcinoma patients after intensity-modulated radiation therapy: A cross-sectional study

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KEYWORDS
nasopharyngeal carcinoma;
radiation caries;
radiation dose;
radiation therapy;
tooth loss

Abstract *Background/purpose:* The exact dose of intensity-modulated radiation therapy (IMRT) associated with tooth damage is mostly unknown. We aim to evaluate the severity of dental caries after IMRT and the correlation with the radiation dose to the dentition in patients with nasopharyngeal carcinoma (NPC).

Materials and methods: This was a cross-sectional study of 42 patients with NPC who completed IMRT in 2011. Each premolar tooth was divided into 13 sites. Teeth were evaluated using a validated index and subsequently categorized at each divided site. The relationship between dose distribution and the caries severity score was analyzed using logistic models. The odds of developing caries damage were evaluated using odds ratios.

Results: A total of 4342 sites from 334 premolar teeth were evaluated. For sites exposed to 30 −60 Gy, the odds of developing caries damage were 12−200 times greater compared with sites

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Buccal drug delivery technologies for patient-centred treatment of radiation-induced xerostomia (dry mouth)

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Abstract

Radiotherapy is a life-saving treatment for head and neck cancers, but almost 100% of patients develop dry mouth (xerostomia) because of radiation-induced damage to their salivary glands. Patients with xerostomia suffer symptoms that severely affect their health as well as physical, social and emotional aspects of their life. The current management of xerostomia is the application of saliva substitutes or systemic delivery of saliva-stimulating cholinergic agents, including pilocarpine, cevimeline or bethanechol tablets. It is almost impossible for substitutes to replicate all the functional and sensory facets of natural saliva. Salivary stimulants are a better treatment option than saliva substitutes as the former induce the secretion of natural saliva from undamaged glands; typically, these are the minor salivary glands. However, patients taking cholinergic agents systemically experience pharmacology-related side effects including sweating, excessive lacrimation and gastrointestinal tract distresses. Local delivery direct to the buccal mucosa has the potential to provide rapid onset of drug action, i.e. activation of minor salivary glands within the buccal mucosa, while sparing systemic drug exposure and off-target effects. This critical review of the technologies for the local delivery of saliva-stimulating agents includes oral disintegrating tablets (ODTs), oral disintegrating films, medicated chewing gums and implantable drug delivery devices. Our analysis makes a strong case for the development of ODTs for the buccal delivery of cholinergic agents: these must be patient-friendly delivery platforms with variable loading capacities that release the drug rapidly in fluid volumes typical of residual saliva in xerostomia (0.05 to 0.1 mL).

Keywords

Radiation-induced xerostomia, saliva, salivation, salivary substitutes, salivary stimulants, orally disintegrating films, orally disintegrating tablets, patient-centred, pilocarpine HCl, dry mouth, head and neck cancer.

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Radiation-Induced Oral Mucositis

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Radiation-induced oral mucositis (RIOM) is a major dose-limiting toxicity in head and neck cancer patients. It is a normal tissue injury caused by radiation/radiotherapy (RT), which has marked adverse effects on patient quality of life and cancer therapy continuity. It is a challenge for radiation oncologists since it leads to cancer therapy interruption, poor local tumor control, and changes in dose fractionation. RIOM occurs in 100% of altered fractionation radiotherapy head and neck cancer patients. In the United Sates, its economic cost was estimated to reach 17,000.00 USD per patient with head and neck cancers. This review will discuss RIOM definition, epidemiology, impact and side effects, pathogenesis, scoring scales, diagnosis, differential diagnosis, prevention, and treatment.

Keywords: chemotherapy, oral mucositis, radiation, radiotherapy, normal tissue injury, pathobiology, mesenchymal stromal/stem cells

