PENGARUH PERAWATAN RADIOTERAPI PADA PASIEN KANKER NASOFARING TERHADAP PERUBAHAN SALIVA DAN KELENJAR SALIVA

Literature Review

Untuk Memenuhi Sebagian Persyaratan
Mencapai Gelar Sarjana Kedokteran Gigi

Diajukan Oleh:
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FAKULTAS KEDOKTERAN GIGI
UNIVERSITAS ISLAM SULTAN AGUNG
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KARYA TULIS ILMIAH

Literature Review

PENGARUH PERAWATAN RADIOTERAPI PADA PASIEN KANKER NASOFARING TERHADAP PERUBAHAN PADA SALIVA DAN KELENJAR SALIVA

Yang dipersiapkan dan diajukan oleh:

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Telah dipertahankan di depan Dewan Penguji

Pada tanggal 3 Mei 2021

Dan dinyatakan telah memenuhi syarat

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MOTTO DAN PERSEMBAHAN

MOTTO*:*

Barangsiapa yang mengerjakan kebaikan sekecil apapun, niscaya dia akan melihat (balasan)nya

(Q.S Al-Zalzalah)

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Semarang, 3 Mei 2021

Cici Amalia Sumardani

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2DRT	: *Two-Dimentional Radiotherapy*
3DCRT	: *Three-Dimentional Conformal Radiotherapy*
DNA	: *Deoxyribonucleic acid*
DSB	: *Double Strand Breaks*
IMRT	: *Intensity-Modulated Accelerated Radiation Therapy*
KNF	: Kanker Nasofaring
QoL	: *Quality of Life*
SFR	: *Stimulated Saliva Flow Rate*
SPSS	: *Statistical Package for the Social Science*
SSB	: *Single Strand Break*
USFR	: *Unstimulated Saliva Flow Rate*
WHO	: *World Health Organization*

ABSTRAK

Radioterapi digunakan sebagai salah satu perawatan yang diberikan pada penderita kanker nasofaring. Pemberian radiasi dapat merusak sel kanker serta dapat merusak sel-sel normal yang ada di sekitarnya, salah satunya dapat mengganggu fungsi dari kelenjar saliva. Disfungsi kelenjar saliva mengakibatkan menurunnya laju aliran saliva sehingga volume saliva berkurang. Tujuan dari *review* ini adalah untuk mengetahui pengaruh perawatan radioterapi pada pasien kanker nasofaring terhadap volume saliva dan kelenjar saliva pasien. Metode pengumpulan data yang digunakan dalam *literature review* ini adalah metode PICO dengan menelusuri basis data elektronik PubMed, *Science Direct, Cochrane,* dan Google Scholar. Kata kunci yang digunakan adalah *Salivary Gland Following Radiotherapy in Nasopharyngeal Cancer Patients* dan *Salivary Gland in Nasopharyngeal Cancer Patients.* Hasil review ditemukan terdapat kerusakan sel akibat radioterapi pada kelenjar saliva yang menyebabkan penurunan fungsi dan menurunnya sekresi kelenjar saliva. Kerusakan yang terjadi pada kelenjar saliva diakibatkan karena rusaknya DNA dari sel asinar di kelenjar saliva, sehingga menyebabkan penyusutan volume kelenjar saliva. Kelenjar parotis dan kelenjar submandibular merupakan kelenjar yang paling terdampak efek radiasi yang diakibatkan radioterapi. Pasien kanker nasofaring yang menjalani perawatan radioterapi mengalami penurunan laju aliran saliva 1 bulan hingga 1 tahun setelah perawatan radioterapi.

Kata kunci: radioterapi, kanker nasofaring, laju aliran saliva, kelenjar saliva

ABSTRACT

Radiotherapy is used as one of the treatments for patients with nasopharyngeal cancer. Radiation can damage cancer cells and normal cells around it, also can disrupt the function of salivary glands. Salivary gland dysfunction results a decrease of salivary flow so the volume of saliva decreases. The purpose of this review is to determine the effect of radiotherapy treatment in nasopharyngeal cancer patients on salivary volume and salivary glands of patients. The method used in this literature review is PICO method by browsing electronic databases of PubMed, Science Direct, Cochrane, and Google Scholar. The keywords used are Salivary Gland Following Radiotherapy in Nasopharyngeal Cancer Patients and Salivary Gland in Nasopharyngeal Cancer Patients. The results of the review found that there was cell damage due to radiotherapy in the salivary glands which caused a decrease in function and decreased salivary gland secretion. The damage is caused by DNA damage from acinar cells in the salivary glands, causing a decrease in the volume of salivary glands. The parotid and submandibular glands are the most affected glands by the radiation effects of radiotherapy. Nasopharyngeal cancer patients undergoing radiotherapy treatment experienced decrease in saliva flow rate 1 month to 1 year after radiotherapy treatment.

Keywords: radiotherapy, nasopharyngeal cancer, saliva flow rate, salivary glands

BAB I
PENDAHULUAN

1.1 Latar Belakang

Kanker Nasofaring yang selanjutnya akan disebut KNF adalah salah satu tipe kanker kepala dan leher. Kanker ini dimulai dari nasofaring, bagian atas dari tenggorokan dibelakang hidung dan dekat dengan dasar tengkorak (Abdel Razek *et al*., 2012). Pertumbuhan sel yang tidak terkendali dan ganas berupa sel-sel ephitelial pelapis rongga yang berada di belakang hidung yang cenderung menginfiltrasi jaringan disekitarnya dengan proses metasis adalah kondisi yang terjadi pada KNF. KNF merupakan salah satu jenis kanker kepala dan leher yang menduduki peringkat pertama dengan persentasi hampir 60% dari semua jenis kanker kepala dan leher. Angka kejadian kanker nasofaring cukup tinggi di Indonesia yaitu 4,7:100.000 kasus per tahun (Primadina *et al*., 2017).

Beberapa teknik radioterapi yang sering digunakan dalam perawatan kanker nasofaring adalah 2DRT (*two-dimensional radiotherapy),* 3DCRT *(three-dimensional conformal radiotherapy,* dan IMRT (*intensity modulated radiotherapy*) (Fang *et al.*, 2010). Radiasi sinar gamma merupakan salah satu terapi untuk keganasan. Radiasi sinar gamma diberikan dalam bentuk dosis tunggal atau fraksinasi. Radiasi sinar gamma dapat menyebabkan kematian pada sel dengan merusak DNA, salah satunya ialah apoptosis. Indikator terjadinya apoptosis yang biasanya digunakan adalah caspase-3 yang merupakan mediator utama. Berdasarkan hasil dari

beberapa penelitian, didapatkan kesimpulan bahwa pemberian radiasi sinar gamma dosis tunggal 10 Gy (1x10 Gy) dapat menyebabkan ekspresi *caspase-3* yang lebih tinggi daripada pemberian radiasi sinar gamma dosis fraksinasi 10 Gy (5x2 Gy) pada sel trakea (Devi *et al.*, 2016). Salah satu efek dari radioterapi adalah xerostomia, xerostomia merupakan kondisi dimana mulut terasa kering disebabkan oleh disfungsi sekresi kelenjar saliva dan dapat mengganggu fungsi berbicara maupun mastikasi (Fitriatuzzakiyyah *et al.*, 2017).

Kelenjar saliva adalah kelenjar yang memproduksi saliva. Kelenjar saliva terdiri dari kelenjar mayor dan minor (Tamin *et al.*, 2011). Kelenjar mayor ialah sepasang kelenjar parotid yang berada di seberang molar pertama maxilla, dan kelenjar submandibula dan sublingual yang terletak di dasar mulut. Kelenjar minor yang menghasilkan saliva terdapat di bibir bagian bawah, lidah, palatum, pipi, dan faring. Pembagian kelenjar mayor dan minor berdasarkan ukuran dari kelenjar. Kelenjar mayor menghasilkan lebih banyak saliva daripada kelenjar minor, akan tetapi kualitas dari kelenjar tersebut bermacam-macam (Vining, 2017).

Kelenjar parotid merupakan kelenjar saliva terbesar, dengan berat antara 15-30gram dan berukuran sekitar 6x3 cm. Kelenjar parotid memiliki sekitar 3-24 limfa yang terletak di lateral N. Facialis di lobus superfisial (Waschke, 2013). Volume saliva yang dihasilkan kelenjar parotid 2,5 kali lebih besar dari kelenjar mandibula dan 6 kali lebih besar dari kelenjar sublingualis. Saliva dari kelenjar parotid dialirkan ke rongga mulut melalui

Stensen's ducts yang bermuara di daerah setinggi molar dua atas (Arpa, 2017). Kelenjar submandibula memiliki berat sekitar 50% dari berat kelenjar parotid dengan berat antara 7-15 gram (Helmerhorst, 2012). Duktus kelenjar submandibula bermuara di duktus Warthon yang terletak di dasar mulut pada kedua sisi frenulum lingualis. (Amano *et al.*, 2012). Kelenjar sublingualis merupakan kelenjar yang berukuran paling kecil dengan berat antara 2-4 gram. Kelenjar ini tidak memiliki kapsula fasial yang jelas dan duktus yang dominan, namun terdapat 10 duktus kecil yang disebut *ducts of Rivinus* (Kasuma, 2015).

Rata-rata produksi saliva dalam sehari bervariasi, pada individu sehat berjumlah sekitar 1-1,5 L (Humphrey *et al.*, 2001). Jumlah saliva yang diproduksi tiap kelenjar pada kondisi tidak terstimulasi ialah 20% dari kelenjar parotid, 65% dari kelenjar submandibular, 7%-8% dari kelenjar sublingual, dan kurang dari 10% berasal dari kelenjar minor. Persentase tiap kelenjar berubah pada kondisi terstimulasi. Kelenjar parotid menghasilkan saliva paling banyak dari pada kelenjar lainnya, sekitar 50% dari total saliva yang dihasilkan (Indriana, 2010).

Normalnya, laju aliran saliva tanpa stimulasi berjumlah sekitar 0,3-0,65 ml/menit dan 1,5-6 ml/menit untuk laju aliran saliva yang terstimulasi. Produksi saliva berkurang setelah tindakan radioterapi. Kelenjar parotid yang terpapar radiasi dengan dosis lebih dari 40 Gy memproduksi saliva yang sedikit pada tahun pertama setelah radioterapi, disertai dengan peningkatan terbatas secara bertahap (Arrifin *et al.*, 2018).

Allah tidak hanya menurunkan penyakit ke dunia, tetapi Allah juga menurunkan penawar bagi penyakit tersebut. Hal ini telah disebutkan dalam hadits shahih riwayat Imam Bukhari, bahwa Rasullullah shallallahu ‘alaihi wa sallam bersabda:

مَا أَنْزَلَ اللهُ دَاءً إِلَّا أَنْزَلَ لَهُ شِفَاءً

Artinya: “Tidaklah Allah menurunkan penyakit kecuali Dia juga menurunkan penawarnya.” (HR Bukhari).

Penelitian terdahulu menunjukkan bahwa perawatan radioterapi mempengaruhi turunnya laju aliran saliva atau disebut dengan hiposalivasi, dengan hasil pada pasien kanker kepala dan leher berkisar antara 0-0,5 mL/10 menit (25%); 0,51-1,00 mL/10 menit (29,2%) dan 1,01-1,50 mL/10 menit (33%). Penelitian tersebut menyebutkan sebesar dua pertiga pasien kanker kepala dan leher mengalami hiposalivasi (<0,16 mL/menit) (Surjadi and Amtha, 2013). Penelitian terdahulu juga menunjukkan bahwa terdapat pengaruh dosis radioterapi yang diberikan dengan teknik fraksinasi standar terhadap laju aliran saliva pasien (Lal *et al.*, 2010). Penelitian yang dilakukan oleh Lin., *et al* mengemukakan bahwa pasien kanker nasofaring yang menjalani perawatan radioterapi mengalami penurunan saliva flow rate 1 bulan setelah radioterapi hingga 1 tahun, dan setelah 1 tahun mulai terdapat peningkatan saliva flow rate (Lin *et al.*, 2015). Penelitian lain oleh Sim., *et al* menunjukkan bahwa volume kelenjar parotis pasien kanker nasofaring yang menjalani perawatan radioterapi mengalami penurunan 3 bulan pasca radioterapi (Sim *et al.*, 2018). Radiasi dengan dosis yang tinggi

pada area kepala dan leher dapat merusak struktur jaringan kelenjar saliva. Kelenjar diganti oleh limfosit, sel plasma, dan jaringan ikat fibrosa, sehingga kelenjar menjadi atrofi dan fibrotik yang menyebabkan volume kelenjar berkurang jika dibandingkan dengan volume sebelum terpapar radiasi (Chitapanarux and Iamaroon, 2020; Wu *et al.*, 2020)

Beberapa penelitian membuktikan bahwa perawatan radioterapi pada pasien kanker kepala dan leher dapat berpengaruh pada kondisi saliva pasien. Tujuan dari tinjauan pustaka ini adalah untuk mengetahui apakah terdapat pengaruh perawatan radioterapi terhadap kelenjar saliva pada pasien kanker nasofaring.

1.2 Rumusan Review

1. Apakah terdapat pengaruh perawatan radioterapi pada pasien kanker nasofaring terhadap kelenjar saliva pasien?
2. Apakah terdapat pengaruh perawatan radioterapi pada pasien kanker nasofaring terhadap saliva pasien?

1.3 Tujuan Review

1. Mengetahui pengaruh perawatan radioterapi pada pasien kanker nasofaring terhadap kelenjar saliva pasien.
2. Mengetahui pengaruh perawatan radioterapi pada pasien kanker nasofaring terhadap saliva pasien.

BAB II
METODE PENELITIAN

2.1. Pencarian Literatur

Pencarian literatur publikasi dilakukan pada basis data elektronik *Google Scholar*, NCBI (PubMed), Cochrane dan *Science Direct* dengan menggunakan metode PICO (*Population/Patient, Intervention, Comparison, and Outcome*). Kata kunci yang digunakan adalah *Salivary Gland Following Radiotherapy in Nasopharyngeal Cancer Patients* AND *Salivary Gland in Nasopharyngeal Cancer* Patients. Jurnal yang didapatkan diseleksi sesuai dengan kriteria inklusi dan eksklusi pada tinjauan pustaka ini. Data jurnal yang didapatkan dikumpulkan pada Mendeley, sebuah perangkat lunak yang berfungsi untuk manajemen referensi dan untuk mengelola dan berbagi makalah penelitian, mencari data penelitian, dan bekerja sama secara daring.

2.2. Kriteria Inklusi dan Eksklusi

2.2.1 Kriteria Inklusi

1) Jurnal penelitian yang dipublikasikan pada tahun 2005-2020 yang menggunakan Bahasa Inggris dan Bahasa Indonesia.
2) Jurnal yang dipublikasikan dapat diakses *free full text*.
3) Subjek pada penelitian merupakan manusia.
4) Tipe *outcome* yang diukur adalah kondisi kelenjar saliva pada pasien kanker nasofaring.

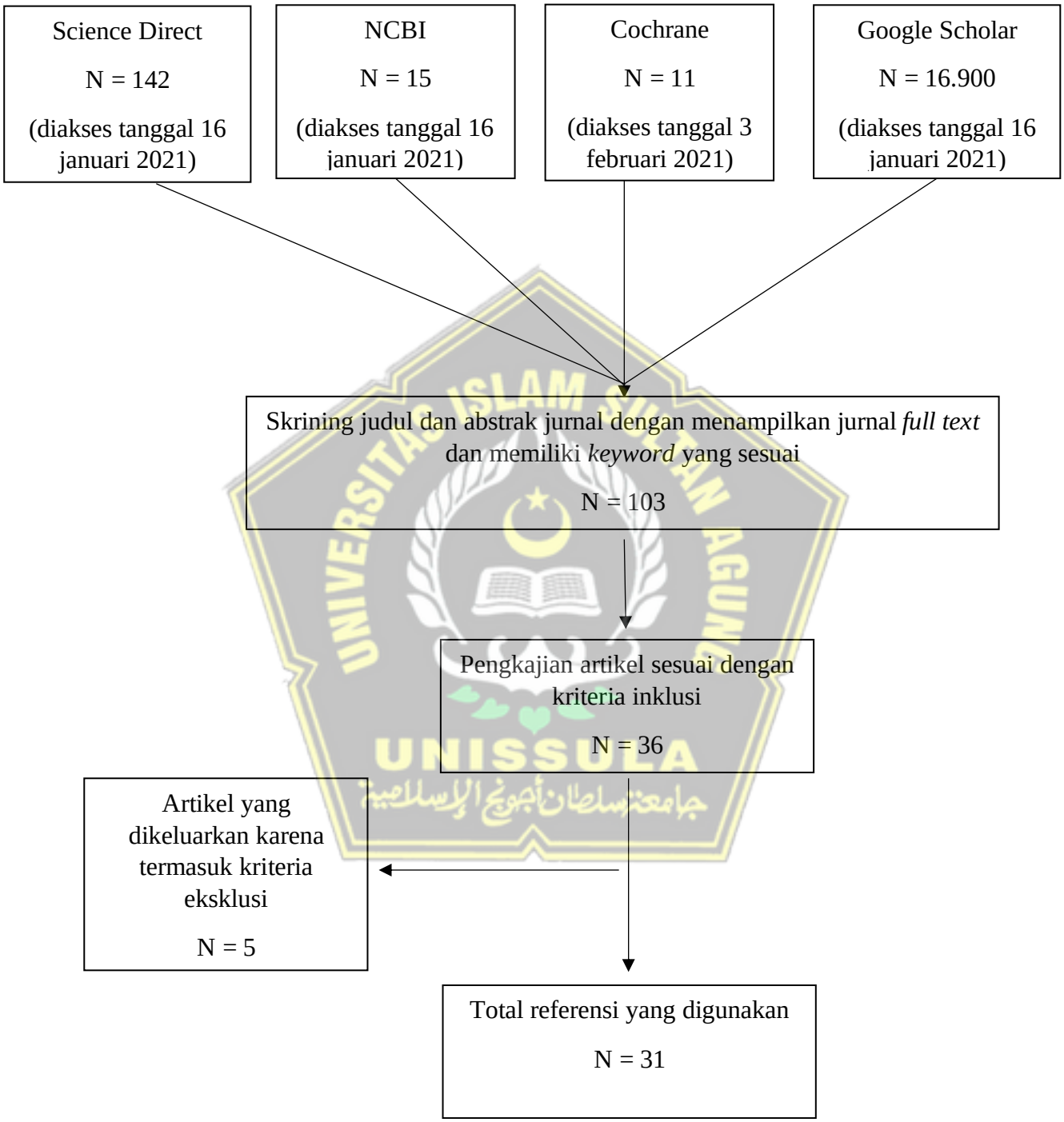
2.2.2 Kriteria Eksklusi

1) Jurnal penelitian dengan metode yang tidak jelas tercantum pada jurnal.