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DEFINITION

Radiation-induced oral mucositis (RIOM) (**Figures 1**, **4** and **5C**) is one of the major ionizing radiation toxicities and normal tissue injuries that result from radiotherapy (1). RIOM was first termed in 1980 as a side effect of radiotherapy (RT) in cancer patients (2). RIOM is a normal tissue injury lasting between 7 and 98 days, which starts as an acute inflammation of oral mucosa, tongue, and pharynx after RT exposure (1, 3). This coincides with recruitment of various inflammatory cells and release of inflammatory cytokines, chemotactic mediators, and growth factors. RIOM can progress to an acute life-threatening stage as a result of severe physical obstruction of food and water intake with subsequent weight loss and septic complication due to lost protective epithelial and basement membrane barriers. This leads to limitations of local tumor control due to cancer treatment interruption and alterations in radiation dose fractionation (4–7). Studies suggested the stages of progression of RIOM as initial hyperemia and erythema during the preulcer phase, during which there is a release of various pro-inflammatory cytokines from epithelial, vascular, and connective tissue cells at the site of tissue injury. This is followed by the epithelial phase with various degrees of desquamation and basement membrane damage with loss of the protective barrier, which ends with the physical appearance of the ulceration. The postulcerative phase varies depending on the extent of the tissue toxicity. A secondary infection with Gram-negative bacteria or yeast may occur, with microcoagulation of the vasculature that worsens the inflammation by the local ischemia with more necrotic tissue yield. The final stage will be the healing phase and fibrosis (2, 8, 9).

RIOM EPIDEMIOLOGY (INCIDENCE, PREDICTORS, AND RISK FACTORS)

Radiation-induced oral mucositis occurs in up to 80% of head and neck cancer irradiated patients and reaches up to 100% in patients with altered fractionation head and neck cancer. RIOM of grade 3 and 4 have been recorded in 56% of head and neck cancer patients treated with radiotherapy (1, 12).

Review Article

Saliva as a Mirror of the Body Health

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Abstract

Saliva has an old history of study. It is of physiological importance. Saliva has hundreds of components which help detect systemic diseases and also provide biomarkers of health and disease status. Saliva has three major functions: digestion, protection and lubrication. Saliva also functions in maintenance of tooth integrity. Also, the carbohydrates of salivary glycoprotein carry the ABH blood group antigens, expressing in the salivary glands and secreted in the saliva. Saliva is a good indicator of the plasma levels of various substances such as hormones and drugs. The use of saliva as a diagnostic and monitoring method for periodontal diseases and many other infectious diseases, has been studied. The relatively easy and non-invasive nature of sample collecting is considered as a simple low-cost stage but the problem is the low concentrations of the markers in comparsion to the plasma.

INTRODUCTION

Saliva has an old history of study but its physiological importance has only been recognized recently [1]. Saliva has hundreds of components that may serve to detect systemic diseases or as evidence of exposure to various harmful substances, as well as providing biomarkers of health and disease status. Nowadays, the saliva research field is rapidly advancing due to the use of novel approaches including metabolomics, genomics, proteomics and bioinformatics [2].

SALIVA PHYSIOLOGY

Saliva is a complex liquid consisting of secretions from the major and minor salivary glands. As estimated there are 450-750 minor accessory salivary glands, situated on tongue, buccal mucosa and palate except the anterior part of the hard palate and gums [3-4].The average daily volume of saliva production is 500-1000 ml. Submandibular glands produce 70% of the overall volume, the parotid glands 25%, and the sublingual glands about 5% [5]. The greatest volume of saliva is produced before, during and after meals, reaching its maximum peak at around 12 a.m. and falls considerably at night, while sleeping. Several physiological and pathological conditions can modify saliva production quantitatively, e.g. smell and taste stimulation, chewing, psychological and hormonal status, drugs, age, hereditary , oral hygiene and physical exercise [3,6-9] . Each salivary gland contains different regions, the acinar region, which is also referred to as the secretary end piece, and the ductal region. All the salivary fluid is produced from the local vascular bed in the acinar region, and is transported through the duct system, where excess sodium and chloride are reabsorbed and some additional proteins are secreted, and then empties into the oral cavity. A sodium gradient that is actively generated within the secretary end piece causes fluid to flow into the lumen through the tight junctions between the acinar cells [10,11]. Saliva is sterile when it leaves the salivary glands. The basis of

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Image-guided radiotherapy for locally advanced head and neck cancer

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Treatment of locally advanced head and neck cancer remains a challenge because of the head and neck complex anatomy and the tumor invasion to the adjacent organs and/or metastases to the cervical nodes. Postoperative irradiation or concurrent chemoradiation may lead to damage of radiosensitive structures such as the salivary glands, mandible, cochlea, larynx, and pharyngeal muscles. Xerostomia, osteoradionecrosis, deafness, hoarseness of the voice, dysphagia, and aspiration remain serious complications of head and neck irradiation and impair patient quality of life. Intensity-modulated and image-guided radiotherapy by virtue of steep dose gradient and daily imaging may allow for decreased radiation of the organs at risk for complication while preserving loco-regional control.

Keywords: head and neck cancer, image-guided radiotherapy, preservation of radiosensitive organs

TREATMENT OF LOCALLY ADVANCED HEAD AND NECK CANCER

Treatment of locally advanced head and neck cancer remains a challenge because of the high rate of loco-regional failures and the potential for serious complications following treatment. The tumor frequently invades adjacent organs and/or regional neck nodes. Standard of care has been either postoperative irradiation or concurrent chemoradiation (1). Regardless of the modality chosen, serious complications may occur because of the presence of radiosensitive organs such as the salivary glands, cochlea, mandible, larynx, and pharyngeal muscles in the radiation field. Xerostomia, deafness, osteoradionecrosis, dysphagia, weight loss, chronic hoarse voice, and aspiration are potential long-term complications of radiation treatment with conventional radiotherapy techniques. Intensity-modulated radiotherapy (IMRT) has been introduced to decrease the toxicity of irradiation because of the steep dose gradient allowing for sparing of radiosensitive organs. Randomized studies have demonstrated significant sparing of the parotid glands following IMRT of head and neck cancer and decreased severity of the xerostomia with improvement of patient quality of life (QOL) (2, 3). However, a significant amount of normal tissues is still irradiated because the inclusion of the tumor and areas at high risk for invasion with a large rim of normal tissue called planning target volume or PTV, to avoid marginal miss. Recently, image-guided radiotherapy (IGRT) by combining the steep dose gradient of IMRT and daily imaging may potentially improve further the toxicity of head and neck irradiation because of the possibility of safe PTV reduction given the reduced inter-fraction movement through daily imaging.

Significant reduction of spinal cord dose may be achieved with IGRT compared to IMRT by a reduced PTV margin (4). However, the flip side of IGRT is also the risk of under-dosing the tumor if the target area is not adequately outlined. Thus, pre-treatment imaging to meticulously delineate the tumor and areas at risk of invasion is a critical component for the success of IGRT.

IMAGING STUDIES CRITICAL FOR IGRT PLANNING

Positron-emission tomography (PET) scan or PET-computed tomography (PET-CT) allows accurate delineation of the tumor and cervical lymph nodes that can be incorporated into the planning CT. PET-CT is superior to CT for tumor imaging because of its ability to detect the tumor metabolic activity in addition to its anatomic location. In a study of 102 unresectable head and neck cancer, PET-CT significantly changed the staging and management of those patients compared to CT alone (5). Twelve patients had modifications of the radiotherapy planning following review

Therapeutics and Clinical Risk Management

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REVIEW

Xerostomia induced by radiotherapy: an overview of the physiopathology, clinical evidence, and management of the oral damage

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Background: The irradiation of head and neck cancer (HNC) often causes damage to the salivary glands. The resulting salivary gland hypofunction and xerostomia seriously reduce the patient's quality of life.
Purpose: To analyze the literature of actual management strategies for radiation-induced hypofunction and xerostomia in HNC patients.
Methods: MEDLINE/PubMed and the Cochrane Library databases were electronically evaluated for articles published from January 1, 1970, to June 30, 2013. Two reviewers independently screened and included papers according to the predefined selection criteria.
Results: Sixty-one articles met the inclusion criteria. The systematic review of the literature suggests that the most suitable methods for managing the clinical and pathophysiological consequences of HNC radiotherapy might be the pharmacological approach. For example, through the use of cholinergic agonists when residual secretory capacity is still present, and the use of salivary substitutes. In addition, a modified diet and the patient's motivation to enhance oral hygiene can lead to a significant improvement.
Conclusion: Radiation-induced xerostomia could be considered a multifactorial disease. It could depend on the type of cancer treatment and the cumulative radiation dose to the gland tissue. A preventive approach and the correct treatment of the particular radiotherapeutic patient can help to improve the condition of xerostomia.
Keywords: radiation-induced xerostomia, salivary gland hypofunction, management strategies

Introduction

Xerostomia is a term used to describe the subjective symptoms of a dry mouth deriving from a lack of saliva. A large variety of causes can lead to xerostomia, eg, radiotherapy and chemotherapy,[1–4] the chronic use of drugs,[5–7] and rheumatic and dysmetabolic diseases.[8,9]