Tabel 2.1 Hasil temuan pencarian *literature review*

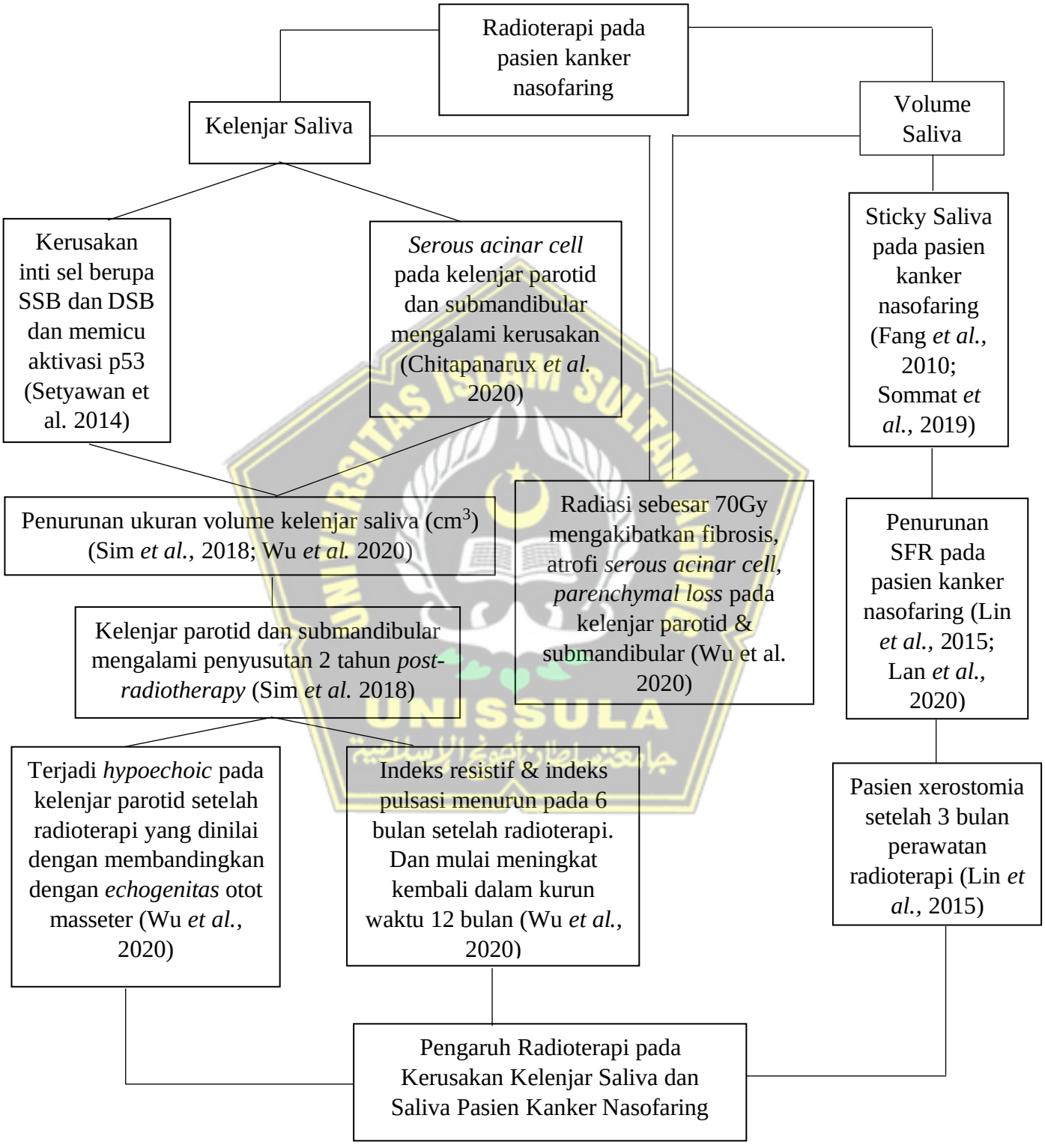
Pangkalan Data	Temuan	Literature Terpilih
Science Direct	32	4
NCBI	20	3
Cochrane	11	4
Google Scholar	40	20
JUMLAH	103	31

2.3. Alur Pencarian literatur



Gambar 2. 1 Alur Pencarian Literatur

2.4. Peta Literatur



Gambar 2. 2 Peta Literatur

BAB III
HASIL KAJIAN LITERATUR DAN PEMBAHASAN

3.1 Hasil Kajian *Literature Review*

Proses pengumpulan literatur dilakukan dengan cara melakukan pemilihan jurnal atau artikel dari 103 menjadi 31 artikel, 30 jurnal internasional dan 1 jurnal nasional. Proses pencarian literatur dilakukan melalui pangkalan data elektronik yang terindeks seperti *Google Scholar* (n=20), NCBI (n=3), *Science Direct* (n=4), dan *Cochrane* (n=4).

Tabel 3. 1 Hasil Kajian *Literature Review*

No	Judul	Pengarang	Tujuan penelitian	Metode penelitian (meliputi: subjek, rancangan, instrument, cara penelitian)	Hasil penelitian
1.	*Effects of radiotherapy on salivary glands function in patient with head and neck cancer*	(Lin *et al.*, 2015)	Penelitian ini bertujuan untuk memeriksa perubahan pada fungsi kelenjar saliva dari pasien kanker kepala dan leher setelah radioterapi, termasuk pH saliva, laju aliran saliva terstimulasi, dan saliva *buffering capacity*. pH dari saliva termasuk dari kelenjar parotid, submandibu	Subjek penelitian ini adalah 62 pasien kanker kepala dan leher (11 diambil sebelum & sesudah radioterapi, 51 diambil 1 kali setelah radioterapi). Cara penelitian: Penentuan pH saliva dilakukan dengan pengumpulan sampel saliva dengan GC *saliva-check buffer kits*. Sampel diambil sebelum atau 2 jam sesudah makan. Kertas uji saliva diletakkan di pembukaan *Stenson's duct* selama 10 detik. Saat pasien istirahat, pasien diminta meludah perlahan ke *collecting cups*. Kertas uji diletakkan dalam *cups* selama 10 detik.	Pada grup dengan pengukuran berulang, semua yang diuji mengalami penurunan setelah 1 bulan radioterapi, membaik kembali selama 3 atau 6 bulan tapi jumlah *Saliva flow rate* pasien tidak kembali seperti semula. Pada grup dengan sekali pengukuran menunjukkan bahwa jangka waktu setelah radioterapi merupakan pengaruh yang sangat besar terhadap pH

			lar & *total resting saliva.*	Penentuan *stimulated saliva flow rate* dilakukan dengan pengunyahan *bite wax* di GC *Saliva Check-Buffer Kit* selama 30 detik, pasien diinstruksikan untuk meludah perlahan ke dalam *collecting cups* dan sampel pertama dikecualikan, pasien diminta terus mengunyah selama 5 menit dan meludah setiap 15-20 detik yang direkam sebagai *stimulated saliva flow rate* (mL/5 menit), dilakukan juga pengukuran pH pada saliva ini. Sampel *stimulated saliva* diaplikasikan ke 3 *pads* selama 10 detik untuk *saliva buffering capacity*, dan warna *pads* akan berubah sesuai indikasi.	kelenjar submaksila & *total resting saliva*. Semua aspek yang diperiksa mengalami penurunan 1 tahun setelah radioterapi, kemudian setelah 1 tahun pH *resting saliva* mulai meningkat seiring waktu.
2.	*Saliva electrolyte analysis and xerostomia-related quality of life in nasopharyngeal cancer patient following IMRT*	(Lan *et al.*, 2020)	Penelitian ini bertujuan untuk mengetahui konsentrasi dari elektrolit saliva yang dipengaruhi IMRT dan efek terhadap kualitas hidup masih belum diketahui.	Subjek penelitian ini adalah 76 pasien kanker nasofaring di Rumah Sakit Hongkong. Cara Penelitian: Saliva dikumpulkan dari pasien 5 kali, sebelum radioterapi, 1 bulan setelah radioterapi, 3 bulan setelah radioterapi, 6 bulan setelah radioterapi, & 12 bulan setelah radioterapi. Pasien diminta untuk puasa aktivitas seperti makan, minum, sikat gigi, dll. Sebelum pengumpulan saliva subjek diminta untuk	*Saliva flow rate* menurun setelah IMRT (*mean value* dari 0.57 mL/menit menjadi < 0.1 mL/menit, p<0.000). Penurunan nilai rata-rata pH diobservasi tapi tidak terdapat perbedaan secara statistik (p = 0.086). Konsentrasi potassium, iodine, & calcium menurun dan konsentrasi

				membersihkan mulut dengan 20 mL air suling selama 1 menit dilakukan 2 kali, kemudian pasien diminta menunggu 10 menit untuk menghindari *dilution* dari sampel saliva. 2% asam sitrat diletakkan di dorsum lidah untuk menstimulasi sekresi saliva. Saliva subjek dikumpulkan dalam mulut dan diludahkan ke botol steril, saliva dikumpulkan selama 10 menit. Selama pengumpulan sampel saliva, *stimulated saliva flow rate* (mL/min) & pH diukur dengan H135 *minilab pocket pH meters.* Sampel saliva disimpan dalam *icebox* dan dibawa ke lab dalam 60 menit. Konsentrasi elektrolit saliva diukur dengan ICP-OES. 0.1 mL saliva diencerkan dengan 4.9 mL 2% asam nitrat untuk mendeteksi konsentrasi. Konsentrasi elektrolit dihitung dengan regresi linier dari *standard solution*. Untuk *quality of life* pasien diukur dengan kuesioner XeQoLS mengukur dampak disfungsi kelenjar saliva. Total skor rata-rata dari 0-4, dengan skor tertinggi memiliki indikasi memberikan dampak buruk yang lebih	chloride meningkat setelah setelah IMRT, sedangkan konsentrasi sodium, magnesium, zinc sama seperti sebelum radioterapi. Kualitas hidup yang berkaitan dengan xerostomia berdampak buruk karena IMRT tetapi sebagian akan pulih setelah 1 tahun.

				besar pada kehidupan sehari-hari.	
3.	*Multivariat analysis of quality of life outcome for nasopharyngeal cancer patient after treatment*	(Fang *et al.*, 2010)	Penelitian ini bertujuan untuk menganalisis faktor prognostik kualitas hidup pasien kanker nasofaring setelah perawatan, dengan berfokus pada manfaat terapeutik dari kemajuan teknologi dalam radioterapi.	Subjek penelitian ini adalah 356 pasien kanker nasofaring dengan kelangsungan hidup bebas kanker lebih dari 2 tahun. Sebanyak 106 pasien dirawat 2DRT, 108 pasien dirawat 2DRT+3DCRT boost, 58 pasien dengan 3DCRT, dan 84 pasien dengan IMRT. Cara penelitian: *Quality of Life* pasien dinilai dengan kuesioner EORTC QLQ-C30 dan modul QLQ-H&N35. Perbedaan klinis dari skor *Quality of Life* diantara grup-grup tersebut dikalkulasi dengan *Cohen's D coefficient.*	Pasien kanker nasofaring yang memiliki edukasi lebih tinggi atau memiliki pendapatan tahunan keluarga yang lebih tinggi dan menerima perawatan radioterapi yang lebih maju memiliki *outcome Quality of Life* yang lebih baik, salah satunya pada tingkat xerostomia pasien kanker nasofaring pasca radioterapi. 3DCRT jika dibandingkan dengan 2DRT memiliki dampak yang kecil di hampir semua skala dengan nilai *moderate* (Cohen's D: 0,53-0,67) dalam fungsi emosional, nyeri, dan *mouth opening.* Dampak dari IMRT moderate di 9 skala dan large (Cohen's D: 0,8-0,88) dalam menelan, makan, dental, dan *mouth opening.* Pasien yang menjalani radioterapi dan menerima dosis

					43,6-56,2 menderita xerostomia.
4.	*Clinical & dosimetric predictors of physician & patient reported xerostomia following IMRT for nasopharyngeal cancer – a prospective cohort analysis*	(Sommat *et al.*, 2019)	Penelitian ini bertujuan untuk membandingkan xerostomia pada *physician* dan pasien kanker nasofaring yang dirawat dengan IMRT dan kemoterapi.	Subjek penelitian ini adalah 172 pasien kanker nasofaring stadium lanjut. Cara penelitian: Xerostomia dievaluasi berdasarkan 3 kategori yaitu *physician-rated xerostomia* (E1), *patient-rated dry mouth* (E2), *patient-rated sticky saliva* (E3) pada kuesioner (EORTC) QLQ-H&N35.	Tingkat xerostomia yang dilaporkan oleh dokter (E1) secara konsisten lebih rendah daripada pasien yang melaporkan kondisi *dry mouth* (E2) dari waktu ke waktu.
5.	*Salivary gland transfer to prevent radiation-induced xerostomia: a system*	(Sood *et al.*, 2014)	Penelitian ini bertujuan untuk menganalisis keefektifan dari *salivary gland transfer* dalam mencegah xerostomia dan pemeliharaan *saliva flow*	Subjek penelitian ini adalah 177 pasien dengan *follow u*p rata-rata 22,7 bulan. Cara penelitian: *systematic review* & *meta-analysis* dengan poin 1: keefektifan *salivary gland transfer* dalam mencegah xerostomia setelah paparan radiasi. Poin 2: perubahan *baseline unstimulated saliva* setelah radioterapi.	*Salivary gland transfer* mencegah xerostomia karena paparan radiasi sebesar 82,7% 12 bulan setelah radioterapi, *unstimulated & stimulated saliva flow rate* meningkat hingga 88% dan 76% dari *baseline value*.

	atic review and meta-analysis		*rate* setelah radioterapi.		
6.	*The tubarial salivary glands: a potential new organ at risk for radiation*	(Valstar *et al.*, 2020)	Penelitian ini bertujuan untuk menjelaskan karakteristik dari entitas yang tidak diketahui dan potensi implikasi klinisnya untuk radioterapi.	Subjek penelitian ini adalah 100 pasien (99 laki-laki dan 1 perempuan dengan *median age* 69,5 dan *range*: 53-84) Cara penelitian: kondisi pada *molecular imaging* adanya PSMA-*positive tissue* pada nasofaring dievaluasi dari PSMA PET/CT *Scan* dari *retrospective cohort study*. Karakteristik kelenjar pada cadaver (n=2), dengan daerah yang diseksi sebesar 3x3x3 cm (1 *male*, 1 *female*). Karakteristik jaringan dilihat dengan *histochemistry* (H&E) dan *immunohistochemistry* (PSMA. Alpha-amylase).	Semua pasien menunjukkan daerah positif bilateral PSMA-*positive*. Pada kanker kepala dan leher, dosis radioterapi rata-rata untuk daerah kelenjar secara signifikan berhubungan dengan *physician-rated post-treatment xerostomia* & disfagia ≥ *grade* 2 pada 12 bulan. Setelah *follow up* pada 24 bulan hasil yang dimiliki mirip seperti sebelumnya.
7.	*Xerostomia, salivary characteristics & glands volumes following IMRT for NPC:*	(Sim *et al.*, 2018)	Penelitian ini bertujuan untuk mengevaluasi perubahan status xerostomia, karakteristik saliva dan volume kelenjar saliva 2 tahun setelah radioterapi	Subjek penelitian ini adalah 24 partisipan pasien kanker nasofaring direkrut untuk mendeteksi perbedaan *stimulated saliva flow rate* dari 0,4 mL/min dengan kekuatan 90%. Cara penelitian: Semua partisipan mendapatkan penanganan sesuai *American Joint Committee on Cancer Guideline* yakni menggunakan MRI *post*	Dosis radiasi rata-rata untuk rongga mulut, kelenjar parotis dan submandibular (SMG) adalah 44.5, 65.0 dan 38.6 Gy. Volume parotis dan SMG menurun 33% pada 3 bulan pasca radioterapi; volume pada 2 tahun pasca radioterapi

	a two year follow up		pasien kanker nasofaring.	*nasal space, CT chest/abdomen & bone scan.* Semua partisipan menerima IMRT sesuai dosis yang ditentukan dari 70 GY dalam 33-35 fraksinasi pada PTV dari *gross tumour,* mengirimkan 2-2,12 Gy/fraksinasi selama 6,5-7 minggu. Semua partisipan didiagnosis dengan CT scan untuk menilai respon, pada bulan ketiga dan 2 tahun *post radiotherapy.* Gambar DICOM yang dihasilkan diimpor ke sistem perencanaan perawatan yang sama & kelenjar saliva dikontur ulang dan volumenya diukur. Untuk menentukan *clinician-rated xerostomia*, skor xerostomia diukur dengan RTOG/EORTC sebelum radioterapi, *mid-radiotherapy*, 2 minggu *post-radiotherapy*. Untuk menentukan *participant-rated xerostomia*, menggunakan *xerostomia-related Questionnaire* (XQ) berisi 8 pertanyaan mengevaluasi *chewing, swallowing, speaking,* dan *sleeping function,* dengan rate 0-10, skala Likert.	masing-masing adalah 84% dan 51% dari tingkat sebelum radioterapi. Korelasi diamati antara penurunan persen volume kelenjar parotis dan dosis radiasi dan antara penurunan laju aliran saliva istirahat dan rasio volume SMG pasca radioterapi / pra-radioterapi. Laju aliran saliva dan pH saliva istirahat tetap rendah secara signifikan pada 2 tahun pasca radioterapi (kedua laju aliran, P = 0,001; pH saliva istirahat, P = 0,005). Demikian pula, skor xerostomia tetap secara signifikan lebih tinggi dibandingkan dengan tingkat pra-radioterapi.

8.	*How does intensity-modulated radiotherapy versus conventional two-dimensional radiotherapy influence the treatment results in nasopharyngeal carcinoma patients?*	(Lai *et al.*, 2011)	Penelitian ini bertujuan untuk membandingkan hasil IMRT dengan 2DCRT pada pengobatan pasien karsinoma nasofaring (KNF).	Sebuah tinjauan retrospektif data dari 1.276 pasien dengan kanker nasofaring nonmetastatik yang terbukti secara biopsi. Semua pasien telah menjalani *magnetic resonance imaging* (MRI) dan ditampilkan sesuai dengan edisi keenam dari *American Joint Committee on Cancer staging criteria*. Dan dipastikan perawatan yang digunakan hanya radioterapi saja sebagai pengobatan utama untuk pasien.	Dari 1.276 pasien, 512 dirawat dengan IMRT dan 764 dengan 2D-CRT. Kelangsungan hidup bebas kambuh lokal 5 tahun (LRFS), kelangsungan hidup bebas kekambuhan nodal (NRFS), kelangsungan hidup bebas metastasis jauh (DMFS), dan tingkat kelangsungan hidup bebas penyakit (DFS) adalah 92.7%, 97.0%, 84.0%, dan 75.9%, masing-masing, untuk kelompok AKB, dan 86.8%, 95.5%, 82.6%, dan 71.4% untuk kelompok 2D-CRT. Pada pasien tahap T1, peningkatan LRFS pada kelompok IMRT bahkan lebih tinggi secara signifikan dibandingkan pada kelompok 2D-CRT (100% vs. 94.4%; p = 0,016). Peningkatan DFS diamati pada kelompok IMRT dibandingkan dengan kelompok 2DCRT tapi tanpa

					mencapai signifikansi statistik. Tingkat NRFS dan DMFS serupa pada kedua kelompok. Peningkatan yang lebih besar dari hasil pengobatan dengan IMRT dibandingkan dengan 2D-CRT ditunjukkan terutama dengan mencapai tingkat pengendalian tumor lokal yang lebih tinggi pada pasien NPC, terutama pada pasien tahap awal T. Tujuan dari kontrol yang lebih baik dari kegagalan lokal pada pasien NPC nonmetastatik lanjut dan kegagalan jauh harus dibahas dalam penelitian selanjutnya.
9.	*Diffusion-weighted MRI of salivary glands with gustatory stimulation: compa*	(Zhang *et al.*, 2013)	Penelitian ini bertujuan untuk menginvestigasi nilai dari DWI untuk mengukur perubahan fisiologis kelenjar parotid selama stimulasi	Subjek penelitian ini adalah 28 pasien kanker nasofaring. Cara penelitian: MRI dilakukan pada 28 pasien sebelum dan sesudah radioterapi, dan dilakukan pemeriksaan xerostomia secara klinis. DWI *sequence* dilakukan sekali dalam kondisi istirahat dan terus diulang 7x selama	Sebelum radioterapi: ADC menunjukkan peningkatan awal (P: 0,001) dan berfluktuasi selama stimulasi. Setelah radioterapi: karena xerostomia pindah dari *grade* 0 ke *grade* 2, rata-rata ADC saat istirahat meningkat

	rison before & after radiotherapy		pernafasan sebelum dan sesudah radioterapi.	stimulasi dengan asam askorbat. ADC untuk kelenjar parotid pada waktu yang berbeda dan kisaran peningkatan dengan stimulasi juga dihitung. Uji *t-test two tailed* berpasangan digunakan untuk membandingkan ADC *value* sebelum dan sesudah stimulasi serta sebelum dan sesudah radioterapi.	dibandingkan saat sebelum radioterapi (P: 0,001). Kisaran peningkatan antara ADC maksimal selama stimulasi & nilai *baseline* saat istirahat lebih tinggi setelah radioterapi daripada sebelum radioterapi (P: ¼ 0,022). ADC minimum saat stimulasi lebih tinggi dari nilai *baseline* setelah radioterapi (P: 0,028), tapi tidak ada perbedaan sebelum radioterapi (P: ¼ 0,603).
10.	*Which nasopharyngeal cancer patient need adaptive radiotherapy ?*	(Hu *et al.*, 2018)	Penelitian retrospektif ini bertujuan untuk mengidentifikasi factor-faktor yang mendukung adaptive radioterapi.	Subjek penelitian ini adalah 40 pasien kanker nasofaring yang menerima 2 fase. Fase I: *Volumetric Modulated Arc Radiotherapy* (VMAT), fase II: menjalani *Computed Tomography* (CT) Cara penelitian: membuat rencana bayangan *non adaptive radiotherapy* (ART) dengan *hybrid method* sebagai perbandingan ART *plans*. Uji t-test berpasangan digunakan untuk mengevaluasi perbedaan dosis antara 2 rencana ini. Analisis subkelompok melalui uji	Volume kelenjar parotid ipsilateral (23,2 vs 19,2 mL, p<0) Volume kelenjar parotid kontralateral (23 vs 18,4 mL, p<0) Target klinis volume-1 (CTV-1, 32,2 vs 20,9 mL, p<0) PTV-1 (125,8 vs 107,3 mL, p<0) Semuanya menyusut secara signifikan. Hanya kelenjar parotid ipsilateral yang menunjukkan pengurangan dosis