Saliva is an important host defense component of the oral cavity. Major salivary glands contribute to most of the secretion volume and electrolyte content of saliva (the parotid, submandibular, and sublingual glands, which account for 90% of saliva production), whereas minor salivary glands contribute little secretion volume and most of the blood-group substance.[10] Saliva components interact in related functions in the following general areas:

1) bicarbonates, phosphates, and urea act to modulate pH and the buffering capacity of saliva;
2) macromolecule proteins and mucins serve to cleanse, aggregate, and/or attach oral microorganisms and contribute to the dental plaque metabolism;

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cells

MDPI

Review

Physiology, Pathology and Regeneration of Salivary Glands

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Abstract: Salivary glands are essential structures in the oral cavity. A variety of diseases, such as cancer, autoimmune diseases, infections and physical traumas, can alter the functionality of these glands, greatly impacting the quality of life of patients. To date, no definitive therapeutic approach can compensate the impairment of salivary glands, and treatment are purely symptomatic. Understanding the cellular and molecular control of salivary glands function is, therefore, highly relevant for therapeutic purposes. In this review, we provide a starting platform for future studies in basic biology and clinical research, reporting classical ideas on salivary gland physiology and recently developed technology to guide regeneration, reconstruction and substitution of the functional organs.

Keywords: salivary glands; oral epithelium; xerostomia; exocrine glands; salivary gland-resident stem cells

1. Introduction

Structures secreting fluid to facilitate feeding emerge progressively throughout evolution and can be found in very simple organisms (e.g., *Caenorabditis elegans*) and more complex species (e.g., *Drosophila melanogaster*, placental mammals). In humans, major and minor salivary glands produce and secrete digestive fluids or protein-rich fluids. The three pairs of major salivary glands (i.e., parotid, submandibular and sublingual glands) are responsible for the production and secretion of saliva in the oral cavity, whose moisturizing effect preserves oral hygiene and allows taste, speech and mastication [1].

The parotid gland (PG) is mainly composed of serous acini-secreting α-amylase-rich saliva [2]. The sublingual gland (SL) secretes mucous, a viscous solution rich in mucins [3–5]. The submandibular gland (SMG) is composed by a mixed population of acini with a mucous and serous function [1,4,6]. These three major salivary glands account for more than 90% of salivary secretion. Minor salivary glands are distributed throughout the oral cavity, specifically in the labial and lingual mucosa, as well as palate and floor of the mouth.

Saliva is an essential fluid for oral cavity maintenance and functionality. Digestive enzymes within saliva initiate the digestion process, and at the same time, saliva acts as a lubricant of solid nutrition, thus helping its passage through the esophagus. By moisturizing the tongue and other tissues of the oral cavity, saliva has an essential role in speech and taste sensitivity [7]. It also balances the pH of the mouth, thus protecting the soft oral tissues and teeth from an extended exposure to an acidic environment. Saliva contains several signalling molecules, such as EGF, FGF, NGF and TGF-α, that are essential for the regeneration of oral and oesophageal mucosa. Finally, the antibacterial and antifungal components of the saliva, such as lysozymes, Immunoglobulins and lactoferrin, inhibit the progression of bacterial infection and dental caries.

Physiological functions and the histological appearance of salivary glands are rather conserved between species and individuals, but clear distinctions exist in terms of anatomical position and

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PERIODONTOLOGY 2000

The physiology of salivary secretion

GORDON B. PROCTOR

Saliva performs a number of important functions that are essential for the maintenance of oral health. Most of these functions depend upon the interaction of saliva with oral surfaces of varying texture and polarity – soft epithelial tissue surfaces with differing degrees of keratinization and roughness, along with the tooth surfaces that are hard and composed of tooth mineral. Saliva clears substances from the mouth, buffers pH, maintains tooth mineralization, facilitates wound healing, neutralizes some harmful dietary components, influences the oral microbiome and protects, lubricates and hydrates oral mucosal surfaces. The properties and effectiveness of saliva are largely determined by secretions from the major and minor salivary glands. Saliva is an accessible biofluid that contains components derived from the mucosal surfaces, gingival crevices and tooth surfaces of the mouth. Saliva also contains microorganisms that colonize the mouth and other exogenous substances and so can potentially provide an insight into the relationship of the host with the environment. These features make saliva a complex fluid. It is therefore important to understand how saliva is formed so that we can make informed interpretations of how changes in the composition of saliva are associated with physiology or disease.