				t-test berpasangan untuk mengevaluasi faktor yang mendukung ART.	yang signifikan dengan rencana ART (5,3 vs 6 Gy, p=0,004). ART secara signifikan dapat meningkatkan cakupan volume target daripada rencana bayangan (*phantom*). Faktor-faktor yang mendukung penggunaan ART antara lain ialah berat awal yang besar, BMI besar, penurunan berat badan jelas, *concurrent chemoradiotherapy*, stadium III-IV (p < 0,000).
11.	*Magnetic resonance sialography for investigating major salivary gland duct system after IMRT of nasopharyngeal cancer*	(Ou *et al.*, 2013)	Penelitian ini bertujuan untuk mengetahui nilai dari *magnetic resonance sialography* untuk mengevaluasi xerostomia yang diakibatkan oleh perawatan IMRT pada pasien kanker nasofaring.	Subjek penelitian ini adalah 14 pasien kanker nasofaring yang dirawat dengan IMRT. Cara penelitian: Fungsi saliva dinilai dengan *magnetic resonance sialography* dan kriteria evaluasi secara subjektif sebelum perawatan, 1 minggu setelah radioterapi, dan 1 tahun setelah radioterapi. Sistem penilaian kategoris *magnetic resonance sialography* digunakan untuk membandingkan visibilitas kelenjar saliva.	Dosis rata-rata yang digunakan untuk kelenjar parotid adalah 38,93 Gy, sedangkan untuk kelenjar submandibular adalah 59,34 Gy. Nilai visibilitas kedua kelenjar sebelum radioterapi meningkat setelah stimulasi. Nilai visibilitas kedua kelenjar setelah 1 minggu radioterapi menurun. Nilai visibilitas kelenjar parotid meningkat 1 tahun setelah

					radioterapi, baik dalam kondisi istirahat maupun dengan stimulasi, tetapi tidak dengan kelenjar submandibular. Dengan waktu *follow up* 12,3 bulan, 8/12 pasien memiliki xerostomia derajat 1 sedangkan 4/12 pasien memiliki xerostomia derajat 2.
12.	*Late sensorial alterations in differed radiotherapy techniques for nasopharyngeal cancer*	(Riva *et al.*, 2015)	Penelitian ini bertujuan untuk mengevaluasi secara objektif gangguan penciuman (olfaktori) dan gangguan pengecapan (gustatori) pada pasien yang menjalani kemoradioterapi untuk kanker nasofaring. Korelasi antara perubahan bau dan rasa, xerostomia, dan teknik radiasi diselidiki.	Subjek penelitian ini adalah 30 subjek sehat dan 30 pasien yang diobati dengan terapi kemoradiasi untuk NPC, dengan setidaknya masa tindak lanjut 2 tahun, dievaluasi. Cara penelitian: Semua subjek menjalani evaluasi gejala, pemeriksaan hidung serat optik endoskopi, strip rasa, *Sniffin' stick test*, Grup Onkologi Terapi Radiasi / Organisasi Eropa untuk Penelitian dan Pengobatan Kanker sistem penilaian morbiditas radiasi terlambat. Pasien dibagi menjadi 2 kelompok: 2DRT/3DCRT dan IMRT.	Persentase yang lebih tinggi dari rinorea, obstruksi hidung, xerostomia, hiposmia, hipogeusia, iperemia mukosa, dan adanya sekresi nasofaring ditemukan pada subjek yang diradiasi (P <0,05). Mengenai skor penciuman dan pengecapan, menunjukkan perbedaan yang signifikan secara statistik antara subjek sehat dan pasien yang diradiasi (P <0,05), dengan skor total pengecapan yang lebih rendah pada kelompok IMRT (P <0,01). Kemoradioterapi

					untuk NPC menyebabkan gangguan bau dan rasa jangka panjang, yang dapat mengganggu kualitas hidup. Meskipun berdasarkan sampel kecil, penting juga untuk mempertimbangkan bahwa IMRT dapat menyebabkan disfungsi rasa yang lebih tinggi dibandingkan dengan teknik tradisional.
13.	*A longitudinal study on parotid & submandibular gland changes assessed by magnetic resonance imaging & ultrasonography in post-radiot*	(Wu *et al.*, 2020)	Penelitian ini bertujuan untuk mengevaluasi perubahan yang disebabkan radiasi pada kelenjar parotid dan submandibular dalam ukuran kelenjar, echogenisitas, dan parameter hemodinamik.	Subjek penelitian ini adalah 21 pasien kanker nasofaring dirawat dengan IMRT dan scan ultrasound pada bulan ke 6,12, 18, & 24 setelah perawatan. Volume kelenjar parotid dan submandibular diukur dengan MRI. Echogenisitas parotid dan parameter hemodinamik meliputi indeks resistif, indeks pulsasi, kecepatan sistolik puncak & kecepatan diastolic akhir dievaluasi dengan USG. Korelasi antara dosis kelenjar dan perubahan pasca radioterapi juga dipelajari.	Volume kelenjar parotid dan submandibular menunjukkan penurunan yang signifikan 6 bulan setelah radioterapi daripada sebelum radioterapi. Kelenjar parotid berubah *hyperechoic* (sebelum radioterapi) menjadi *isoechoic* atau *hypoechoic* (setelah radioterapi). Indeks resistif & indeks pulsasi menurun pada 6 bulan setelah radioterapi dibandingkan dengan sebelum radioterapi. Akan

	herapy nasopharyngeal cancer patients				tetapi mulai meningkat kembali dalam kurun waktu 12 bulan. Kecepatan puncak sistolik dan kecepatan diastolik akhir meningkat setelah 6 bulan radioterapi, kemudain mengalami penurunan hingga 24 bulan setelah radioterapi. Terdapat korelasi ringan antara dosis kelenjar setelah radioterapi dan volume kelenjar, tapi tidak dengan perubahan hemodinamik.
14.	*Long-term outcomes of early-stage nasopharyngeal carcinoma patients treated with intensity-modulated radiotherapy alone*	(Su *et al.*, 2012)	Penelitian ini bertujuan untuk mengevaluasi hasil kelangsungan hidup jangka panjang dan toksisitas pasien NPC stadium awal yang diobati dengan IMRT saja.	Subjek penelitian ini adalah 198 pasien kanker nasofaring stadium awal T_{1-2b} N_{0-1} M_0 yang telah menjalani perawatan IMRT saja antara februari 2001-januari 2008. Cara penelitian: Data dianalisis secara retrospektif. Pasien dirawat dengan dosis 68 Gy pada 2,27 Gy/fraksi yang diresepkan. Penilaian *Radiation Therapy Oncology Group* digunakan untuk menilai toksisitas.	Pada median tindak lanjut 50,9 bulan (kisaran, 12-104), perkiraan kelangsungan hidup penyakit spesifik 5 tahun, kelangsungan hidup bebas kekambuhan lokal, dan tingkat kelangsungan hidup bebas metastasis jauh adalah 97,3%, 97,7%, dan 97,8%, masing-masing. Tingkat kelangsungan hidup bebas kekambuhan

					lokal 5 tahun adalah 100% untuk mereka dengan Tahap T1 dan T2a dan 94,2% untuk mereka dengan lesi Tahap T2b (p = 0,252). Tingkat kelangsungan hidup bebas metastasis jauh 5 tahun untuk pasien Tahap T1N0, T2N0, T1N1, dan T2N1 masing-masing adalah 100%, 98,8%, 100%, dan 93,8% (p =. 073). Semua kekambuhan lokal terjadi pada pasien dengan lesi T2b. Lima pasien mengalami metastasis jauh. Toksisitas akut yang paling umum terutama adalah Tingkat 1 atau 2. Pada 24 bulan setelah IMRT, tidak ada xerostomia Tingkat 3 atau 4 yang berkembang, dan 62 (96,9%). Pasca 12 dan 24 bulan setelah radioterapi semua pasien diobservasi menderita xerostomia akut.
15.	*Radiation*	(Xu *et al.*, 2016)	Penelitian ini bertujuan	Subjek penelitian ini adalah 30 pasien kanker	Volume GTV & kelenjar parotid

	induced CT number changes in GTV & parotid glands during the course of radation therapy for nasopharyngeal cancer		untuk menyelidiki perubahan jumlah CT number dalam *gross tumour volume* (GTV) dan organ yang beresiko selama terapi radiasi untuk kanker nasofaring.	nasofaring dirawat dengan dosis 70 Gy dalam 30-33 fraksi dengan *helical tomotherapy* dianalisis secara retrospektif. Cara penelitian: Kontur GTV dan organ yang beresiko pada MVCT harian diperoleh dengan mengisi merencanakan kontur dari perencanaan CT hingga MVCT harian dengan pengeditan manual. Perubahan volume GTV dan organ yang beresiko dan histogram CTN di GTV dan organ yang beresiko selama pelepasan radioterapi dianalisis.	berkurang selama pengobatan radiasi dengan tingkat penyusutan rata-rata 0,23%/hari dan 1,2%/hari masing-masing. Perubahan CT *number* rata-rata pada GTV & kelenjar parotid ipsi & kontra lateral adalah dikurangi masing-masing sebesar 52 ± 35, 8 ± 20, 17 ± 22 Hu. Ditemukan penurunan untuk GTV, volume CTN dan GTV yang berkorelasi satu sama lain (p<0,0001).
16.	*Diffusion-weighted imaging as a follow up modality for evaluation of major salivary gland function in nasopharyngeal cancer patient*	(Fan *et al.*, 2020)	Penelitian ini bertujuan untuk menyelidiki nilai DWI dalam menilai perubahan dinamis dari fungsi kelenjar saliva major selama *follow up* setelah radioterapi pada pasien kanker nasofaring.	Subjek penelitian ini adalah 31 pasien berturut-turut dengan kanker nasofaring yang dikonfirmasi secara patologis yang dijadwalkan untuk radioterapi menjalani 6 pemeriksaan MRI tindak lanjut termasuk urutan DWI sebelum radioterapi dan 1, 3, 6, 9, dan 12 bulan setelah radioterapi. Cara penelitian: nilai rata-rata koefisien difusi jelas dari kelenjar parotid bilateral dan kelenjar submandibular diukur. Pengukuran objektif *unstimulated saliva flow rate* & *stimulated saliva flow rate* serta penilaian	Pada setiap *timepoint*, ADC kelenjar parotid secara signifikan lebih rendah daripada kelenjar submandibular. *Unstimulated saliva flow rate* secara signifikan lebih rendah dari *stimulated saliva flow rate*. Untuk kelenjar parotid & submandibular, ADC setelah radioterapi secara signifikan lebih tinggi dari ADC sebelum radioterapi.

	: a prelim inary study			xerostomia secara subjektif menurut pasien dengan kuesioner sebelum Tindakan MRI.	ADC 1 bulan setelah radioterapi awalnya meningkat dan berubah sedikit menjadi ADC 3 bulan, 6 bulan, 9 bulan, dan 12 bulan setelah radioterapi, kemudian mengalami penurunan secara bertahap seiring waktu. ADC pasien dengan xerostomia subjektif berat signifikan lebih tinggi, sedangkan pasien dengan xerostomia subjektif sedang menunjukkan kecenderungan kearah ADC yang lebih tinggi dibanding dengan orang-orang dengan xerostomia ringan sejak 6-12 bulan setelah radioterapi.
17.	*Clinic al observ ation of subma ndibul ar gland transfe r for the preven*	(Zhang *et al.*, 2014)	Penelitian ini bertujuan untuk mengevalua si efikasi klinis transfer submandibu lar untuk pencegahan xerostomia pasca radioterapi	Metode penelitian ini adalah *randomized controlled clinical research.* Subjek penelitian ini adalah 65 pasien kanker nasofaring dibagi secara acak menjadi kelompok eksperimen yang terdiri dari 32 pasien dan kelompok kontrol yang terdiri dari 33 pasien.	Setelah tindak lanjut selama 3, 6, 12 bulan setelah kejadian xerostomia sedang-berat secara signifikan lebih rendah pada kelompok eksperimen dibanding kelompok kontrol.

	tion of xerostomia after radiotherapy for nasopharyngeal carcinoma: a prospective randomized controlled study of 32 cases		untuk kanker nasofaring.	Cara penelitian: kelenjar submandibular dialihkan ke daerah submental pada 32 pasien dengan kanker nasofaring sebelum mereka menerima radioterapi konvensional (digunakan blok timbal untuk melindungi daerah submental selama terapi). Sebelum radioterapi, fungsi kelenjar submandibular dinilai dengan *imaging*. Pengukuran dilakukan dengan 99mTc *radionuclide scanning* pada 60 bulan setelah radioterapi. Data kuesioner mengenai derajar xerostomia diselidiki dan sekresi saliva diukur pada 3, 6, 12, dan 60 bulan setelah radioterapi.	Jumlah rata-rata saliva yang dihasilkan kelompok eksperimen dan kelompok kontrol masing-masing adalah 1,6 g dan 0,68 g. Setelah tindak lanjut selama 60 bulan, fungsi penyerapan dan sekresi kelenjar submandibular pada kelompok eksperimen lebih tinggi daripada kelompok kontrol. Kejadian xerostomia sedang/berat pada kelompok eksperimen lebih rendah disbanding kelompok kontrol. Tingkat kelangsungan hidup 5 tahun dari kelompok eksperimen sebesar 81,3% sedangkan pada kelompok control sebesar 78,8%, tidak terdapat perbedaan yang signifikan.
18.	*Salivary glands & dental complications after*	(Chitanaparux *et al.*, 2020)	Dalam studi ini, registrasi gambar yang dapat diubah bentuk dari perencanaan	Subjek penelitian ini adalah 42 kelenjar parotid dari 21 pasien karsinoma nasofaring. Cara penelitian: berkas dari rencana perawatan masing-masing pasien diaplikasikan ke CBCT	Dari 21 pasien yang dilibatkan dalam penelitian ini, delapan terdapat xerostomia, dan 13 sisanya tidak. Baik perencanaan dan

	radiotherapy for nasopharyngeal carcinoma		*computed tomography* (CT) dan *cone-beam* CT (CBCT) digunakan untuk mengesampingkan nilai satuan Hounsfield dari CBCT, dan CBCT yang dimodifikasi diperkenalkan untuk memperkirakan dosis radiasi yang diberikan selama pengobatan.	yang dimodifikasi untuk membangun dosis yang diberikan mingguan. Kemudian, dosis mingguan dijumlahkan untuk mendapatkan dosis yang terkumpul. Dosis yang diberikan ke kelenjar parotis meningkat secara signifikan dibandingkan dengan dosis perencanaan. V20, V30, V40, Dmean, dan D50 masing-masing meningkat sebesar 11.3%, 28.6%, 44.4%, 9.5%, dan 8.4%.	pemberian PG *Dmean* untuk semua pasien melebihi toleransi (26 Gy). Di antara 21 pasien, dosis perencanaan dan dosis pengiriman *Dmean* masing-masing adalah 30,6 Gy dan 33,6 Gy, untuk pasien dengan xerostomia, dan 26,3 Gy dan 28,0 Gy, untuk pasien tanpa xerostomia. D50 dari perencanaan dan dosis pengiriman untuk pasien berada di bawah toleransi (30 Gy). Hasil penelitian menunjukkan bahwa *p-value* V20, V30, D50, dan *Dmean* perbedaan dosis persalinan antara pasien xerostomia dan pasien tanpa xerostomia kurang dari 0,05. Namun, untuk dosis perencanaan, perbedaan dosimetri yang signifikan antara kedua kelompok hanya ada di D50 dan *Dmean*. Xerostomia terkait erat dengan V20, V30, D50, dan *Dmean.*

19.	*Evaluation of radiation-induced changes to parotid glands following conventional radiotherapy in patient with nasopharyngeal cancer*	(Wu *et al.*, 2011)	Penelitian ini bertujuan untuk mengevaluasi hubungan perubahan kelenjar parotid setelah radioterapi dengan dosis yang diterima.	Subjek penelitian ini adalah 18 pasien kanker nasofaring dengan perawatan radioterapi antara tahun 1997-2001. Cara penelitian: volume kelenjar parotid diukur dan dibandingkan antara gambar CT sebelum dan sesudah radioterapi. USG Doppler digunakan untuk menilai kondisi hemodinamik kelenjar setelah radioterapi, hasil USG dibandingkan 18 peserta normal yang cocok. Kuesioner digunakan untuk mengevaluasi kondisi xerostomia pasien. Rencana perawatan radioterapi dari peserta diambil dari sistem perencanaan perawatan Eclipse. Dilakukan evaluasi korelasi dosis kelenjar parotid & perubahan setelah radioterapi.	Kelenjar parotid setelah radioterapi secara signifikan lebih kecil (p 0,001) dibandingkan dengan sebelum radioterapi. Kecepatan *vascular* lebih rendah, indeks resistif & pulsasi dari peserta normal. Derajat penyusutan volume dan keparahan subjektif xerostomia menunjukkan ketergantungan dosis, tetapi ketergantungan tersebut tidak pasti pada perubahan hemodinamik.
20.	*Radiation caries in nasopharyngeal carcinoma patient after IMRT: a cross-section*	(Liang *et al.*, 2016)	Penelitian ini bertujuan untuk mengevaluasi keparahan lesi gigi setelah IMRT & korelasi dengan dosis radiasi dengan gigi pada pasien dengan kanker nasofaring.	Subjek penelitian ini adalah 42 pasien kanker nasofaring dengan perawatan IMRT yang sudah selesai pada tahun 2011. Cara penelitian: setiap gigi premolar dibagi menjadi 13 bagian. Gigi dievaluasi dengan indeks yang telah divalidasi & kemudian dikategorikan pada setiap regio yang dibagi. Hubungan antara distribusi dosis & skor	Sebanyak 4342 bagian dari 334 gigi premolar dievaluasi. Untuk bagian yang terkena 30-60 Gy, kemungkinan terjadi kerusakan karies 12-200 kali lebih besar dibanding bagian yang tidak terpapar IMRT. Kemungkinan lesi karies muncul ketika dosis

	al study			keparahan karies dianalisis dengan menggunakan model logistic. Rasio *odds* digunakan untuk mengetahui peluang terjadinya kerusakan karies.	diberikan >35,8 Gy setelah 17 hari radioterapi (p<0,05). 76,19% dari total pasien dilaporkan mengalami xerostomia.
21.	*Nasal cytological changes as late effects of radiotherapy for nasopharyngeal carcinoma*	(Riva *et al.*, 2016)	Penelitian ini bertujuan untuk mengevaluasi perubahan sitologi yang tertunda pada pasien kanker nasofaring yang menjalani radioterapi.	Metode penelitian ini adalah *case control study.* Subjek penelitian ini adalah 30 pasien sehat & 30 pasien yang dirawat dengan kemoterapi dan radioterapi untuk kanker nasofaring antara 2003-2011, dengan *median follow up* selama 59 bulan. Cara penelitian: semua subjek menjalani evaluasi gejala *amnestic* (*rhinorrea, nasal obstruction*) *endoscopic fiber optic nasal examination, skin-prick test,* dan *nasal scrapping* untuk pemeriksaan sitologi.	Sebanyak 83% dari total pasien kanker nasofaring yang diobservasi pada penelitian ini menderita xerostomia. Persentase yang lebih tinggi dari *rhinorrea, nasal obstruction, mucosal hyperemia,* dan adanya sekresi nasofaring pada pemeriksaan endoskopik serat optic ditemukan pada subjek yang diradiasi. Analisis sitologi nasal menunjukkan persentase inflamasi neutrophil dan *squamous cell metaplasia* dan *metaplasia mucous cell* pada pasien yang diobati. Tidak ada atypia sitologis yang terlihat. Tidak ada korelasi yang signifikan secara statistic antara

					perubahan sitologis nasal dan temuan objektif, usia pasien, merokok, & refluks gastroesofagus yang ditemukan pada kelenjar radioterapi.
22.	*Early prediction of acute xerostomia during radiotherapy for nasopharyngeal carcinoma based on delta radiomics from CT images*	(Liu *et al.*, 2019)	Penelitian ini bertujuan untuk memprediksi xerostomia akut selama radioterapi untuk kanker nasofaring dengan menginvestigasi perubahan radiasi yang diinduksi dari CT *radiomic* di kelenjar parotid dan jumlah saliva.	Data CT dan SA (*saliva amount*) dari 35 pasien dengan stadium I-IVB dikumpulkan secara acak dari uji klinis NPC yang ada di *clinicaltrials.gov*. Semua mendapat perawatan IMRT dengan dosis 68,1 Gy dalam 30 fraksi. Pasien memiliki 5 set CT (pada fraksi ke 0, 10, 20, 30 selama radioterapi, dan 3 bulan setelah radioterapi. Kelenjar parotid untuk setiap set CT digambarkan oleh ahli onkologi radiasi dan diverifikasi secara *independent* oleh yang lain. Saliva pasien dikumpulkam setiap 10 hari selama radioterapi. Xerostomia akut dievaluasi berdasarkan skor toksisitas akut RTOG dan SA.	Tingkat xerostomia akut yang diinduksi radiasi bisa lebih awal diprediksi berdasarkan SA dan perubahan radiomic dari kelenjar parotid selama perawatan IMRT. SA NFV_0, NFV_{10}, dan terutama ΔNFV_{10-0} memberikan kinerja terbaik pada prediksi xerostomia akut untuk setiap pasien berdasarkan metode *RidgeCV_RFE_LinearRegression* dari delta radiomic.
23.	*Xerostomia and Quality of Life after*	(Pow *et al.*, 2006)	Penelitian ini bertujuan untuk membandingkan secara langsung efek IMRT	Subjek penelitian ini adalah 51 pasien kanker nasofaring T_2, N_0, N_1, M_0 menerima IMRT/CRT. Cara penelitian: *stimulated whole saliva* dan parotid diukur dan	46 pasien (88%) berada dalam remisi penyakit 12 bulan setelah radioterapi. Setelah 12 bulan radioterapi, 12