Salivary gland anatomy and structure

Salivary glands are exocrine glands and secrete onto a mucosal surface. During embryonic development, major salivary glands form as initial proliferating epithelial buds from the oral epithelium and grow into the underlying mesenchyme. A tree-like ductal structure develops through a process of branching morphogenesis and canalization. The development process requires a controlled exchange of molecular signals between epithelial cells and mesenchymal cells (61). The ductal structure of the major adult salivary glands is well demonstrated by sialography, an imaging technique in which X-ray contrast medium is injected into the opening of the main excretory ducts of the gland on the oral epithelium: Stenson's (parotid) duct or Wharton's (submandibular) duct (Fig. 1).

At the ends of the fine branches of the major salivary gland ductal tree are glandular secretory end pieces referred to as acini (grape-like), which are collections of saliva-secreting epithelial cells. The mechanisms by which acinar cells secrete saliva are discussed later, but the histological appearance of acinar cells is determined by the types of secretory proteins synthesized by the cells and stored in large granules, which can fill the cytoplasm. The content of the storage granules is an indicator of the types of saliva produced, which can be broadly divided into mucin-containing and nonmucin -containing saliva. Mucins are the main components of mucous, a protective layer found on most mucosal surfaces in the body, and saliva containing high amounts of mucin tend to be viscoelastic, an important characteristic for retention of saliva on oral mucosal surfaces and maintenance of lubrication and hydration of the surfaces (95). Parotid gland acinar cells produce watery saliva with little or no mucin and characteristically stain strongly with the routinely used histological dyes hematoxylin and eosin (Fig. 2A). The submandibular gland contains a mixed population of acinar cells, some of which are mucin producing and stain weakly with hematoxylin and eosin. Most of the acinar cells in sublingual glands are mucin producing and consequently the saliva secreted tends to be viscoelastic. Some acinar cells in these glands contain low amounts of mucin, possibly because it is not fully formed within the storage granules of cells, and have a 'serous' appearance with hematoxylin and eosin staining. Most of the minor salivary glands in the oral submucosae are mucin producing and the acinar cells of these glands stain similarly to those of the

Anatomy and Physiology

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Salivary Secretion: Mechanism and Neural Regulation

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Abstract

Maintenance of a film of saliva on oral surfaces is dependent upon nerve-mediated, reflex salivary gland secretion. Afferent signalling arises from taste, olfaction and mastication and is modified by signalling from other centres in the central nervous system before efferent signals are delivered to salivary glands in autonomic nerves. Salivary fluid secretion is largely dependent upon cholinergic signalling from parasympathetic nerves whilst the protein content of saliva is additionally dependent upon signalling by neuropeptides and, in the major (parotid, submandibular and sublingual) salivary glands, by sympathetic nerves and the release of noradrenaline. There have been significant recent advances in our understanding of the membrane transport proteins involved in intracellular calcium signalling in salivary acinar cells in response to nerve stimulation and of the ion transport proteins responsible for acinar cell secretion of saliva. Salivary glands retain an ability to regenerate following extreme atrophy, and autonomic nerves have an important role in both gland development and maintenance of long-term normal function. Continued advances in the understanding of the nerve-mediated regulation of salivary glands should help in the development of strategies for preventing chronic oral dryness resulting from drugs or atrophic disease associated with inflammation and irradiation.

Salivary glands fulfil a huge range of functions in different species, and even amongst mammals there is great variety in salivary gland morphology and the control of salivation by nerves, reflecting adaptation to diet and environment [1]. In man, the paired major salivary glands, parotid, submandibular and sublingual, along with hundreds of small, minor submucosal salivary glands provide a film of mixed saliva that coats and protects the oral mucosal and tooth surfaces. Salivary secretion is maintained at a 'default' rate in man creating a mobile but slow-moving film and replenishing/replacing proteins adsorbed to the underlying soft and hard oral surfaces. Upon this 'default' secretion of 'unstimulated' or 'resting' saliva there is superimposed a secretion of much greater volumes of saliva in response to taste, smell and chewing during periods of food intake [2]. The term 'unstimulated' saliva is a convenient way to discriminate from a saliva secreted in response to an overt taste or chewing stimulus but is in some ways a misnomer since salivary secretion of fluid is only unstimulated in the complete absence of neural activation, which does not apply in the conscious subject with an intact innervation.

Resting whole-mouth saliva is subject to a circadian rhythm in flow rate and salt content reach-

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Xerostomia: Current streams of investigation

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Saliva: an all-rounder of our body

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Review

Development and regeneration of salivary gland toward for clinical application

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ABSTRACT

Salivary gland hypofunction, also termed as xerostomia, is caused by radiation therapy for head and neck cancer or Sjögren's syndrome, leading to a detrimental impact on oral health and quality of life. This review describes current studies on salivary gland development and the translational approaches of basic science to treating patients with dysfunction and hypofunction of the salivary gland. Here, we review the most recent studies that have offered better insight into the mechanisms of salivary gland development and regeneration. Furthermore, we highlight proposed approaches with the aim of recovering salivary gland function using both gene- and cell-based therapy. A thorough understanding of the mechanisms involved in salivary gland development is necessary in order to design effective therapies for regeneration and repair of damaged salivary glands.

Contents

1. Introduction

Many papers have reported the potential of regenerative medicine. However, many scientific challenges need to be overcome. In particular, many clinicians in the field of dentistry hope to realize the regeneration of the tooth and bone. Since cultured epidermal skin was developed using tissue engineering [1], cultured dermis has also been developed and recently made available to clinics worldwide. The epithelial cells of the oral membrane are similar to skin keratinocytes. Bioengineered oral mucosae have also been developed as well as bioengineered skin. Various reports regarding the development and clinical implementation of bioengineered oral mucosa sheets have been published since 1990. Bioengineered oral mucosa sheets are expected to be a useful tool for clinical

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Effect of Low-Level Laser Therapy on Radiotherapy-Induced Hyposalivation and Xerostomia: A Pilot Study

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Abstract

Objective: The present pilot study aimed to assess the effect of low-level laser therapy (LLLT) on hyposalivation and xerostomia as a consequence of head and neck radiotherapy. ***Background data:*** The benefits of LLLT in salivary flow have been shown; however, there are no studies investigating its effects on patients who have already undergone radiotherapy and present hyposalivation and xerostomia as a sequela. ***Methods:*** Twenty-three patients with a history of head and neck malignancy, who were treated by fractioned teletherapy (dosimetry ranging from 45 to 70 Gy) in the cervicofacial region were selected. They all presented with xerostomia and severe hyposalivation. Patients were randomly distributed into a laser group ($n=12$) and a control group ($n=11$). A GaAlAs laser (830 nm, 100 mW, illuminated area 0.028 cm^2, 3.57 W/cm^2, 20 sec, 2.0 J, 71 J/cm^2) was used punctually in the major salivary glands, twice a week for 6 weeks, with a 12 session total. Stimulated and unstimulated salivary flow rate (SFR) were assessed, as well as the xerostomia and quality of life related to oral health (QLROH). ***Results:*** The analysis did not show any significant difference between the groups with regards to the SFR and xerostomia, and the QLROH. However, at the end of the treatment, the xerostomia and the QLROH showed significant improvement in both groups compared with assessments performed at baseline, highlighting the importance of advice given to the irradiated patients, and their follow-up. ***Conclusions:*** With the parameters used, LLLT was not able to increase SFR or decrease xerostomia. The results may be associated with the late effects of radiotherapy on glandular structure, such as fibrosis and acinar atrophy.

Introduction

The major salivary glands are commonly involved in the radiation sites, as they are close to primary tumor and lymph chains of the head and neck region. As a consequence of radiotherapy, they go through a degenerative process, resulting in hyposalivation and xerostomia.[1] Approximately 70% of the irradiated patients have developed such alterations,[2] with several complications, such as total or partial loss of taste; mouth burning and pain; susceptibility to oral ulcerations, cavities, and other infections; dysphagia and dysphonia; and psychological alterations that negatively influence their quality of life.[3]

The dose of ionizing radiation, amount of salivary tissue exposed, and patient's individual response are the main factors influencing glandular alterations.[4–6] Damage becomes irreversible after cumulative doses ranging from 26 to 39 Gy, and the salivary flow rate (SFR) can decrease by 10% from the one presented before radiation.[7,8] Despite being stable, as they do not have high mitotic rates, acinar cells respond quickly to radiation.[9,10] The mechanisms that lead to tissue destruction and salivary gland radiosensitivity have not been totally understood so far. Salivary gland alterations start with the damage to the cell membrane, with loss of response to the autonomic controls, and progression to edema, degeneration, and acinar cell apoptosis. Acute effects start 24 h after therapy starts, and stabilize within 72 h. Late effects are the consequence of fibrosis and acinar atrophy,[11,12] which occur as a result of mesenchymal alterations, including changes in the extra cellular matrix, specifically in the lamilin and in collagen IV.[11,13]