	IMRT vs conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial		vs.CRT pada *salivary flow* dan QoL pada pasien kanker nasofaring stadium awal.	*medical outcomes short form* 36 (sf-36), kuesioner EORTC, EORTC modul kepala dan leher diselesaikan pada *baseline*, 2, 6, 12 bulan setelah radioterapi.	(50%) & 20 pasien (83,3%) pada kelompok IMRT telah pulih setidaknya 25% dari aliran SWS dan SPS sebelum radioterapi, dibanding dengan 1 & 2 pasien masing-masing dalam kelompok CRT. Skor Kesehatan global menunjukkan peningkatan QoL yang berkelanjutan setelah radioterapi. 12 bulan setelah radioterapi, kelompok IMRT lebih bagus daripada CRT pada peran fisik, nyeri tubuh, & fungsi fisik. *Dry mouth* dan *sticky saliva* merupakan masalah IMRT & CRT 2 bulan setelah radioterapi. Pada kelompok IMRT terdapat perbaikan konsisten dari waktu ke waktu terkait xerostomia dibandingkan CRT.
24.	*Temporal Evolution of*	(Juan *et al.*, 2015)	Penelitian ini bertujuan untuk mengukur	Subjek penelitian ini adalah 11 pasien kanker nasofaring (9 laki-laki dan 2 perempuan; 48,7 ±	Hasil penelitian ini menunjukkan bahwa penurunan volume parotid

	Parotid Volume and Parotid Apparent Diffusion Coefficient in Nasopharyngeal Carcinoma Patients Treated by Intensity-Modulated Radiotherapy Investigated by Magnetic Resonance Imaging: A Pilot Study		secara bersamaan perubahan yang diinduksi radiasi dan evolusi temporal dari volume parotid dan koefisien difusi semu parotid (ADC) pada pasien karsinoma nasofaring (NPC) yang dirawat dengan radioterapi modulasi intensitas dengan menggunakan *magnetic resonance imaging* (MRI).	11,7 tahun, 22 kelenjar parotis). Cara penelitian: Dosis radiasi, *volume parotid sparing*, keparahan xerostomia, dan interval radiasi-ke-MR (RMI) dicatat. Studi MRI diperoleh empat kali, termasuk satu sebelum dan tiga setelah radioterapi. Volume parotis dan ADC parotis diukur. Analisis statistik dilakukan dengan menggunakan SPSS dan *MedCalc*. Koreksi Bonferroni diterapkan untuk beberapa perbandingan. Nilai P kurang dari 0,05 dianggap signifikan secara statistik.	dan peningkatan ADC parotis didominasi oleh efek kehilangan asinar daripada edema pada fase awal hingga menengah dan pemulihan volume parotis dan ADC berikutnya menuju nilai dasar mungkin mencerminkan regenerasi asinar kelenjar parotis.
25.	*Effectiveness of oxygen nebulization at*	(Xu *et al.*, 2014)	Penelitian ini bertujuan untuk mengevaluasi efektivitas nebulisasi O_2 dalam	Subjek penelitian ini adalah 60 pasien kanker nasofaring dengan IMRT. Cara penelitian: pasien secara simultan ditugaskan secara acak	Terdapat perbedaan yang signifikan pada kejadian *mucositis grade* III & IV, volume dan pH saliva serta *dry*

	preventing radiotherapy-induced mucositis in patient with nasopharyngeal carcinoma		mencegah mucositis yang diinduksi radioterapi pada pasien kanker nasofaring.	ke kelompok nebulisasi O_2 atau nebulisasi *ultrasonic*, pengobatan sekali sehari selama 20 menit. Kemudian dilakukan pembandingan pH dan volume saliva, asupan makanan, & perubahan mukosa mulut selama radioterapi, serta *dry mouth* & sakit tenggorokan setelah radioterapi antara kedua kelompok subjek.	*mouth* dan sakit tenggorokan antara kedua kelompok dengan dosis total 33 Gy. Kelenjar saliva mayor yang menerima dosis rata-rata 20-40 Gy akan mengalamu penurunan fungsi, dan apabila >40 Gy maka akan terjadi penurunan fungsi secara dramatis.
26.	*Prospective evaluation of Quality of Life & nutrition before and after treatment of nasopharyngeal carcinoma*	(Oates *et al.*, 2007)	Penelitian ini bertujuan untuk menilai kualitas hidup secara prospektif pada pasien yang menjalani terapi kemoradiasi untuk kanker nasofaring.	Subjek penelitian ini adalah 14 pasien kanker nasofaring dirawat selama 7 minggu menjalani kemoradioterapi. Cara penelitian: dilakukan evaluasi prospektif kualitas hidup & status gizi sebelum & sesudah perawatan kanker nasofaring. Pasien diminta mengisi kuesioner EORTC *Core* QoL & *head and Neck module* sebelum perawatan, 3, 6, 12, & 24 bulan setelah perawatan. Perubahan skor dianalisis dan dikorelasikan dengan tingkat efek toksik.	QoL *issue* selama 24 bulan follow up adalah Kesehatan global yang lebih buruk, kehilangan nafsu makan, kesulitan menelan, masalah perasa, *difficulty social eating*, *dental problem*, trismus, xerostomia, *sticky saliva*, *cough*, merasa sakit, nyeri, dan fungsi emosional. Isu-isu tersebut meningkat secara signifikan dibandingkan dengan sebelum perawatan. Pasien kanker nasofaring yang menjalani perawatan dilaporkan menderita *dry mouth* 2 tahun pasca perawatan.

					Penurunan BB rata-rata sebesar 7 kg, Sebagian besar penurunan terjadi selama pengobatan, meskipun terdapat dukungan nutrisi dengan selang makanan gastrotomi. Efek toksik yang diberikan oleh dokter berkorelasi buruk dengan skor kualitas hidup.
27.	*IMRT with or without chemotherapy for nasopharyngeal carcinoma: radiation therapy oncology group phase II trial 0225*	(Lee *et al.*, 2009)	Penelitian ini bertujuan untuk menyelidiki kelayakan IMRT dengan atau tanpa kemoterapi, dan untuk menilai toksisitas, pola kegagalan, dan kelangsungan hidup pada pasien dengan kanker nasofaring.	Subjek penelitian ini adalah 68 pasien dengan NPC stadium I hingga IVB (di antaranya 93,8% adalah WHO tipe 2 dan 3) antara Februari 2003 dan November 2005. Cara penelitian: Radiasi terdiri dari 70 Gy yang diberikan untuk volume target perencanaan tumor primer ditambah N apapun penyakit dan 59,4 Gy diberikan untuk penyakit subklinis, diberikan selama 33 hari pengobatan. Pasien dengan stadium T2b atau lebih atau dengan penyakit N juga menerima cisplatin bersamaan (100 mg / m 2) pada hari ke 1, 22, dan 43 diikuti oleh cisplatin adjuvan (80 mg / m 2) pada hari 1; fluorouracil (1.000 mg / m 2 / d) pada hari 1 sampai 4 diberikan setiap 4 minggu selama tiga siklus. Tumor, status	IMRT dengan atau tanpa kemoterapi dalam pengobatan KNF dapat dibawa ke *multi-institutional setting* dengan tingkat LRPF 90% menghasilkan laporan yang sangat baik dari satu lembaga. Diperkirakan *Progression-free* (PF) 2 tahun dan kelangsungan hidup secara keseluruhan 72,7% dan 80,2%, masing-masing. Mucositis derajat 4 akut terjadi pada 4,4%, dan toksisitas derajat 3 yang paling parah adalah sebagai berikut: esofagus, 4,7%; selaput lendir, 3,1%; dan xerostomia, 3,1%.

				klinis, dan toksisitas akut / lanjut dinilai. Tujuan utamanya adalah untuk menguji daya angkut IMRT ke lingkungan *multi-institusional.*	Tingkat xerostomia *grade* 2 pada 1 tahun sejak dimulainya IMRT adalah 13,5%. Hanya dua pasien yang mengeluhkan xerostomia derajat 3, dan tidak ada yang mengalami xerostomia derajat 4.
28.	*Prospective randomized stidy of IMRT on salivary gland function in early-age stage nasopharyngeal carcinoma patients*	(Kam *et al.*, 2007)	Penelitian ini bertujuan untuk membandingkan tingkat *delayed-xerostomia* antara 2DRT dan IMRT dalam pengobatan NPC stadium awal.	Subjek penelitian ini adalah 60 pasien kanker nasofaring T_{1-2b} N_{0-1} M_0 secara acak ditugaskan untuk menerima IMRT/2DRT. Cara penelitian: *primary endpoint* adalah kejadian xerostomia berat yang dinilai pada 1 tahun setelah perawatan. Dilakukan penilaian parallel dengan hasil yang dilaporkan pasien, *stimulated parotid flow rate* (SPFR) dan *stimulated whole saliva flow rate* (SWSFR).	Satu tahun setelah pengobatan, pasien IMRT memiliki insiden xerostomia yang lebih rendah dibandingkan pasien 2DRT (39,3% vs 82,1%, p = 0). Sesuai dengan SPFR pasien IMRT lebih tinggi dari 2DRT (0,90 vs 0,05, p < 0,0001) dan SWSFR pasien IMRT juga lebih tinggi (0,41 vs 0,20, p = 0,001). Untuk perasaan subjektif pasien, tidak ada perbedaan yang signifikan antara 2 kelompok.
29.	*Influence of IMRT technique on xerostomia*	(Marucci *et al.*, 2010)	Penelitian ini bertujuan untuk membandingkan teknik IMRT 5 bidang dan 7	Subjek penelitian ini adalah 8 pasien dirawat dengan teknik 5 bidang, 23 pasien dirawat dengan teknik 7 bidang. Cara penelitian: xerostomia dievaluasi	Dosis parotid rata-rata 45,7 Gy dan 29,9 Gy. Toksisitas ≥ G3 dalam 24 bulan 25% (kelompok I)

	and related Quality of Life in patient treated with IMRT for nasopharyngeal carcinoma		bidang dalam hal xerostomia dan kualitas hidup terkait pada pasien kanker nasofaring.	dengan menggunakan skala RTOG, sSFR/uSFR, dan kuesioner terkait xerostomia (XQs). Penilaian dilakukan sebelum radioterapi, 3, 6, 12, 18 dan 24 bulan setelah radioterapi.	dan 19% (kelompok II). 63% (kelompok I) dan 93% (kelompok II) pasien pulih 25% dari nilai sebelum radioterapi dinilai dari sSFR. Skor XQ dari kedua kelompok meningkat dari waktu ke waktu, tapi lebih signifikan pada kelompok II. Kelompok dengan teknik 7 bidang menurunkan rata-rata dosis parotid, mengurangi xerostomia yang dinilai dengan skor RTOG/XQ.
30.	*Outcomes of xerostomia-related quality of life for nasopharyngeal carcinoma treated by IMRT: based on the EORTC QLQ-C30*	(Bian *et al.*, 2015)	Penelitian ini bertujuan untuk meninjau literatur yang membahas apakah IMRT menghasilkan peningkatan QoL terutama terkait xerostomia dari pasien kanker nasofaring seiring berjalannya waktu.	Pencarian literatur melalui *PubMed, Embase, Google Scholar* yang berisi data asli dari skor QoL setelah dirawat dengan IMRT. Kriteria inklusi dipenuhi oleh 14 artikel yang mencakup hasil berdasarkan kuesioner yang ditangani IMRT. Data dari kuesioner EORTC QLQ-C30 dan H&N35 diambil dan dianalisis 4 item (*global health status, dry mouth, sticky saliva, swallowing, social eating,* dan *social contact*) yang memiliki hubungan dekat dengan QoL terkait xerostomia.	Kerusakan maksimal dari sebagian besar skala QoL termasuk status Kesehatan global berkembang selama pengobatan atau pada akhir masa pengobatan dan kemudian diikuti dengan pemulihan bertahap hingga 1 tahun, 1-2 tahun setelah IMRT, dibandingkan dengan tingkat awal mereka, beberapa item kepala & leher tertentu, Sebagian

	and H&N35 questionnaire				besar di EORTC QLQ H&N35, tetap lebih buruk untuk pasien yang masih hidup.
31.	Efek Dasar Radiasi Pada Jaringan	(Setyawan *et al.*, 2014)	Penelitian ini bertujuan untuk mengetahui dan menganalisis efek dasar radiasi pada jaringan tubuh pasien kanker.	Dilakukan pencarian literatur tentang radiasi, efek radiasi pada jaringan, dan radioterapi pasien kanker.	Tidak terdapat perbedaan yang besar respon tumor antara sel normal dan sel kanker seandainya tidak terdapat perbedaan dalam regulasi siklus sel, kinetik populasi sel, dan sruktur organisasi kelompok sel (jaringan). Faktor yang bertanggungjawab terhadap respon radiasi pada prinsipnya sama dengan sifat yang membedakan antara keduanya. Istilah radiosensitif dan radioresistan biasanya digunakan untuk menjelaskan cepat atau lambatnya pengecilan tumor setelah radiasi. Sel kanker biasanya mengekspresikan kerusakan DNA akibat radiasi dengan kematian mitosis, oleh karena itu laju respon tumor tergantung dengan

					tingkat proliferasinya.

3.2 Pembahasan

3.2.1 Radioterapi pada Pasien Kanker Nasofaring

3.2.1.1 Radioterapi

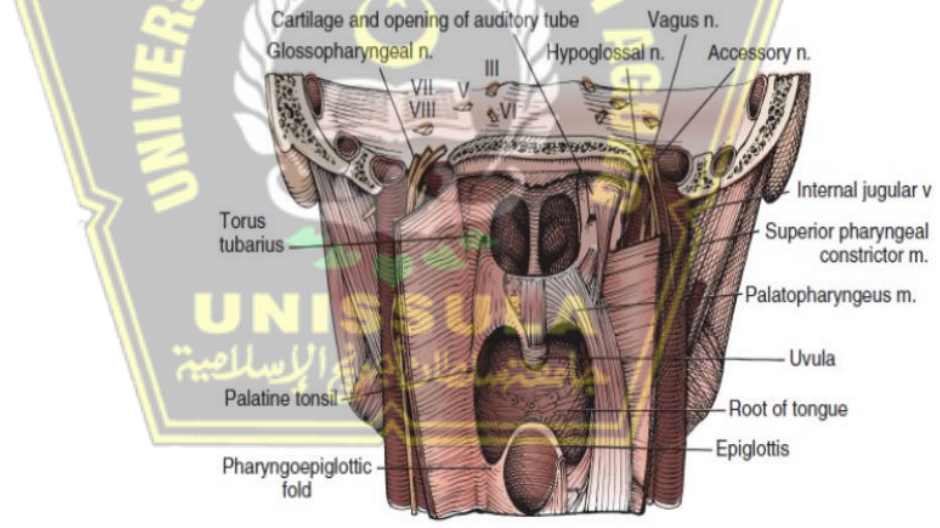
Radioterapi adalah salah satu perawatan untuk penyakit kanker yang menggunakan radiasi elektromagnetik atau partikel berenergi tinggi yang dapat merusak sel-sel kanker. Radioterapi dapat digunakan sebagai terapi preventif yang tujuannya untuk mencegah kejadian metastasis melalui penerapan radioterapi, terapi kuratif sebagai terapi tunggal untuk penyembuhan suatu kanker, maupun terapi paliatif untuk meningkatkan kualitas hidup dengan menghilangkan gejala dari kanker (Fitriatuzzakiyyah, 2017). Berdasarkan cara penghantaran radiasi pada lokasi kanker dibagi menjadi dua yakni, radiasi internal (*brachytherapy*) dan radiasi eksternal. *Brachytherapy* adalah terapi radiasi dimana sumber radiasi ditempatkan di dalam rongga tubuh, biasanya digunakan pada kanker yang membutuhkan perawatan berulang sedangkan radioterapi eksternal adalah terapi yang dilakukan dengan cara memaparkan radiasi ke tubuh secara eksternal dengan menggunakan mesin perawatan (Anindita, Raymondalexas and Suryo, 2010).

Jenis radioterapi selain dibedakan berdasarkan cara penghantarannya juga dibagi menjadi 2 yaitu radioterapi konvensional dan *Intensity-modulated radiation therapy* (IMRT) (Wu, Ying and Kwong, 2011). Data dari publikasi terbaru menunjukkan bahwa IMRT dapat meningkatkan hasil pengobatan dan meningkatkan kualitas hidup pasien dengan Kanker Nasofaring dibandingkan dengan 2D-CRT (2 *dimentional Conventional Radiotherapy)*. Alasan utama IMRT lebih baik daripada 2DCRT adalah adanya peningkatan cakupan sasaran; penggunaan *Intensity-Modulated Accelerated Radiation Therapy*, yang dapat mengurangi percepatan repopulasi klonogen tumor dengan mempersingkat waktu pengobatan secara keseluruhan; dan jaminan kualitas dan kontrol kualitas yang lebih baik dengan menggunakan IMRT (Su *et al*., 2012).

IMRT menjadi pendekatan pengobatan utama dalam pengelolaan kanker kepala dan leher karena kemampuannya untuk mencapai peningkatan iradiasi target sambil membatasi dosis radiasi ke jaringan normal sehingga mengurangi efek samping pengobatan yang menyebabkan morbiditas fungsional dan psikososial (Pow *et al.,* 2006).

3.2.1.2 Kanker Nasofaring

Kanker Nasofaring adalah salah satu jenis kanker kepala dan leher yang memiliki prevalensi paling besar yakni sekitar 60%. KNF merupakan keganasan terbanyak ke-4 di Indonesia setelah kanker payudara, kanker leher rahim, dan kanker paru. Berdasarkan globocan (2012), 87.000 kasus baru nasofaring muncul tiap tahunnya (dengan 61.000 kasus baru terjadi pada laki-laki dan 26.000 kasus baru pada perempuan) serta 51.000 kematian akibat KNF (36.000 laki laki dan 15.000 pada perempuan) (Kemenkes RI, 2015).



Gambar 3. 1 Penampang koronal nasofaring dan struktur sekitar (Lee *et al*., 2000)

KNF merupakan pertumbuhan sel yang tidak terkendali dan ganas berupa sel-sel ephitelial pelapis rongga yang berada di belakang hidung yang cenderung menginfiltrasi jaringan disekitarnya dengan proses metasis yang berada di nasofaring, bagian atas dari tenggorokan

dibelakang hidung dan dekat dengan dasar tengkorak (Meka, 2017). KNF disebabkan karena interaksi gen yang lemah, faktor lokal seperti adanya paparan dari karsinogen kimia, dan infeksi dari Virus Epstein-Barr. Pasien KNF biasanya menunjukkan gejala lokal seperti epistaxis dan hidung yang tersumbat, serta disertai dengan pendengaran yang berkurang, otalgia, sakit kepala, atau keterlibatan Nervus Cranialis (Abdel, 2012).

3.2.1.3 Perawatan Radioterapi terhadap Kanker Nasofaring

Kanker kepala dan leher didiagnosis pada lebih dari 500.000 orang setiap tahun di dunia, dan hampir 60% merupakan kanker nasofaring. Terapi radiasi diindikasikan untuk kanker nasofaring dan sangat efektif pada kanker nasofaring tipe III. Radioterapi di daerah kepala dan leher juga akan mempengaruhi fungsi mulut dan berpengaruh penting pada kualitas hidup pasien yang menjalani radioterapi (Liang *et al.*, 2016).

Radioterapi merupakan pengobatan utama untuk kanker nasofaring karena tumor sangat sensitif terhadap radiasi dan akses bedah ke organ nasofaring sulit untuk dilakukan. Pasien yang telah menjalani perawatan radioterapi konvensional, memiliki tingkat kelangsungan hidup bebas kekambuhan dalam 5 tahun untuk kanker nasofaring dilaporkan 75-95% untuk tahap T1-2 dan 45–80% untuk stadium T3–4,

dengan persentase kelangsungan hidup secara keseluruhan 50–70%. Komplikasi terkait iradiasi struktur normal sensitif yang berdekatan dengan nasofaring dan berada di jalur iradiasi cukup besar dan sering tidak dapat kembali sesuai dengan semula, tetapi radioterapi tetap menjadi pengobatan pilihan untuk kanker nasofaring (Pow *et al.*, 2006).

Reaksi mukosa rongga mulut terhadap radioterapi merupakan salah satu komplikasi yang paling sering pada pasien karsinoma nasofaring. Lingkungan mulut yang lembab dan kaya akan suplai darah, dan epitel skuamosa bertingkat, yang meregenerasi dirinya sendiri dengan cepat, sangat sensitif terhadap radiasi. Sekresi kelenjar saliva (parotid, submandibular, sublingual) menurun setelah radioterapi, dan *saliva flow rate* menurun, yang menyebabkan pH oral menurun, menyebabkan mulut kering dan gangguan pada mulut. Pada saat yang sama, radiasi dapat merusak mukosa secara langsung, mempersempit atau menyumbat pembuluh darah mikrosirkulasi lokal, mengakibatkan hiperemia mukosa dan edema, menyebabkan iskemia dan hipoksia dan menyebabkan reaksi mukosa mulut terhadap radioterapi (Xu *et al.*, 2014). Kanker nasofaring, terlepas dari radiosensitivitasnya, telah lama menjadi tantangan bagi ahli onkologi radiasi karena kedekatannya dengan struktur normal kritis, seperti batang otak, sumsum

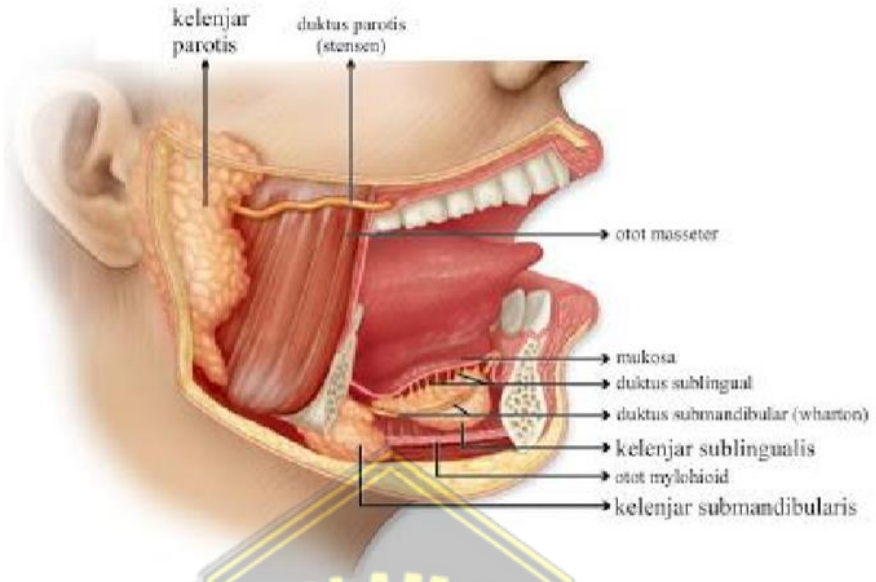
tulang belakang, dan kelenjar parotis, yang membatasi tingkat dosis yang diperlukan untuk pengendalian tumor lokal. Terapi radiasi modulasi intensitas (*Intensity-modulated radiation therapy* / IMRT) adalah kemajuan teknis penting yang menawarkan kemungkinan penyesuaian dosis yang tinggi di sekitar target, sekaligus meminimalisir kerusakan jaringan normal di sekitarnya. Penelitian mono-institusional dan studi multi-institusional baru-baru ini telah melaporkan hasil yang sangat menjanjikan dalam pengobatan kanker nasofaring dengan IMRT dilihat dari identifikasi dan cakupan target (Marucci *et al.*, 2010). Saat ini, pilihan pertama untuk mengobati karsinoma nasofaring biasanya adalah teknologi IMRT. Sebuah studi klinis fase III terkontrol secara acak mengkonfirmasi efek perlindungan IMRT pada fungsi kelenjar parotis; namun, kerusakan radiasi pada kelenjar sulit untuk dihindari. SIB-IMRT meningkatkan kemanjuran radioterapi; pada saat yang sama, peningkatan dosis radioterapi memperburuk reaksi mukosa mulut. Tindakan mendesak diperlukan untuk mengurangi reaksi mukosa akut pada pasien dan meningkatkan toleransi pasien terhadap radioterapi. Laju aliran kelenjar saliva berhubungan dengan dosis radiasi rata-rata: dosis toleransi kelenjar saliva minor adalah 10–15 Gy. Kelenjar saliva mayor yang menerima dosis rata-rata 20-40 Gy akan mengalami penurunan fungsi

secara bertahap, dan jika dosis rata-rata melebihi 40 Gy akan menyebabkan fungsi kelenjar saliva mayor akan menurun drastis (kehilangan > 75%) (Xu *et al.*, 2014).

3.2.2 Kelenjar Saliva pasien Kanker Nasofaring

3.2.2.1 Kelenjar Saliva

Kelenjar saliva adalah kelenjar yang memproduksi saliva. Kelenjar saliva terdiri dari kelenjar mayor dan minor (Tamin and Yassi, 2011). Kelenjar mayor ialah sepasang kelenjar parotid yang berada di seberang molar pertama maxilla, dan kelenjar submandibula dan sublingual yang terletak di dasar mulut. Kelenjar minor yang menghasilkan saliva terdapat di bibir bagian bawah, lidah, palatum, pipi, dan faring. Pembagian kelenjar mayor dan minor berdasarkan ukuran dari kelenjar. Kelenjar mayor menghasilkan lebih banyak saliva daripada kelenjar minor, akan tetapi kualitas dari kelenjar tersebut bermacam-macam (Vining, 2017).



Gambar 3. 2 Kelenjar Saliva Mayor (Waschke, 2013)

Kelenjar parotid merupakan kelenjar saliva terbesar, dengan berat antara 15-30gram dan berukuran sekitar 6x3 cm. Kelenjar parotid memiliki lobus superfisial yang luas dan lobus profundal dengan N. Facialis yang terltak di antara kedua lobus. 20% kelenjar parotid memiliki kelenjar aksesori dan duktus yang terletak di sekitar M. Masseter. Kelenjar parotid memiliki sekitar 3-24 limfa yang terletak di lateral N. Facialis di lobus superfisial (Waschke, 2013) Volume saliva yang dihasilkan kelenjar parotid 2,5 kali lebih besar dari kelenjar mandibula dan 6 kali lebih besar dari kelenjar sublingualis. Saliva dari kelenjar parotid dialirkan ke rongga mulut melalui duktus ekskretori yang berukuran 5-7 cm. Duktus ini disebut dengan *Stensen's ducts* yang bermuara di

daerah setinggi molar dua atas (Arpa, 2017). Pada *stimulated saliva*, kelenjar parotid menghasilkan saliva paling dominan dibandingkan dengan kelenjar saliva mayor lainnya. Pada kondisi istirahat laju aliran saliva kelenjar parotid dan kelenjar submandibula sama, sedangkan pada saat mastikasi laju aliran saliva dari kelenjar parotid lebih besar dibandingkan dengan kelenjar submandibula (Kasuma, 2015).

Kelenjar submandibula terletak di segitiga submandibular yang terdiri dari bagian anterior dan posterior M. Digastricus dan tepi inferior mandibula. Beratnya sekitar 50% berat kelenjar parotid dengan berat antara 7-15 gram (Helmerhorst, 2012). Duktus kelenjar submandibula bermuara di duktus Warthon yang terletak di dasar mulut pada kedua sisi frenulum lingualis. Duktus Warthon berukuran 4-5 cm dan melintasi bagian superior N. Lipoglosus dan bagian inferior menuju N. lingualis. Kelenjar submandibula memiliki 3-6 nodus limfa yang ditemukan di segitiga submandibular. Refleks saraf seperti stimulus mekanik karena pergerakan lidah dan bibir berperan dalam sel sekretori tertuma pada kelenjar submandibular (Amano *et al.*, 2012).

Kelenjar sublingualis merupakan kelenjar yang berukuran paling kecil dengan berat antara 2-4 gram. Kelenjar sublingualis terletak di dalam dasar mulut antara mandibula dan M. Genioglosus. Kelenjar ini tidak memiliki kapsula fasial yang jelas dan duktus yang dominan, namun terdapat 10 duktus kecil yang disebut *ducts of Rivinus* (Kasuma, 2015). Umumnya beberapa duktus di bagian anterior menyatu membentuk satu duktus yang lebih besar yaitu duktus Bartholin yang mensekresikan saliva melalui duktus Warthon. Duktus Bartholin dan duktus Warthon menyatu di sublingual *caruncula* pada kedua sisi frenulum lingualis (Vining, 2017).

Kelenjar saliva minor terletak di submukosal di bawah lamina propria. Kelenjar ini tersebar di bukal, palatal, labial, palatoglossal, dan lingual. Kelenjar bukal dan labial mengandung komponen *serous* dan *mucous*, kelenjar palatal dan palatoglossal mengandung komponen *mucous*, kelenjar lingual terdiri dari komponen *mucous* kecuali Von-Ebner yang terdiri dari komponen *serous* (Helmerhorst, 2012). Kelenjar saliva minor memiliki 600-1000 kelenjar berukuran 1-5 mm pada rongga mulut sampai orofaring (Kasuma, 2015).

Rata-rata produksi saliva dalam sehari bervariasi, pada individu sehat berjumlah sekitar 1-1,5 L (Humphrey,

2001). Jumlah saliva yang diproduksi tiap kelenjar pada kondisi tidak terstimulasi ialah 20% dari kelenjar parotid, 65% dari kelenjar submandibular, 7%-8% dari kelenjar sublingual, dan kurang dai 10% berasal dari kelenjar minor. Pada kondisi terstimulasi, persentase tiap kelenjar berubah. Kelenjar parotid menghasilkan saliva paling banyak dari pada kelenjar lainnya, sekitar 50% dari total saliva yang dihasilkan (Indriana, 2010).

3.2.2.2 Saliva Flow Rate

Laju aliran saliva adalah parameter yang menentukan normal, tinggi, rendah, atau sangat rendahnya aliran saliva yang dinyatakan dalam satuan ml/menit. Pada individu dewasa yang sehat, laju aliran normal *stimulated saliva* adalah 1,5-2 ml/menit, laju aliran lambat sebesar 0,7-1 ml/menit, dan hiposalivasi apabila laju aliran saliva kurang dari 0,7-1 ml/menit. Laju aliran normal *unstimulated saliva* sebesar 0,3-0,4 ml/menit. laju aliran yang rendah sebesar 0,1-0,25 ml/menit, dan hiposalivasi jika aliran saliva kurang dari 0,1 ml/menit (Helmerhorst, 2012).

Faktor-faktor yang mempengaruhi sekresi *unstimulated saliva* adalah hidrasi, posisi tubuh, stimulasi sebelumnya, ritme sirkardian dan sirkanual, obat-obatan, usia, berat badan, stimulasi fungsional. Faktor-faktor yang mempengaruhi sekresi *stimulated saliva* ialah sumber stimulus, merokok, ukuran

kelenjar, refleks muntah, refleks penciuman (olfaction), stimulasi unilateral dan makanan (Kasuma, 2015).

a. Hidrasi

Pada saat tubuh kekurangan air, aliran saliva berkurang karena kelenjar saliva mengurangi sekresi untuk mempertahankan jumlah air dalam tubuh sehingga menyebabkan laju aliran saliva meningkat ketika keadaan tubuh hiperhidrasi (Larasati, 2016).

b. Posisi tubuh

Pada saat berdiri laju aliran saliva tinggi, sedangkan saat berbaring laju aliran saliva menjadi lebih rendah daripada saat duduk (Fithrony, 2012).

c. Pencahayaan

Dalam kondisi gelap aliran saliva berkurang 30-40% namun tidak berpengaruh pada orang buta, karena orang buta atau yang ditutup matanya beradaptasi terhadap kurangnya cahaya yang diterima oleh mata (Kasuma, 2015).

d. Jenis kelamin

Perempuan memiliki kelenjar saliva yang lebih kecil daripada laki-laki sehingga aliran saliva wanita lebih rendah daripada laki-laki (Larasati, 2016).

e. Usia

Secara histologi, semakin bertambahnya usia maka sel-sel parenkim pada glandula salivarius akan terus tergantikan oleh sel-sel adiposa dan jaringan fibrovaskular dan volume dari acini berkurang (Kasuma, 2015).

f. Merokok

Pada individu yang merokok terdapat peningkatan temporer laju aliran *unstimulated saliva*. Efek iritasi tembakau menyebabkan meningkatnya ekskresi kelenjar dan nikotin menyebabkan perubahan fungsi dan morfologi kelenjar saliva (Larasati, 2016).

g. Siklus sirkardian dan sirkanual

Aliran saliva akan mencapai puncak pada tengah hari dan menurun saat tidur, oleh karena itu komposisi saliva tidak konstan dan berhubungan dengan siklus sirkardian. Irama sirkanual juga mempengaruhi sekresi saliva. Pada saat musim panas, volume saliva kelenjar parotid lebih rendah, sedangkan pada saat musim dingin, volume saliva mencapai puncaknya (Kasuma, 2015).

h. Latihan fisik

Latihan fisik juga dapat mempengaruhi sekresi saliva dan menginduksi perubahan pada berbagai macam komponen saliva seperti imunoglobulin, hormon, laktat, protein, dan elektrolit (Kasuma, 2015).

i. Medikasi

Obat-obatan yang bersifat *anticholinergic* seperti antidepresan, anxiolitik, antipsikotik, antihistamin, dan antihipertensi menyebabkan berkurangnya laju aliran saliva dan mengubah komposisinya. ~~Selain itu,~~ obat-obatan antikonvulsan, agen sitotoksik, dan *muscle relaxant* dapat menyebabkan hipofungsi kelenjar saliva sehingga mempengaruhi laju aliran saliva (Fithrony, 2012).

j. Karakteristik kelenjar saliva

Aliran *stimulated saliva* berhubungan dengan karakteristik kelenjar saliva salah satunya adalah ukuran dari kelenjar saliva, semakin besar kelenjar saliva maka semakin cepat aliran saliva yang distimulasi (Kasuma, 2015).

k. Konsumsi alkohol

Mengkonsumsi ethanol dengan dosis tinggi dapat langsung menurunkan sekresi aliran *stimulated saliva* secara signifikan. Konsumsi alkohol yang berkepanjangan akan menyebabkan disfungsi kelenjar saliva dan pembesaran kelenjar parotid bilateral sehingga dapat mempengaruhi laju aliran saliva (Kasuma, 2015).

l. Paparan radiasi

Paparan dari radiasi dapat menyebabkan disfungsi kelenjar saliva. Paparan radiasi yang dilakukan pada area kepala dan

leher mengakibatkan perubahan fungsi maupun kerusakan pada kelenjar saliva. Kelenjar saliva yang mengalami kerusakan paling besar adalah kelenjar parotis, karena kelenjar parotis memiliki sel asinar *serous* yang *sensitive* terhadap radiasi (Fithrony, 2012).

3.2.2.3 Metode Deteksi Volume Kelenjar Saliva dan Saliva Flow Rate

a. Draining method

Saliva dibiarkan menetes melalui bibir bawah ke dalam *sampling tube*. Subjek diinstrusikan untuk meludah pada akhir durasi pengumpulan. Pada *tube* dapat dilengapi dengan *funnel* agar memudahkan pengambilan saliva. jumlah saliva ditentukan dengan *weighing*/menimbang (dengan asumsi gravitasi 1 g/cm3) atau dengan membaca skala pada *test tube*.

b. Spitting method

Saliva dibiarkan terkumpul di dasar mulut, kemudian subjek meludah ke *preweighed/graduated test tube* setiap 60 detik atau pada saat pasien akan menelan saliva yang terkumpul di mulut. Tabung dapat dilengkapi dengan *funnel*. Jumlah saliva yang dikumpulkan ditentukan dengan *weighing* atau membaca skala pada tabung. *Spitting method* tidak disarankan untuk mengumpulkan *unstimulated saliva*, karena spitting dapat menstimulasi sekresi saliva. *Spitting*

method lebih baik digunakan untuk mengumpulkan *stimulated saliva*.

c. *Suction method*

Saliva diaspirasi dari dasar mulut ke *graduated test tube* melalui *saliva ejector*/aspirator.

d. *Absorbent method*

Saliva yang dikumpulkan/diabsorbsi dengan *preweight swab, cotton roll,* atau kassa yang ditempatkan di mulut pada orifis kelenjar saliva mayor, kemudian ditimbang kembali pada akhir durasi (Kasuma, 2015).

Model Lyman – Burman – Kutcher, sudah digunakan oleh Eisbruch dan Roesink untuk memprediksi toksisitas kelenjar saliva, digunakan untuk memprediksi kejadian xerostomia. Perhitungan radiobiologi menunjukkan bahwa skor RTOG dapat dimodelkan secara memadai sebagai fungsi faktor dosis-volume parotis, meskipun tidak ada pemodelan eksplisit kontribusi dari kelenjar submandibular. Kontribusi kelenjar submandibular ke aliran kelenjar saliva yang terstimulasi adalah nol, hanya kelenjar saliva parotis yang menghasilkan sebagian besar (60% hingga 65%) dari hasil oral saliva dan merupakan penentu utama pemulihan postradiasi fluks saliva. dikonfirmasi oleh analisis lebih lanjut dengan jumlah pasien yang lebih besar dan masa tindak lanjut yang

lebih lama, NTCP dapat menjadi alat yang berguna dalam evaluasi rencana tandingan (Marucci *et al.*, 2010).

3.2.3 Efek Radioterapi terhadap Kelenjar Saliva pada Pasien Kanker Nasofaring

3.2.3.1 Efek Radioterapi terhadap Sel

Radioterapi menyebabkan kerusakan molekul DNA pada jaringan target. Mekanisme kerusakan DNA karena radiasi pengion dibagi menjadi 2 yakni ionisasi langsung yang disebabkan kerusakan struktur atom jaringan yang dirusak oleh energi kinetik partikel melalui radiasi partikel. dan ionisasi tidak langsung yang disebabkan karena pembentukan sekunder yang terbentuk karena radiasi elektromagnetik, radikal bebas ini yang akan berinteraksi dengan DNA dan akan menyebabkan kerusakan berupa *single strand breaks* (SSB) dan *double strand breaks* (DSB) (Fitriatuzzakiyyah, 2017). Efek langsung ialah terjadinya proses ionisasi atom-atom pada DNA kromosom di dalam nukleus sel akibat paparan dari sinar radiasi sehingga menyebabkan pemutusan rantai *double helix* secara parsial (*single strain break*) atau total (*double strain breaks*). Efek tidak langsung dari penyinaran radiasi adalah pemutusan rantai *double helix* DNA melalui peningkatan aktivitas pemutusan rantai DNA oleh radikal-radikal bebas (HO,OH-,H3O+) yang dihasilkan

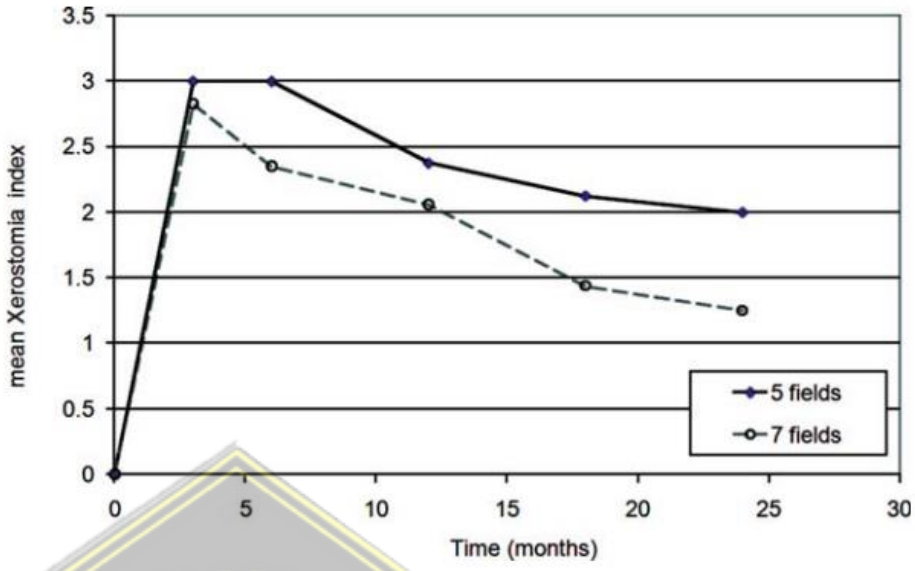
oleh cairan sitoplasma saat terpapar sinar radiasi (Dwikuntari, 2017). Kerusakan inti sel DNA akan memicu aktivasi mekanisme sel tertentu, seperti aktivasi p53. Aktivasi p53 terjadi sebagai respon dari berbagai stres pada sel, sehingga p53 dapat dikatakan sebagai penjaga genom serta dapat menghambat ekspansi dan proliferasi berbagai sel yang rusak. Pentingnya peran p53 sebagai supresi tumor dipertegas dengan fakta terjadinya gangguan fungsi p53 akibat mutasi spontan, pengurangan jumlah gen serta peningkatan kerentanan terhadap terjadinya tumor. Mutasi yang diinduksi oleh sinar UV berdampak pada gen p53 (p53) sebagai salah satu tumor-suppressor gene yang terletak pada kromosom lengan 17p13. diperkirakan berperan penting pada kasus KSB (Setyawan and Djakaria, 2014).