Low-level laser therapy (LLLT) is a simple low-cost tool that can be used as an adjuvant to conventional treatments, or alone and electively in some diseases.[14–18] Its effects are based on the modulation of several metabolic, biochemical, and photophysical processes that transform laser light into

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REVIEW ARTICLE

Saliva proteome research: current status and future outlook

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Abstract

Human saliva harbours proteins of clinical relevance and about 30% of blood proteins are also present in saliva. This highlights that saliva can be used for clinical applications just as urine or blood. However, the translation of salivary biomarker discoveries into clinical settings is hampered by the dynamics and complexity of the salivary proteome. This review focuses on the current status of technological developments and achievements relating to approaches for unravelling the human salivary proteome. We discuss the dynamics of the salivary proteome, as well as the importance of sample preparation and processing techniques and their influence on downstream protein applications; post-translational modifications of salivary proteome and protein–protein interactions. In addition, we describe possible enrichment strategies for discerning post-translational modifications of salivary proteins, the potential utility of selected-reaction-monitoring techniques for biomarker discovery and validation, limitations to proteomics and the biomarker challenge and future perspectives. In summary, we provide recommendations for practical saliva sampling, processing and storage conditions to increase the quality of future studies in an emerging field of saliva clinical proteomics. We propose that the advent of technologies allowing sensitive and high throughput proteome-wide analyses, coupled to well-controlled study designs, will allow saliva to enter clinical practice as an alternative to blood-based methods due to its simplistic nature of sampling, non-invasiveness, easy of collection and multiple collections by untrained professionals and cost-effective advantages.

Keywords: Saliva, clinical proteomics, blood, challenges, diagnostics

Saliva an alternative diagnostic biological fluid

There is a growing interest in clinical and translational research for the discovery and development of biomarkers that are indicative of a disease status and progression (1,2). Biomarkers of clinical relevance are predominantly proteins, and the advent of new Mass Spectrometry (MS) technology platforms and the sequencing of the human genome have accelerated protein biomarker discovery, particularly in readily available body fluids such as blood, saliva, and urine (3–5). Human saliva mirrors the body's health and well-being and most of the biomolecules that are present in blood or urine can also be found in salivary secretions (6). However, biomolecular concentrations in saliva are usually one tenth to one thousandth of the levels found in blood (7). Sensitive detection technology platforms are therefore required to enable the detection of biomolecules in saliva. Another roadblock to the advancement of salivary diagnostics is the lack of information with regard to the baseline levels (reference ranges) of molecules in saliva within a healthy control group to discriminate the molecular composition and levels during a disease stage. In spite of these impediments, the use of saliva in a clinical setting is on the rise, partly due to an increase in knowledge of the basic biochemistry and physiology of human saliva and also as a result of ease of collection relative to blood for clinical applications (2,8–10). The purpose of this review is to provide an overview of current developments and challenges in the field of saliva proteomic research. We have focussed our review on the potential diagnostic utility

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INVITED MEDICAL REVIEW

Current ideas to reduce or salvage radiation damage to salivary glands

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Radiation-induced hyposalivation is still a major problem after radiotherapy for head and neck cancer. Current and promising new thoughts to reduce or salvage radiation damage to salivary gland tissue are explored. The main cause underlying radiation-induced hyposalivation is a lack of functional saliva-producing acinar cells resulting from radiation-induced stem cell sterilization. Current methods to prevent that damage are radiation techniques to reduce radiation-injury to salivary gland tissue, surgical techniques to relocate salivary glands to a region receiving a lower cumulative radiation dose, and techniques to make salivary gland cells more resistant to radiation injury. These preventive techniques cannot be applied in all cases, also reduce tumor sensitivity, or do not result in a sufficient amelioration of the dryness-related complaints. Therefore, alternative methods on techniques to salvage salivary glands that are damaged by radiation are explored with promising results, such as stem cell therapies and gene transfer techniques to allow the radiation-injured salivary gland tissue to secrete water.