Salah satu efek dari radioterapi adalah xerostomia, xerostomia merupakan kondisi dimana mulut terasa kering disebabkan oleh disfungsi sekresi kelenjar saliva dan dapat mengganggu fungsi berbicara maupun mastikasi. Pada penelitian yang dilakukan oleh Surjadi *et al* sekitar 87,6% pasien kanker kepala dan leher yang menjalani radioterapi menunjukkan penurunan laju salivasi. Pasien mulai mengeluhkan kondisi mulutnya yang kering (xerostomia) dalam waktu 1 hingga 2 minggu setelah dilakukan

radioterapi, Biasanya kondisi ini akan membaik kurang lebih 2 tahun setelah dilakukan radioterapi (Fitriatuzzakiyyah, 2017).

3.2.3.2 Efek Radioterapi terhadap Kelenjar Saliva dan Saliva Flow Rate

Publikasi terbaru telah menganalisis dampak penyelamatan kelenjar parotis terhadap kualitas hidup pada pasien kanker nasofaring stadium awal (T1-2, N0-1). Pemberian dosis rata-rata 38 sampai 42 Gy menyebabkan mayoritas pasien yang pulih setidaknya 25% pada 12 bulan setelah radioterapi jika dibandingkan dengan aliran saliva sebelum terapi, dan kualitas hidup secara signifikan lebih baik pada pasien yang diobati dengan IMRT dibandingkan 2DCRT. Dosis yang lebih rendah ke kelenjar parotid menghasilkan perbaikan yang lebih jelas dan lebih cepat seperti yang ditunjukkan oleh Indeks Xerostomia pada Gambar 3. 3. Dalam penelitian ini, menggunakan aliran saliva untuk menilai efek yang terjadi, kelompok II memiliki pemulihan rata-rata 57% dari *Stimulated Salivary Flow* sebelum terapi pada 24 bulan, sedangkan kelompok I hanya memiliki pemulihan 40% (Gambar 3.4) (Marucci *et al.*, 2010).

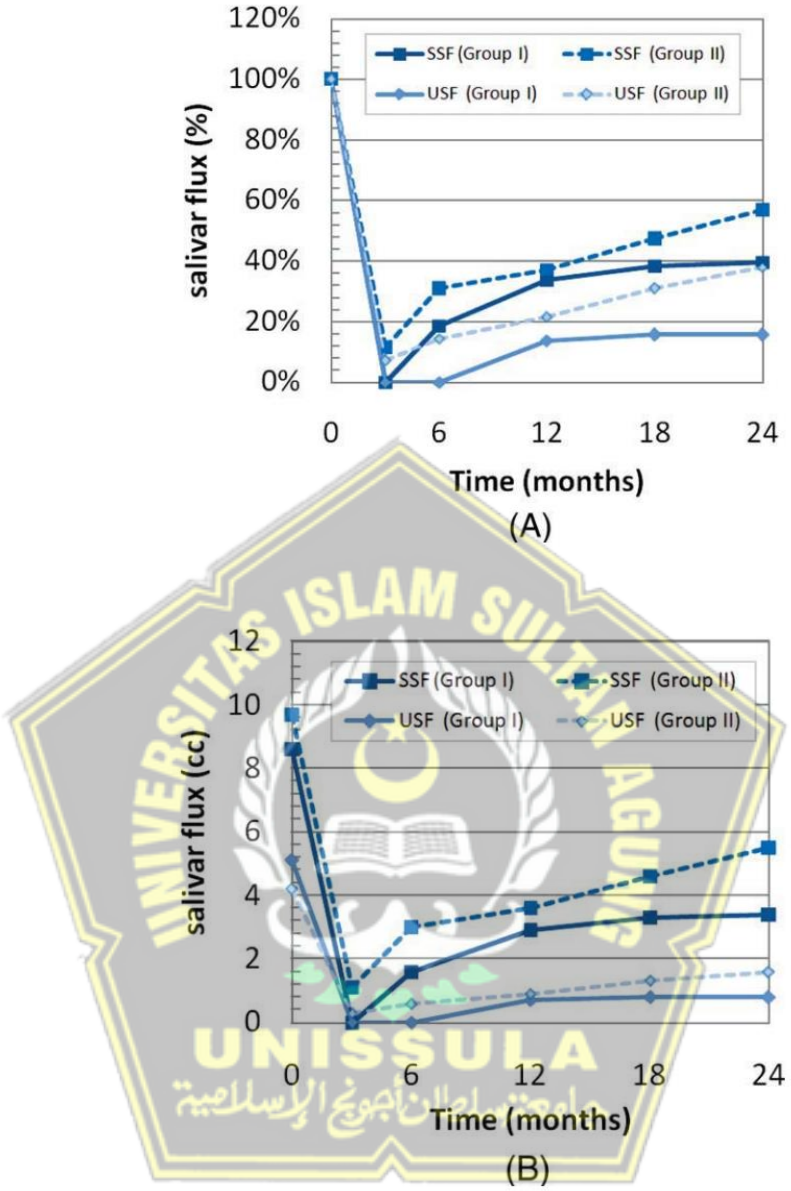


Gambar 3. 3 Indeks Xerostomia (XI) untuk pasien yang dirawat dengan teknik 5-bidang (kelompok I) dan 7-bidang (kelompok II), mewakili nilai rata-rata pada titik waktu yang berbeda (Marucci *et al*., 2010)

Dosis rata-rata 20-40 Gy yang diterima kelenjar saliva mayor akan menyebabkan fungsinya menurun secara bertahap. Sedangkan dosis rata-rata lebih dari 40 Gy yang diterima akan menyebabkan penurunan fungsi kelenjar mayor secara drastis (kehilangan sekitar 75% fungsinya). Penyebab utama menurunnya sekresi kelenjar saliva adalah karena apoptosis sel kelenjar, sehingga menyebabkan penurunan jumlah sel dan penurunan fungsi sekresi. Sekresi kelenjar saliva normal sekitar 0,5 mL/menit. Kelenjar parotis mensekresikan saliva sekitar 60-65% dan kelenjar submandibular mensekresikan saliva sekitar 20-30%, sehingga apabila kelanjar saliva mengalami kerusakan akan mengakibatkan menurunnya volume saliva yang menyebabkan pasien mengalami

xerostomia. Penelitian yang dilakukan oleh Xu., *et al* (2014) menunjukkan bahwa pH oral dan *saliva flow rate* pada pasien yang menjalani radioterapi mengalami penurunan ketika dosis radiasi meningkat (Xu *et al.*, 2014). Kelenjar parotid berubah *hyperechoic* (sebelum radioterapi) menjadi isoechoic atau *hypoechoic* (setelah radioterapi). Indeks resistif & indeks pulsasi menurun pada 6 bulan setelah radioterapi dibandingkan dengan sebelum radioterapi, tetapi mulai meningkat kembali dalam kurun waktu 12 bulan setelah radioterapi (Wu *et al.*, 2020).

Saliva flow rate pasien kanker nasofaring yang telah menerima perawatan IMRT berkorelasi terbalik dengan dosis rata-rata kelenjar parotid. Salah satu manfaat yang dapat ditemukan pada pasien yang menjalani IMRT adalah penurunan xerostomia sehingga terdapat peningkatan kualitas hidup terkait kesehatan mulut. Pengobatan dengan IMRT dan radioterapi saja tampaknya cukup untuk mengobati penyakit kanker nasofaring stadium awal dan dengan volume yang rendah. Saat ini, bukti tingkat tertinggi yang mendukung manfaat IMRT menjaga kelenjar parotis untuk kanker kepala dan leher dalam hal pengurangan komplikasi dan peningkatan kualitas hidup telah dikumpulkan dari studi klinis prospektif longitudinal dan kontrol kasus yang sesuai (Pow *et al.*, 2006).



Gambar 3. 4 Pemulihan aliran saliva rata-rata yang tidak distimulasi (USF) dan aliran saliva terstimulasi (SSF) dengan waktu setelah radioterapi, 4 (A) dalam persentase, 4 (B) dalam nilai absolut (C) (Marucci *et al*., 2010)

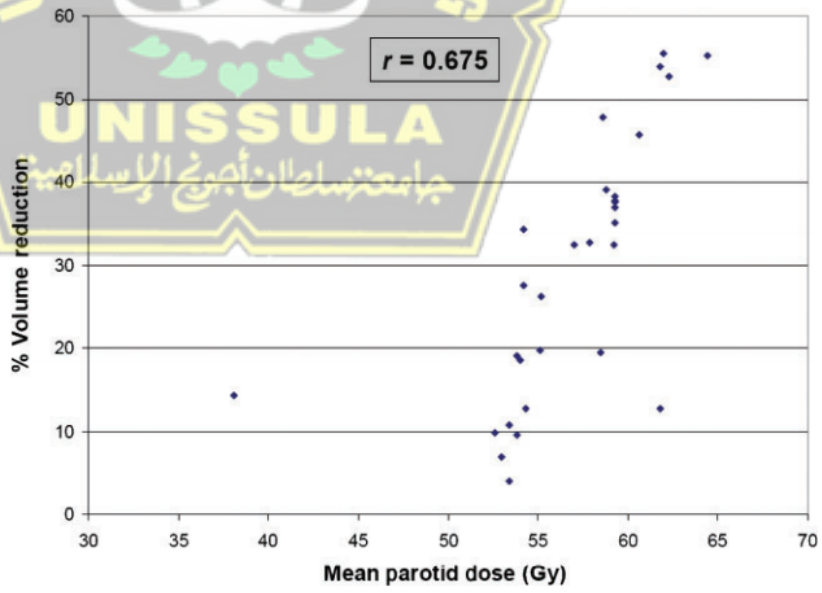
Volume kelenjar parotid pada pasien kanker nasofaring pasca-radioterapi lebih kecil jika dibandingkan dengan ukuran kelenjar saliva pra-radioterapi. Berdasarkan penelitian Wu., *et al* (2011) menunjukkan bahwa persentase

perbedaan volume dari 36 kelenjar parotis pasien kanker nasofaring sangat signifikan, dengan memperhitungkan sisi kiri dan kanan (t-test berpasangan, p = 0,001). Rata-rata pengurangan volume kelenjar saliva 12.2 ± 7.2 cm^3, yaitu sekitar 35% dari volume kelenjar sebelum radioterapi. Derajat pengurangan volume menunjukkan korelasi yang tinggi dengan total dosis rata-rata yang diterima oleh kelenjar parotis (Gambar 3.5). Perubahan ukuran volume kelenjar saliva disebabkan atrofi sel asinar dan parenkim yang mengakibatkan menurunnya sekresi saliva (Wu, Ying and Kwong, 2011).

Berdasarkan penelitian oleh Wu., *et al* (2020), semua pasien menyelesaikan pengobatan IMRT dengan lancar. Dosis yang sama diterima oleh kelenjar parotis dan kelenjar submandibular, dengan dosis maksimum di atas 70 Gy dan dosis rata-rata sekitar 37 Gy. Persentase volume kelenjar parotis menunjukkan penurunan yang signifikan dari pra-radioterapi hingga 6 bulan pasca-radioterapi (p = 0,037) dan menjadi cukup stabil dalam interval waktu berikutnya (p> 0,05 antara dua interval berturut-turut). Pengurangan volume rata-rata keseluruhan adalah 2,9 ± 4,0 cm^3, yang merupakan 25,8% dari volume kelenjar parotis pra-RT. Kelenjar submandibular mengikuti kecenderungan yang sama dengan kelenjar parotid. Volumenya menunjukkan penurunan yang signifikan pada 6

bulan setelah radioterapi (p = 0,031) dan tidak menunjukkan perbedaan yang signifikan dalam interval waktu (p> 0,05). Pengurangan volume rata-rata keseluruhan adalah 1,7 ± 1,0 cm^3, yang merupakan 21,8% dari volume kelenjar submandibular pra-radioterapi (Wu *et al.*, 2020).

Kelenjar parotid pasca-RT menunjukkan hilangnya parenkim kelenjar dan atrofi sel asinar dan pada gambar CT akan menunjukkan penyusutan volume kelenjar parotid. Kelenjar parotid pasca-RT menunjukkan penurunan volume rata-rata 35% dibandingkan dengan kelenjar normal, yang diukur dari gambar CT dengan perbedaan yang sangat signifikan (p, 0,001) (Wu, Ying and Kwong, 2011).



Gambar 3. 5 Plot sebar dari persentase volume pasca radioterapi penurunan kelenjar parotis (d V) terhadap total dosis kelenjar parotis rata-rata (Wu, Ying and Kwong, 2011).

Besarnya penyusutan dikaitkan dengan total dosis rata-rata yang dikirim ke kelenjar parotis. Temuan ini sejalan dengan penelitian oleh Wang., et al dan Teshima., et al, yang melaporkan bahwa pengurangan volume kelenjar berkorelasi secara signifikan dengan dosis rata-rata. Hal ini mengungkapkan fakta bahwa dosis radiasi yang lebih tinggi pada kelenjar parotis akan menyebabkan kehilangan dan atrofi sel asinar yang lebih besar, yang selanjutnya menyebabkan penyusutan pada kelenjar. Penyebab utama yang diyakini sebagai penyebab gangguan sekresi kelenjar yang membuat pasien merasakan xerostomia adalah atrofi sel asinar (Wu, Ying and Kwong, 2011).

BAB IV
KESIMPULAN DAN REKOMENDASI

4.1 Kesimpulan

Kelenjar saliva merupakan salah satu organ tubuh yang terdampak akibat radioterapi yang dilakukan di area kepala dan leher, khususnya pada pasien kanker nasofaring. Kerusakan pada kelenjar saliva mengakibatkan berkurangnya volume saliva yang dihasilkan sehingga menyebabkan pasien mengalami xerostomia. Kerusakan yang terjadi diakibatkan karena rusaknya DNA dari sel asinar di kelenjar saliva, sehingga menyebabkan penyusutan volume kelenjar saliva. Kelenjar parotis dan kelenjar submandibular merupakan kelenjar yang paling terdampak efek radiasi yang diakibatkan radioterapi. Pasien kanker nasofaring yang menjalani perawatan radioterapi mengalami penurunan saliva flow rate 1 bulan hingga 1 tahun setelah perawatan radioterapi. Penurunan *saliva flow rate* (hiposalivasi) ini disebabkan karena kerusakan pada DNA dari sel asinar di kelenjar saliva yang berupa *double helix* secara parsial (*single strain break*) atau total (*double strain breaks*).

4.2 Rekomendasi

Belum banyak penelitian yang meneliti korelasi antara perawatan radiasi terhadap kelenjar saliva pasien kanker nasofaring, sehingga perlu dilakukan penelitian lebih lanjut untuk hal tersebut.

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ORIGINAL ARTICLE

Effects of radiotherapy on salivary gland function in patients with head and neck cancers

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Abstract *Background/purpose*: We explored changes in salivary gland function of head-and-neck cancer patients after radiotherapy, including pH of saliva, stimulated salivary flow rate, and saliva buffering capacity. The pH of saliva included that of parotid gland, submaxillary gland, and total resting saliva. We also investigated whether the acidity of dental plaque lowered pH of saliva.

Materials and methods: From a total of 62 patients, 11 had repeated measurements taken before and every month after radiotherapy. The remaining 51 patients had a single measurement taken after radiotherapy. Seven normal patients served as the control group.

Results: In the repeated measurement group, all examinations decreased dramatically in the 1st month after radiotherapy ($P < 0.0001$), and recovered from the 3rd month to the 6th month, but the flow rate could not return to pretreatment level. In the single measurement group, unilabiate linear regression analysis showed that the time-period after radiotherapy was a significant predictor influencing the pH of the submaxillary gland and total resting saliva. Pearson correlation coefficient analysis showed that the pH of dental plaque had a positive linear correlation with that of saliva. Concerning the influence of time-period, within 1 year after radiotherapy, all examinations were dropped. After 1 year the pH of resting saliva and plaque began to increase over time. The stimulated flow rate, pH of stimulated saliva, and buffering capacity, dropped < 1 year after radiotherapy group, increased 1–5 years after radiotherapy group, but dropped again > 5 years after radiotherapy group.

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

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Quality of life after radiotherapy

Multivariate analysis of quality of life outcome for nasopharyngeal carcinoma patients after treatment

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ABSTRACT

Purpose: The study analyzed the prognostic factors of quality of life (QoL) for patients with nasopharyngeal carcinoma (NPC) after treatment, with focusing on the therapeutic benefits of the technological advances in radiotherapy (RT).

Materials and methods: A cross-sectional investigation was conducted to assess the QoL of 356 NPC patients with cancer-free survival of more than 2 years. Among them, 106 patients were treated by two-dimensional RT (2DRT), 108 by 2DRT plus three-dimensional conformal RT (3DCRT) boost, 58 by 3DCRT alone, and 84 by intensity-modulated RT (IMRT). The QoL was assessed by the EORTC QLQ-C30 questionnaire and QLQ-H&N35 module. The clinical difference of QoL scores between groups was calculated using Cohen's D coefficient.

Results: We found NPC survivors who had a higher education level or annual family income and who had received more advanced RT treatments had better QoL outcomes. Compared with 2DRT, the impact of 3DCRT was small on most scales and moderate (Cohen's D: 0.53–0.67) on emotional functioning, pain, and mouth opening; the impact of IMRT was moderate on nine scales and large (Cohen's D: 0.80–0.88) on swallowing, social eating, teeth, and mouth opening.

Conclusions: In addition to socioeconomic levels, advances in RT technique played a significant role in improving QoL of NPC patients.

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Conventionally, the endpoints of medical care for cancer patients usually focused on the survival rate, local control rate, or complication rate. These endpoints were typically assessed from the physician's points of view and lacked knowledge of patients' mental or emotional well being. Quality of life (QoL) refers to the perception of the effects of disease and its impact on the patient's daily functioning; QoL is a multi-dimensional issue, incorporating physical, psychological, social, and emotional domains, and it must be self-reported according to the patient's own experiences [1]. In perhaps no other group of cancer patients is QoL as important as in head and neck cancer (HNC) patients. This is because they may have obvious debilitating problems with swallowing, speech, and hearing, as well as psychological effects associated with loss of function and change in body image [2].

Nasopharyngeal carcinoma (NPC) is a prevalent disease in Taiwan. NPC is unique among forms of HNC. It affects a younger group of patients, usually with no history of smoking or alcohol abuse and with a higher socioeconomic status at the time of presentation. With modern radiotherapy (RT) technology alone or in combination with chemotherapy, many NPC patients can be cured, even at advanced stages of the disease [3,4]. Thus, the assessment of QoL for NPC survivors has become an important issue for the following reasons. First, knowing differences in QoL between NPC survivors treated by different methods might be an indicator of the success of a novel strategy. Second, identifying specific functional impairments after NPC treatment may help clinicians target possible late effects that need special attention during patient follow-up. Third, information on the variables correlated with QoL in NPC survivors may help healthcare planners identify which patients need more services, such as physical rehabilitation, social support, or psychological consultation.

Several well-validated QoL instruments are now available for use in HNC patients. In the current study, we used the European Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), version 3.0, together with the Head and Neck module (QLQ-H&N35) [5,6]. The questionnaires are comprehensive, and their validity, internal consistency, and reliability in patients using different languages, including the Taiwan Chinese version, have been tested with excellent results [7]. The study analyzed the prognostic factors of QoL for NPC patients with cancer-free survival after treatment, with focusing on the therapeutic benefits of the technological advances in RT at our institute at different time periods.

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Original Article

Clinical and dosimetric predictors of physician and patient reported xerostomia following intensity modulated radiotherapy for nasopharyngeal cancer – A prospective cohort analysis

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ABSTRACT

Background and purpose: To compare physician and patient reported xerostomia and correlate xerostomia with dosimetric and clinical parameters for nasopharyngeal cancer (NPC) patients treated with intensity modulated radiotherapy (IMRT) and chemotherapy.

Patients and methods: We analyzed the data of 172 patients with locally advanced NPC. Xerostomia was evaluated via physician-rated xerostomia based on RTOG morbidity score (E1), patient-rated dry mouth (E2) and patient-rated sticky saliva (E3) based on EORTC QLQ-HN35 questionnaire. Primary endpoint was the presence of moderate to severe xerostomia at 2-year after completion of IMRT.

Results: The levels of physician reported xerostomia (E1) were consistently lower than patient reported dry mouth (E2) over time. The incidence of patients with xerostomia at 3-month post RT was 58% based on E1, 70% based on E2, and 51% based on E3. The corresponding incidence rates at 2-year post RT was 26% (E1), 36% (E2) and 21% (E3). The incidence of patients with xerostomia at 1-year post RT was close to that at 2-year post RT for all the 3 endpoints. The average Dmean of parotid glands was 41.5 Gy (range: 31.0 Gy–65.9 Gy, median: 40.7 Gy). No dosimetric parameters were significantly associated with xerostomia.

Conclusion: Significant proportion of patients still experienced long term xerostomia with IMRT. Dose-effect relationships between xerostomia and the parotid glands were not observed in this study.

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In the last two decades, advances in combining systemic therapy and radiation technology such as intensity modulated radiotherapy (IMRT) have allowed for improved survival with decreased rates of toxicities in nasopharyngeal cancer (NPC) [1–7]. Several randomized controlled trials have demonstrated the superiority of IMRT in parotid salivary gland sparing and in reducing xerostomia compared to conventional techniques such as two dimensional radiotherapy and 3DCRT (three dimensional conformal radiotherapy) [8–12]. However, even with modern IMRT planning, xerostomia is still one of the most common and disabling radiation-induced toxicities. In fact, the incidence of late and clinically significant xerostomia is reported in up to 30% of patients after treatment of IMRT [13,15–18].

Long term xerostomia can adversely affect dentition, speech, swallowing and mastication. Most patients with xerostomia experience difficulty eating their usual diet. Chewing and swallowing of food can become uncomfortable or even painful with most patients needing frequent sips of water while they eat, and food particles get stuck in their mouth or throat. Long term xerostomia is frequently associated with dental problems, oral discomfort, dysphagia for solid food and poor quality of life (QOL) [19–21]. Research on xerostomia and how it affects QOL has been the subject of many studies. Deterioration in physical, emotional and social functioning and global QOL was common among patients with radiation-induced xerostomia [20,22–24].

Because of the significant impact xerostomia can have on the QOL of NPC survivors, improvements in treatment delivery or technique are desirable when possible. As such, it is crucial to identify predictors of xerostomia in order to refine planning techniques and intensify rehabilitation efforts for patients at greatest risks of xerostomia. In this study, we prospectively investigated the relation of physician and patient rated xerostomia with the 3-dimensional dose distribution in the parotid and submandibular glands and with clinical and treatment related factors.

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Review

Salivary gland transfer to prevent radiation-induced xerostomia: A systematic review and meta-analysis

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SUMMARY

Salivary gland transfer (SGT) has the potential to prevent radiation-induced xerostomia. We attempt to analyze the efficacy of SGT in prevention of xerostomia and maintenance of salivary flow rates after radiation treatment (XRT). Systematic review and meta-analysis. Primary endpoint was efficacy of SGT in prevention of radiation-induced xerostomia. Secondary endpoint was change from baseline of *unstimulated* and *stimulated* salivary flow rates after XRT. Seven articles, accruing data from 12 institutions, met inclusion criteria. In a total of 177 patients at mean follow-up of 22.7 months, SGT prevented radiation-induced xerostomia in 82.7% (95% CI, 76.6–87.7%) of patients. Twelve months after XRT, *unstimulated* and *stimulated* salivary flow rates rose to 88% and 76% of baseline values, respectively. In comparison to control subjects twelve months after XRT, SGT subjects' *unstimulated* (75% vs. 11%) and *stimulated* (86% vs. 8%) salivary flow rates were drastically higher in SGT patients. Salivary gland transfer appears to be highly effective in preventing the incidence of xerostomia in patients receiving definitive head and neck radiation therapy.

Introduction

Head and neck cancer accounts for nearly 3% of all diagnosed malignancies, making it the sixth most commonly diagnosed cancer worldwide [1–3]. While early stage disease can be treated with either surgery or radiation, definitive treatment for advanced stage head and neck cancer typically mandates multi-modality therapy to include either concomitant chemotherapy and radiation, or surgery with adjuvant radiation [4,5]. It is generally accepted that radiation therapy in head and neck cancer patients causes salivary gland destruction, inevitably leading to radiation-induced xerostomia [6–14]. The exact incidence of xerostomia is unclear, as grading definition and radiation fields may vary [10,15–19]. However, reported percentages in the literature range from 60% to 100% of patients [3,10,20,21]. Regardless, an increasing body of evidence supports the notion that xerostomia appears to occur in a majority of patients receiving radiation for oropharyngeal, hypopharyngeal, laryngeal, and nasopharyngeal carcinomas [6,7,9,10,13,14,22–27].

Some studies suggest radiation therapy induces irreversible salivary gland damage, potentially with as low a dose as 6 Gy [7,28]. While the exact mechanism of radiation-induced gland destruction is unknown, it is hypothesized that radiation has direct cytotoxic effects on salivary tissue and causes indirect changes in vascular blood flow to the gland [29]. The result is predominant salivary gland dysfunction that manifests itself as reduced salivary flow rates, reduction in saliva pH, changes in electrolyte and immunoglobulin saliva composition, and increased cariogenic mouth flora [29,30]. In fact, investigations of fractionated radiation therapy demonstrate up to a 60% decrease in salivary flow during the first few weeks of radiation therapy, further decreasing by 20–30% after 6–7 weeks of conventional radiation therapy [7,9,13,14,28]. These changes have significant impacts on patients' quality of life and may be responsible for, but not limited to, oral discomfort, mucositis, dental caries, mastication difficulties, and deglutition dysfunction that may lead to nutritional deficits [8,31–36]. Further, the emotional impact xerostomia has on patients' psychosocial well-being is significant, with approximately 50% of patients reporting depression, worry, or feelings of tension related to this condition [3].

Despite a variety of therapeutic agents such as pilocarpine, lubricants, salivary substitutes, and acupuncture that are available for the treatment of radiation-induced xerostomia, medical management of this condition is rarely effective [12,20,37–39]. In fact, a recent review stated that *prevention is paramount* to avoid radiation-induced xerostomia [3]. For this reason, recent investigation

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Original Article

The tubarial salivary glands: A potential new organ at risk for radiotherapy

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ABSTRACT

Introduction: The presence of previously unnoticed bilateral macroscopic salivary gland locations in the human nasopharynx was suspected after visualization by positron emission tomography/computed tomography with prostate-specific membrane antigen ligands (PSMA PET/CT). We aimed to elucidate the characteristics of this unknown entity and its potential clinical implications for radiotherapy.

Materials and methods: The presence and configuration of the PSMA-positive area was evaluated in a retrospective cohort of consecutively scanned patients with prostate or urethral gland cancer (n = 100). Morphological and histological characteristics were assessed in a human cadaver study (n = 2). The effect of radiotherapy (RT) on salivation and swallowing was retrospectively investigated using prospectively collected clinical data from a cohort of head-neck cancer patients (n = 723). With multivariable logistic regression analysis, the association between radiotherapy (RT) dose and xerostomia or dysphagia was evaluated.

Results: All 100 patients demonstrated a demarcated bilateral PSMA-positive area (average length 4 cm). Histology and 3D-reconstruction confirmed the presence of PSMA-expressing, predominantly mucous glands with multiple draining ducts, predominantly near the torus tubarius. In the head-neck cancer patients, the mean RT dose to the gland area was significantly associated with physician-rated post-treatment xerostomia and dysphagia ≥ grade 2 at 12 months (0.019/gy, 95%CI 0.005–0.033, p = .007; 0.016/gy, 95%CI 0.001–0.031, p = .036). Follow-up at 24 months had similar results.

Conclusion: The human body contains a pair of previously overlooked and clinically relevant macroscopic salivary gland locations, for which we propose the name tubarial glands. Sparing these glands in patients receiving RT may provide an opportunity to improve their quality of life.

The salivary gland system, with its three paired major glands and roughly 1000 minor glands spread throughout the aerodigestive tract submucosa, has been described in detail [1–4]. Its serous, mucous or mixed exocrine acini produce the saliva required for mastication, swallowing, digestion, tasting and dental hygiene. The nearby auditory tube submucosa also contains microscopic seromucous (tubal or Eustachian tube) glands [5]. The recently introduced molecular imaging modality of positron emission tomography/computed tomography with radio-labelled ligands to the prostate-specific membrane antigen (PSMA[1] PET/CT) can visualize these salivary glands with high sensitivity and specificity [6].

Surprisingly, we observed that PSMA PET/CT also depicted an unknown bilateral structure posterior in the nasopharynx, with

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[1] PSMA= prostate specific membrane antigen.

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Xerostomia, salivary characteristics and gland volumes following intensity-modulated radiotherapy for nasopharyngeal carcinoma: a two-year follow up

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ABSTRACT

Background: To evaluate changes in xerostomia status, salivary characteristics and gland volumes 2 years following radiotherapy in nasopharyngeal carcinoma patients.
Methods: Xerostomia scores, salivary flow rates, pH and buffering capacity were measured at pre-radiotherapy, mid-radiotherapy, 2 weeks, 3 months and 2 years post-radiotherapy. Salivary gland volumes and their correlation with radiation dose were also assessed.
Results: Mean radiation dose to oral cavity, parotid and submandibular glands (SMG) was 44.5, 65.0 and 38.6 Gy respectively. Parotid and SMG volumes decreased 33% at 3 months post-radiotherapy; volumes at 2 years post-radiotherapy were 84% and 51% of pre-radiotherapy levels, respectively. Correlations were observed between parotid gland volume per cent reduction and its radiation dose and between resting salivary flow rate reduction and post-radiotherapy/pre-radiotherapy SMG volume ratio. Salivary flow rates and resting saliva pH remained significantly low at 2 years post-radiotherapy (both flow rates, $P = 0.001$; resting saliva pH, $P = 0.005$). Similarly, xerostomia scores remained significantly higher compared with pre-radiotherapy levels.
Conclusions: Submandibular gland volumetric shrinkage persisted 2 years after radiotherapy. Xerostomia scores remained significantly higher, and salivary flow rates and resting saliva pH remained significantly lower, suggesting that study participants were still at risk for hyposalivation-related oral diseases.

Keywords: Head and neck cancer, intensity-modulated radiotherapy, nasopharyngeal carcinoma, salivary glands, xerostomia.

Abbreviations and acronyms: CT = computed tomography; CTV = clinical target volume; DICOM = digital imaging and communications in medicine; EORTC = European Organization for the Research and Treatment of Cancer; IMRT = intensity-modulated radiotherapy; MRI = magnetic resonance imaging; NPC = nasopharyngeal carcinoma; PG = parotid glands; PTV = planning target volume; RT = radiotherapy; RTOG = Radiation Therapy Oncology Group; SMG = submandibular glands; XQ = xerostomia-related questionnaire.

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INTRODUCTION

Nasopharyngeal carcinoma (NPC) is endemic in select geographic and racial populations, occurring 2–3-times more frequently in males than in females.[1] The majority of cases occur in South-East and East Asia, Northern Africa and Alaska. In males, the reported age-standardized incidence of NPC in South-East Asia is 6.4/100 000 compared with an age-standardized incidence of 0.7/100 000 in Australia/New Zealand.[1] The Chinese and Inuits are predisposed to the disease.[2,3] In Singapore, NPC is the most common head and neck cancer affecting Singaporean males; 92.5% are of Chinese race.[4] It arises from the epithelium of the nasopharynx and is commonly detected at the fossa of Rosenmüller.[2] The nasopharynx is located below the central base of the skull making surgical access difficult. As NPC is highly radiosensitive, radiotherapy (RT) is the primary treatment modality.[2] RT for NPC is extremely challenging due to the proximity of the post-nasal space to many critical organs, including salivary glands, optic nerve and brainstem.

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CLINICAL INVESTIGATION **Head and Neck**

HOW DOES INTENSITY-MODULATED RADIOTHERAPY VERSUS CONVENTIONAL TWO-DIMENSIONAL RADIOTHERAPY INFLUENCE THE TREATMENT RESULTS IN NASOPHARYNGEAL CARCINOMA PATIENTS?

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Purpose: To compare the results of intensity-modulated radiotherapy (IMRT) with those of two-dimensional conventional radiotherapy (2D-CRT) in the treatment of patients with nasopharyngeal carcinoma (NPC).

Methods and Materials: A retrospective review of data from 1,276 patients with biopsy-proven, nonmetastatic NPC was performed. All patients had undergone magnetic resonance imaging and were staged according to the sixth edition of the American Joint Committee on Cancer staging criteria. Radiotherapy was the primary treatment for all patients.

Results: Of the 1,276 patients, 512 were treated with IMRT and 764 with 2D-CRT. The 5-year actuarial local relapse-free survival (LRFS), the nodal relapse-free survival (NRFS), the distant metastasis-free survival (DMFS), and the disease-free survival (DFS) rates were 92.7%, 97.0%, 84.0%, and 75.9%, respectively, for the IMRT group, and 86.8%, 95.5%, 82.6%, and 71.4%, respectively, for the 2D-CRT group. In stage T1 patients, improvement of LRFS in the IMRT group was even significantly higher than in the 2D-CRT group (100% vs. 94.4%; $p = 0.016$). A trend of improvement of DFS was observed in the IMRT group compared with the 2D-CRT group but without reaching statistical significance. NRFS and DMFS rates were similar in the two groups.

Conclusions: A greater improvement of treatment results with IMRT than with 2D-CRT was demonstrated primarily by achieving a higher local tumor control rate in NPC patients, especially in the early T stage patients. The goal of better control of both local failure in advanced, nonmetastatic NPC patients and of distant failure should be addressed in future studies.

Nasopharyngeal carcinoma, Intensity-modulated radiotherapy, Conventional two-dimensional radiotherapy, Treatment result, Radiotherapy.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a radiosensitive disease, and radiotherapy remains the mainstay of treatment for nondisseminated disease. Up until the early 1990s, conventional two-dimensional radiotherapy (2D-CRT) was used to deliver a "tumoricidal" dose (66–70 Gy; 2 Gy per fraction; 6.6–7 weeks) via laterally opposed fields. However, treatment with 2D-CRT transitioned to three-dimensional conformal radiotherapy (3D-CRT), and in particular to intensity-modulated radiotherapy (IMRT), representing a major step forward in the treatment of NPC(1).

Contrary to the local control rates of only 64% to 95% for stage T1/T2 and 44% to 68% for T3/T4 tumors described in the 1992 American Joint Committee on Cancer (AJCC) manual, Lee *et al.* (2) reported excellent outcomes for 4-year local relapse-free survival (LRFS) rates and local-regional progression–free rates of 97% and 98%, respectively, for NPC patients treated with IMRT. Kam *et al.* (1) subsequently

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Original article

Diffusion-weighted MRI of salivary glands with gustatory stimulation: comparison before and after radiotherapy

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Abstract

Background: Xerostomia is the most prominent complication in patients with head and neck carcinoma after radiotherapy (RT). Diffusion-weighted magnetic resonance imaging (DWI) with gustatory stimulation may contribute to the evaluation of salivary gland function.

Purpose: To investigate the value of DWI for quantifying physiological changes of the parotid gland during gustatory stimulation in patients before and after RT.

Material and Methods: Magnetic resonance imaging (MRI) was performed in 28 consecutive patients with nasopharyngeal carcinoma before and after RT and clinical xerostomia was also assessed. A DWI sequence was performed once at rest and continually repeated seven times during stimulation with ascorbic acid. Apparent diffusion coefficient (ADC) maps for parotid glands at different time points and the range of increase with stimulation were calculated. Paired two-tailed Student *t* tests were used to compare the ADC values before and after stimulation, and before and after RT.

Results: Before RT, the ADC showed an initial increase ($P < 0.001$) and then fluctuated during stimulation. After RT, as the clinical xerostomia changed from Grade 0 to Grade 2, the mean ADC at rest increased compared with the pre-RT value ($P < 0.001$). A similar response to stimulation was observed, but the range of increase between the maximum ADC during stimulation and the baseline value at rest was higher post-RT than pre-RT ($P = 0.022$). The minimum ADC during stimulation was higher than the baseline value post-RT ($P = 0.028$), but there was no difference pre-RT ($P = 0.603$).

Conclusion: DWI combined with gustatory stimulation seems to display the physiological changes of the parotid gland following RT and may be a potential tool for non-invasively assessing salivary gland function.

Keywords: Parotid gland, diffusion-weighted imaging, magnetic resonance, radiotherapy

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Salivary gland hypofunction, also called xerostomia, is the most prominent complication in patients with head and neck carcinoma after radiotherapy (RT) because the radiation fields often bilaterally involve the salivary glands, which are particularly radiosensitive (1). Radiation-induced xerostomia is usually accompanied by impaired saliva production and consequent co-morbidities, such as oral infections, dental caries, taste loss, and dysphagia; these significantly reduce the quality of life in long-term survivors following RT. It is important to assess salivary gland function in these patients for diagnostic and management purposes.

Radionuclide imaging using ^{99m}Tc-pertechnetate has been applied as an objective technique to assess salivary gland function. However, this imaging modality cannot avoid radiation exposure and should not be performed repeatedly on the same patient (2). Conventional sialography and salivary flow rate measurement can also be used, although these techniques are similarly invasive or the results are not always comparable between studies (3, 4).

Diffusion-weighted MR imaging (DWI) is an imaging technique that can visualize the random thermal motion

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RESEARCH ARTICLE Open Access

Which nasopharyngeal cancer patients need adaptive radiotherapy?

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Abstract

Background: Adaptive radiotherapy (ART) has potential benefits in patients with nasopharyngeal cancer (NPC). This retrospective study aimed to identify the factors favoring ART.

Materials and methods: Forty NPC patients were retrospectively included in this study. All patients received two-phase volumetric modulated arc radiotherapy (VMAT) and underwent a second computed tomography (CT) for the phase II ART. We generated phantom, non-ART plans by a hybrid method for comparison with ART plans. A paired *t*-test was used to evaluate the dose differences between these two plans. A subgroup analysis through a paired *t*-test was used to evaluate the factors favoring ART.

Results: The second CT images were captured at the median 22 fractions. The median total dose of the planning target volume-one (PTV-1) was 72 Gy, and the phase II dose was 16 Gy. The volumes of the ipsilateral parotid gland (23.2 vs. 19.2 ml, $p < 0.000$), contralateral parotid gland (23.0 vs. 18.4 ml, $p < 0.000$), clinical target volume-1 (CTV-1, 32.2 vs. 20.9 ml, $p < 0.000$), and PTV-1 (125.8 vs. 107.3 ml, $p < 0.000$) all shrunk significantly between these two CT simulation procedures. Among the nearby critical organs, only the ipsilateral parotid gland displayed significant dose reduction by the ART plan (5.3 vs. 6.0 Gy, $p = 0.004$). Compared to the phantom plan, the ART could significantly improve the PTV-1 target volume coverage of D_{98} (15.4 vs. 12.3 Gy, $p < 0.000$). Based on the D_{98} of PTV-1, the factors of a large initial weight (> 60 kg, $p < 0.000$), large body mass index (BMI) (> 21.5, $p < 0.000$), obvious weight loss (> 2.8 kg, $p < 0.000$), concurrent chemoradiotherapy ($p < 0.000$), and stages III–IV ($p < 0.000$) favored the use of ART.

Conclusions: ART could significantly reduce the mean dose to the ipsilateral parotid gland. ART has dosimetrical benefit for patients with a heavy initial weight, large BMI, obvious weight loss, concurrent chemoradiotherapy, and cancer in stages III–IV.

Keywords: Nasopharyngeal cancer, Radiotherapy, Adaptive radiotherapy, Intensity-modulated radiotherapy, Volumetric modulated arc radiotherapy

Background

Nasopharyngeal cancer is an endemic disease in southern China, with an annual incidence of 30 cases per 100,000 persons [1]. In Taiwan, its annual incidence is approximately 13 cases per 100,000 persons [2]. In the past three decades, treatment outcomes for NPC have significantly improved through more accurate staging, improved radiotherapy techniques, and the administration of chemotherapy [1, 3]. Intensity-modulated radiotherapy (IMRT) is widely used because of its efficiency and improvement in volume coverage [1, 3]. IMRT treatments deliver high doses that conform better to targets and further lower the doses to the surrounding critical organs compared with two- or three-dimensional radiotherapy [3, 4]. Prospective randomized studies proved that IMRT contributed higher quality of life and better salivary preservation than three-dimensional radiotherapy [5–7]. However, because of the high complexity of the anatomical structures surrounding nasopharyngeal

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ORIGINAL ARTICLE

Magnetic resonance sialography for investigating major salivary gland duct system after intensity-modulated radiotherapy of nasopharyngeal carcinoma

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Abstract
Background We investigated the value of magnetic resonance sialography for evaluating xerostomia induced by intensity-modulated radiotherapy for nasopharyngeal carcinoma.
Methods Fourteen patients with nasopharyngeal carcinoma were treated with intensity-modulated radiotherapy. Salivary function was assessed by magnetic resonance sialography and subjective evaluation criteria pre-treatment, 1 week and 1 year post-radiotherapy. A magnetic resonance sialography categorical scoring system was used to compare the visibility of salivary ducts.
Results The average mean dose was 38.93 Gy to the parotid glands and 59.34 Gy to the submandibular glands. Before radiotherapy, the visibility scores of both the parotid and submandibular ducts increased after secretion stimulation. The scores decreased and the response to stimulation was attenuated 1 week post-radiotherapy. For most of the parotid ducts, the visibility score improved at 1 year post-radiotherapy both at rest and under stimulation, but not for the submandibular ducts. With a median follow-up of 12.3 months, 8/12 patients had grade 1 xerostomia and 4/12 had grade 2 xerostomia.
Conclusions Magnetic resonance sialography allows non-invasive evaluation of radiation-induced ductal changes in the major salivary glands and enables reliable prediction of radiation-induced xerostomia.