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Keywords: radiotherapy; hyposalivation; xerostomia; IMRT; gene transfer; stem cells

Introduction

In 2012, in the USA, more than 40 000 new patients were diagnosed with head and neck cancer (American Cancer Society, 2012). Worldwide, head and neck cancer accounts for more than 550 000 cases annually (Jemal *et al*, 2011). The majority of these patients were treated with radiotherapy alone or in combination with chemotherapy, cetuximab and/or surgery. The 5-year survival rate of these patients is approximately 50% for non-metastatic locally advanced disease (Piccirillo *et al*, 2007). While radiotherapy significantly improves the patient's chances of survival, at the same time the exposure to ionizing radiation usually results in unavoidable co-irradiation of the normal tissues surrounding the tumor. The salivary glands are among these normal tissues as the ionizing beams have to pass the salivary glands to reach the tumor.

Protocols have been developed to minimize early and late loss of gland function following radiotherapy, but even when applying intensity-modulated radiation therapy (IMRT), the current evidence-based standard technique, commonly applied technique to irradiate head and neck cancer, still 40% of head and neck cancer patients experience a moderate or severe sensation of oral dryness (xerostomia) (Burlage *et al*, 2001; Mahood *et al*, 2007; Jellema *et al*, 2007; Jensen *et al*, 2010; Vissink *et al*, 2010; Beetz *et al*, 2013). In addition, induced by or related to the radiation injury to the salivary glands and consequential hyposalivation, many other post-treatment complications occur, such as hampered speech, increased risk on oral infections and dental caries, difficulties with swallowing and food mastication, impaired taste, and nocturnal oral discomfort. These symptoms can lead to a dramatic loss in quality of life for the patient and remains extremely difficult to manage (Jansma *et al*, 1992; Vissink *et al*, 2003a,b).

In this paper, first the pathophysiology underlying radiation damage to salivary tissue is be briefly reviewed. Next, currently explored and promising new thoughts to reduce or salvage radiation damage to salivary gland tissue are discussed.

Radiation-induced hyposalivation

The salivary glands of rodents and primates are composed basically of two saliva-producing cells types, namely mucous and serous acinar cells, of myoepithelial cells,

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MINI REVIEW
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Molecular Mechanisms of Radiation-Induced Cancer Cell Death: A Primer

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Radiation therapy (RT) is responsible for at least 40% of cancer cures, however treatment resistance remains a clinical problem. There have been recent advances in understanding the molecular mechanisms of radiation-induced cell death. The type of cell death after radiation depends on a number of factors including cell type, radiation dose and quality, oxygen tension, TP53 status, DNA repair capacity, cell cycle phase at time of radiation exposure, and the microenvironment. Mitotic catastrophe (a pathway preceding cell death that happens in mitosis or as a consequence of aberrant mitotic progression) is the primary context of radiation-induced cell death in solid cancers, although in a small subset of cancers such as haematopoietic malignancies, radiation results in immediate interphase apoptosis, occurring within hours after exposure. There is intense therapeutic interest in using stereotactic ablative body radiotherapy (SABR), a precise, high dose form of RT given in a small number of fractions, to prime the immune system for cancer cell killing, but the optimal radiation dose and fractionation remain unclear. Additionally, promising novel radiosensitisers targeting the cell cycle and DNA repair pathways are being trialled. In the context of the increasing use of SABR and such novel agents in the clinic, we provide an updated primer on the major types of radiation-induced cell death, focussing on their molecular mechanisms, factors affecting their initiation, and their implications on immunogenicity.

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INTRODUCTION

Radiation therapy (RT) is a major cancer treatment modality and is responsible for at least 40% of cancer cures (Ringborg et al., 2003), yet treatment resistance remains a clinical problem. A primary reason for this is the capacity for cancer cells to evade radiation-induced cell death. Treatment paradigms have traditionally viewed cancer as a cell-autonomous problem of dysregulated proliferation while side-lining host-tumour interactions, but this dogma has undergone a remarkable revolution in the last few decades, with increasing appreciation of the tumour stroma and immune milieu in shaping tumour evolution. Trials of novel radiosensitisers targeting not only key cell death pathways but also the stromal and immune microenvironment, particularly together with stereotactic ablative body radiotherapy (SABR), have gained intense interest.

Here, we provide an updated primer on the major types of radiation-induced cell death, focussing on their molecular mechanisms, factors affecting their initiation, and their implications

ANALISIS SIFAT FISIKOKIMIA (LAJU ALIR, DERAJAT KEASAMAN, KEKENTALAN) SALIVA PASIEN RADIOTERAPI KANKER KEPALA DAN LEHER

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