Keywords Magnetic resonance sialography · Radiation-induced xerostomia · Nasopharyngeal carcinoma

Introduction

Radiotherapy (RT) for nasopharyngeal carcinoma (NPC) will give a high dose of radiation to the major salivary glands. With conventional treatment techniques, xerostomia has been an unavoidable result in nearly all NPC patients [1]. Despite the highly conformal doses produced by intensity-modulated radiotherapy (IMRT) and the lack of internal organ motion in the head and neck region, it still may not be possible to spare both parotid and submandibular glands, due to their proximate locations to the primary tumor or bulky level II lymph nodes. Hence, xerostomia is still one of the most distressing morbidities of radiotherapy in NPC.

The aim of this study was to develop a magnetic resonance (MR) sialographic method for measuring major salivary gland function pre- and post-RT. MR sialography is a non-invasive technique for visualizing the salivary ducts, and is basically heavily T2-weighted MR imaging with fat suppression. Due to the exceptionally long echo time used in the sequence and the high T2-value of water, tissues containing a large amount of static fluid can be visualized [2]. Therefore, structures such as the salivary

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Original Article

Late Sensorial Alterations in Different Radiotherapy Techniques for Nasopharyngeal Cancer

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Abstract

Intensity-modulated radiation therapy (IMRT) for nasopharyngeal cancer (NPC) allowed a better distribution of the dose to the tumor volume, sparing surrounding structures. Aim of the study is the objective evaluation of olfactory and gustatory impairments in patients who underwent chemo-radiotherapy for NPC. Correlation between smell and taste alterations, xerostomy, and radiation technique was investigated. Thirty healthy subjects and 30 patients treated with chemo-radiation therapy for NPC, with at least a 2-years follow-up period, were evaluated. All subjects underwent symptoms evaluation, endoscopic fiber optic nasal examination, taste strips, Sniffin' sticks tests, Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer late radiation morbidity scoring system. Patients were divided in 2 groups: 2-dimensional radiotherapy/conformal 3-dimensional radiotherapy and IMRT. A higher percentage of rhinorrhea, nasal obstruction, xerostomy, hyposmia, hypogeusia, mucosal hyperemia, and presence of nasopharyngeal secretions was found in irradiated subjects ($P < 0.05$). Concerning olfactory and gustatory scores, we demonstrated a statistically significant difference between healthy subjects and irradiated patients ($P < 0.05$), with lower gustatory total score in IMRT group ($P < 0.01$). In conclusion, chemo-radiotherapy for NPC induces long-term smell and taste impairments, which can compromise quality of life. Although based on small samples, it is also important to consider that IMRT can induce higher taste dysfunction compared with traditional techniques.

Key words: intensity-modulated radiation therapy, nasopharyngeal cancer, radiotherapy, smell, Sniffin' sticks, taste

Introduction

Nasopharyngeal carcinoma (NPC) represents a rare tumor in Europe and United States, whereas its incidence is higher in Eastern countries, such as China and Taiwan. Official surveys of International Agency for Research on Cancer estimated that the incidence of NPC in China in 2002 was 22.2 men and 9.8 women/100 000 inhabitants; in Europe the incidence was 0.3–0.4 men and 0.1–0.2 women/100 000 inhabitants (Parkin et al. 2002; Ma and Cao 2010).

Radiation therapy (RT) is the main treatment of NPC in early and late stages; its efficacy can be improved by the association with concurrent or adjuvant chemotherapy schemes (Airoldi et al. 2009). Late toxicities due to these treatments, such as xerostomy, auditory

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ORIGINAL RESEARCH

A longitudinal study on parotid and submandibular gland changes assessed by magnetic resonance imaging and ultrasonography in post-radiotherapy nasopharyngeal cancer patients

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Objectives: With regard to the intensity modulated radiotherapy (IMRT) of nasopharyngeal carcinoma (NPC) patients, this longitudinal study evaluated the radiation-induced changes in the parotid and submandibular glands in terms of gland size, echogenicity and haemodynamic parameters.

Methods: 21 NPC patients treated by IMRT underwent MRI and ultrasound scans before radiotherapy, and at 6, 12, 18 and 24 months after treatment. Parotid and submandibular gland volumes were measured from the MRI images, whereas the parotid echogenicity and haemodynamic parameters including the resistive index, pulsatility index, peak systolic velocity and end diastolic velocity were evaluated by ultrasonography. Trend lines were plotted to show the pattern of changes. The correlations of gland doses and the post-RT changes were also studied.

Results: The volume of the parotid and submandibular glands demonstrated a significant drop from pre-RT to 6 months post-RT. The parotid gland changed from hyperechoic before RT to either isoechoic or hypoechoic after treatment. The resistive index and pulsatility index decreased from pre-RT to 6 month post-RT, then started to increase at 12 month time interval. Both peak systolic velocity and end diastolic velocity increased after 6 months post-RT then followed a decreasing trend up to 24 months post-RT. There was mild correlation between post-RT gland dose and gland volume, but not with haemodynamic changes.

Conclusions: Radiation from IMRT caused shrinkage of parotid and submandibular glands in NPC patients. It also changed the echogenicity and vascular condition of the parotid gland. The most significant changes were observed at 6 months after radiotherapy.

Advances in knowledge: It is the first paper that reports on the longitudinal changes of salivary gland volume, echogenicity and haemodynamic parameters altogether in NPC patients after radiotherapy. The results are useful for the prediction of glandular changes that is associated with xerostomia, which help to provide timely management of the complication when the patients attend follow-up visits.

INTRODUCTION

Xerostomia is a common radiation-induced complication in post-radiotherapy (RT) nasopharyngeal carcinoma (NPC) patients.[1] This complication affects mastication and swallowing and increases susceptibility to oral infections and dental problems, which subsequently degrade the quality of life in post-RT NPC patients.[2,3] In a radical course of radiotherapy to NPC patients, portions of major salivary glands including the parotid gland and submandibular gland are often irradiated to high dose. It has been demonstrated that xerostomia was dependent on the radiation dose delivered to the salivary glands in NPC patients.[4] Its incidence varied greatly from 39.3 to 82.1% depending on the RT techniques.[5,6] Although the recent introduction of intensity modulated radiotherapy (IMRT) can achieve better sparing of parotid and submandibular glands,[7–10] the irradiation of these glands is still inevitable and xerostomia has been frequently reported.[11] Furthermore, radiotherapy of NPC often delivered with concurrent chemotherapy,

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CLINICAL INVESTIGATION **Head and Neck Cancer**

LONG-TERM OUTCOMES OF EARLY-STAGE NASOPHARYNGEAL CARCINOMA PATIENTS TREATED WITH INTENSITY-MODULATED RADIOTHERAPY ALONE

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Purpose: Reports of intensity-modulated radiotherapy (IMRT) for early-stage nasopharyngeal carcinoma (NPC) have been limited. The present study evaluated the long-term survival outcomes and toxicity of early-stage NPC patients treated with IMRT alone.

Methods and Materials: Between February 2001 and January 2008, 198 early-stage (T1-T2bN0-N1M0) NPC patients had undergone IMRT alone. The data from these patients were retrospectively analyzed. The patients were treated to 68 Gy at 2.27 Gy/fraction prescribed to the planning target volume of the primary nasopharygeal gross tumor volume. The Radiation Therapy Oncology Group scoring system was used to assess the toxicity.

Results: At a median follow-up of 50.9 months (range, 12–104), the 5-year estimated disease-specific survival, local recurrence-free survival, and distant metastasis-free survival rate was 97.3%, 97.7%, and 97.8%, respectively. The 5-year local recurrence-free survival rate was 100% for those with Stage T1 and T2a and 94.2% for those with Stage T2b lesions ($p = 0.252$). The 5-year distant metastasis-free survival rate for Stage T1N0, T2N0, T1N1, and T2N1 patients was 100%, 98.8%, 100%, and 93.8%, respectively ($p = .073$). All local recurrence occurred in patients with T2b lesions. Five patients developed distant metastasis. Of these 5 patients, 4 had had Stage T2bN1 disease and 1 had had Stage T2bN0 disease with retropharyngeal lymph node involvement. The most common acute toxicities were mainly Grade 1 or 2. At 24 months after IMRT, no Grade 3 or 4 xerostomia had developed, and 62 (96.9%) of 64 evaluated patients were free of trismus; only 2 patients (3.1%) had Grade 1 trismus. Radiation encephalopathy and cranial nerve injury were not observed.

Conclusions: IMRT alone for Stage T1N0, T2N0, T1N1, and T2N1 yielded satisfactory survival outcomes with acceptable toxicity, and no differences were found in survival outcomes among these four subgroups. Patients with Stage T2b lesions might have relatively greater risk of local recurrence and those with T2bN1 disease mighth have a greater risk of distant metastasis. © 2012 Elsevier Inc.

Nasopharyngeal carcinoma, Early stage, Intensity-modulated radiotherapy, Prognosis, Toxity.

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is an endemic disease in southern China. Early-stage NPC was defined as Stage I and II using the American Joint Committee on Cancer (AJCC) 2002 staging system. Definitive radiotherapy (RT) has been the main treatment modality for early-stage NPC, and the overall survival rate has been about 84–90% for those NPC patients with conventional two-dimensional conformal radiotherapy (2D-CRT) alone (1–4).

Different survival outcomes were observed in different subgroups of early-stage NPC treated with the 2D-CRT technique alone. Chua *et al.* (1) reported that the distant metastasis rate for those with Stage T1-T2N1 was much greater than that for those with Stage T1-T2N0 and that chemoradiotherapy is necessary for Stage T1-T2N1 disease to improve the prognosis of this group. In our previous report of 362 early-stage patients treated with 2D-CRT alone, we divided the patients with early-stage NPC into four subgroups (Stage T1N0, T2N0, T1N1, and T2N1) and found that the T2N1M0 subgroup was a unique group with the poorest prognosis because of distant metastasis. We suggested that only patients in the T2N1 group might need combined treatment instead of RT alone (2). Several publications have indicated that the combination of RT and chemotherapy improved the treatment outcomes for Stage II patients (5, 6).

Because it optimizes the radiation deposition in the tumor while sparing the adjacent normal structures, intensity-modulated RT (IMRT) has been widely used for NPC and has improved clinical outcomes, especially local control,

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Radiation-induced CT number changes in GTV and parotid glands during the course of radiation therapy for nasopharyngeal cancer

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ORIGINAL ARTICLE

Diffusion-weighted imaging as a follow-up modality for evaluation of major salivary gland function in nasopharyngeal carcinoma patients: a preliminary study

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Abstract

Purpose To investigate the value of diffusion-weighted imaging (DWI) in assessing dynamic changes of major salivary gland function during follow-up post radiotherapy (RT) in nasopharyngeal carcinoma (NPC) patients.

Materials and methods 31 consecutive patients with pathologically confirmed NPC scheduled for RT underwent six routine follow-up MRI examinations including DWI sequence prior to (pre-RT) and 1, 3, 6, 9, and 12 months post RT. Mean apparent diffusion coefficient (ADC) values of bilateral parotid glands (PGs) and submandibular glands (SMGs) were measured. Objective measurement of salivary flow rate (SFR) under unstimulated (uSFR) and stimulated conditions (sSFR) as well as subjective xerostomia assessment according to a patient-rated questionnaire were conducted before each MRI. Variance analysis was used to evaluate dynamic changes of ADC, SFR and xerostomia questionnaire summary scores (XQ-sum) at different timepoints and the correlation between ADC and XQ-sum. Pearson's correlation test was used to evaluate the correlations between pre- and post-RT changes of ADC (ΔADC) and SFR (ΔSFR) or mean RT dose.

Results At each timepoint, ADCs of PGs were significantly lower than of SMGs, uSFR was significantly lower than sSFR. For both PGs and SMGs, $ADC_{post\text{-}RT}$ were all higher than $ADC_{pre\text{-}RT}$, with significant differences. $ADC_{1m\text{-}post\text{-}RT}$ initially increased and changed little to $ADC_{3m\text{-}post\text{-}RT}$, $ADC_{6m\text{-}post\text{-}RT}$, $ADC_{9m\text{-}post\text{-}RT}$, and $ADC_{12m\text{-}post\text{-}RT}$, then gradually declined over time. The dynamic change trends of SFR were negatively paralleled to those of ADC, while that of XQ-sum was similar. Dose–response relationships were detected between salivary gland mean RT dose and ΔADC. In PGs, negative correlations between $\Delta sSFR_{3m\text{-}post\text{-}RT}$ and $\Delta ADC_{3m\text{-}post\text{-}RT}$, and $\Delta sSFR_{12m\text{-}post\text{-}RT}$ and $\Delta ADC_{12m\text{-}post\text{-}RT}$ were detected. In SMGs, negative correlations between $\Delta sSFR_{12m\text{-}post\text{-}RT}$ and $\Delta ADC_{12m\text{-}post\text{-}RT}$, and $\Delta uSFR_{12m\text{-}post\text{-}RT}$ and $\Delta ADC_{12m\text{-}post\text{-}RT}$ were also detected. The ADCs of patients with severe subjective xerostomia were significantly higher, while patients with moderate subjective xerostomia presented a tendency toward higher ADCs compared to those with mild xerostomia from 6 to 12 months post RT.

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RADIATION ONCOLOGY

RESEARCH Open Access

Clinical observation of submandibular gland transfer for the prevention of xerostomia after radiotherapy for nasopharyngeal carcinoma: a prospective randomized controlled study of 32 cases

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Abstract

Background: The aim of this study was to evaluate the clinical efficacy of submandibular gland transfer for the prevention of xerostomia after radiotherapy for nasopharyngeal carcinoma.

Methods: Using the randomized controlled clinical research method, 65 patients with nasopharyngeal carcinoma were randomly divided into an experimental group consisting of 32 patients and a control group consisting of 33 patients. The submandibular glands were averted to the submental region in 32 patients with nasopharyngeal carcinoma before they received conventional radiotherapy; a lead block was used to shield the submental region during therapy. Prior to radiotherapy, the function of the submandibular glands was assessed using imaging. Submandibular gland function was measured using 99mTc radionuclide scanning at 60 months after radiotherapy. The data in the questionnaire regarding the degree of xerostomia were investigated and saliva secretion was measured at 3, 6, 12, and 60 months after radiotherapy. In addition, the 5-year survival rate was calculated.

Results: After follow-up for 3, 6, and 12 months, the incidence of moderate to severe xerostomia was significantly lower in the experimental group than in the control group. The average amount of saliva produced by the experimental and control groups was 1.60 g and 0.68 g, respectively ($P < 0.001$). After follow-up for 60 months, the uptake and secretion functions of the submandibular glands in the experimental group were found to be significantly higher than in the control group ($P < 0.001$ and $P < 0.001$, respectively). The incidence of moderate or severe xerostomia was significantly lower than in the control group (15.4% and 76.9%, respectively; $P < 0.001$). The 5-year survival rates of the experimental group and the control group were 81.3% and 78.8%, respectively, and there was no significant difference between the two groups ($P = 0.806$).

Conclusions: After a 5 year follow-up period involving 32 patients who had their submandibular glands transferred for the prevention of xerostomia after radiotherapy for nasopharyngeal carcinoma, we found that clinical efficacy was good. This approach could improve the quality of life of nasopharyngeal carcinoma patients after radiotherapy and would not affect long-term treatment efficacy.

Keywords: Nasopharyngeal carcinoma, Radiotherapy, Xerostomia, Submandibular gland, Transfer

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Review Article

Page 1 of 8

Salivary glands and dental complications after radiotherapy for nasopharyngeal carcinoma

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Contributions: (I) Conception and design: I Chitapanarux; (II) Administrative support: I Chitapanarux; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: I Chitapanarux; (V) Data analysis and interpretation: I Chitapanarux; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Nasopharyngeal cancer patients undergoing radiotherapy (RT) are vulnerable to serious complications in their oral health, especially in salivary glands and dental complications. For the affected patients who have long-term survived, quality of their lives can be extremely changed by RT. It is important, as the radiation oncologist, to prevent and manage these complications. The use of sophisticate and modern technology in RT, oral health education, and pre-RT dental evaluation are the significant ways to prevent and diminish RT-induced xerostomia. Medications such as cholinergic parasympathomimetic agents have the capacity to reduce xerostomia symptoms and increase saliva production in the responder patients. For lessen the dental complications; complete dental care before the course of RT, application of fluoride to patients' teeth in individual trays, and a comprehensive dental examination every 6 months after RT are strongly recommended.

Keywords: Radiotherapy (RT); complication; salivary gland; dental

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All nasopharyngeal cancer (NPC) required radiotherapy (RT) to both sides of the neck to cover the bilateral cervical lymph nodes. This resulted in a larger volume of salivary glands being irradiated and accounted for late complications to themselves and also to the nearby organs, e.g., teeth, mandible. RT may cause permanent damage to these structures and put the patients at a lifelong risk of complications. Decreasing of salivary function and flow can affect the quality of life of patients, i.e., problems in chewing and swallowing, difficulties in speech, mouth discomfort, taste alteration, oral infection, and dental caries. This review aims to summarize the development of late complications to the salivary glands and teeth following RT for NPC. Additionally, we also provide prevention strategies and the management of these late side effects.

Salivary glands complication after RT for nasopharyngeal carcinoma

Damage to the salivary glands is a major concern with RT for NPC. All of the major saliva glands (parotid/submandibular/sublingual) are the crucial glands for producing saliva. They produce 70–80% of the total saliva. Minor salivary glands scattered all over the oral cavity and pharynx produce a residual of 20–30% (1-3). Parotid glands produce a watery texture and high protein concentration saliva. Parotid glands are also the biggest salivary gland and very sensitive to radiation. Damage to this gland plays a key role in the generation of late suffering sequelae to NPC patients.

Lubrication and protection from the microorganisms of

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Evaluation of radiation-induced changes to parotid glands following conventional radiotherapy in patients with nasopharygneal carcinoma

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Objectives: Xerostomia is a common post-radiotherapy (post-RT) complication in nasopharyngeal carcinoma (NPC) patients. This study evaluated the relation of post-RT parotid gland changes with the dose received.
Methods: Data from 18 NPC patients treated by radiotherapy between 1997 and 2001 were collected. Parotid gland volumes were measured and compared between their pre-RT and post-RT CT images; both sets of CT were conducted with the same scanning protocol. Doppler ultrasound was used to assess the haemodynamic condition of the glands after radiotherapy. Doppler ultrasound results were compared against 18 age-matched normal participants. A questionnaire was used to evaluate the patients' comments of xerostomia condition. Radiotherapy treatment plans of the participants were retrieved from the Eclipse treatment planning system from which the radiation doses delivered to the parotid glands were estimated. The correlations of parotid gland doses and the post-RT changes were evaluated.
Results: The post-RT parotid glands were significantly smaller ($p<0.001$) than the pre-RT ones. They also demonstrated lower vascular velocity, resistive and pulsatility indices ($p<0.05$) than normal participants. The degree of volume shrinkage and subjective severity of xerostomia demonstrated dose dependence, but such dependence was not definite in the haemodynamic changes.
Conclusion: It was possible to predict the gland volume change and subjective severity of xerostomia based on the dose to the parotid glands for NPC patients. However, such prediction was not effective for the vascular changes. The damage to the gland was long lasting and had significant effects on the patients' quality of life.

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Xerostomia is one of the commonest radiation-induced complications in nasopharyngeal carcinoma (NPC) patients after a radical course of radiotherapy [1, 2]. Persistent xerostomia, which is due to the damage of the parotid glands, causes difficulties in mastication and swallowing and enhances the risks of dental problems; these subsequently degrade the quality of life in long-term survivors [3, 4].

With the recent advancements in radiotherapy techniques such as intensity-modulated radiotherapy (IMRT), highly conformal dose distributions are possible and the sparing of parotid gland can be made more effective. However, conventional radiotherapy protocol for NPC is still used in some centres, and the treatment protocol is to employ lateral opposing beams to the face and upper neck plus an anterior beam to cover the lower neck. This inevitably irradiates the parotid glands to a mean dose of over 45 Gy, with the medial portion receiving as high as 60 Gy [5, 6].

Up to now, the mechanism of parotid gland damage and saliva reduction due to radiation is largely unknown. It is postulated that the saliva secretion of the parotid glands is related to the changes in morphology and vascular condition as a result of radiation therapy [7]. CT is a useful imaging tool for monitoring the response of radiation therapy by providing morphological information of the head and neck structures, including the parotid glands. For the assessment of post-radiotherapy (post-RT) vascular changes of parotid glands, there has been a report of dose-dependent increases in the extracellular extravascular space (EES) and decreases in vascular permeability using MRI [8]. However, the variation of haemodynamics in post-RT intraparotid vessels, which is useful for better understanding of the physiological changes of the parotid glands, is still unclear. Doppler ultrasonography is effective in the evaluation of the gland haemodynamics such as the blood flow velocity and resistive index, which are useful parameters in the assessment of the vasculature of the parotid gland [7]. Our study hypothesised that high-dose radiation to the parotid gland would destroy the acini and granules, which would alter the pressure on the blood vessels and result in changes of the blood velocity. More importantly, there is scant information about the relationships between these parameters with the radiation dose delivered to the glands. The knowledge of these relationships can provide useful references for the prediction of the severity of

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Journal of Dental Sciences

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 lesions 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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Nasal cytological changes as late effects of radiotherapy for nasopharyngeal cancer

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ABSTRACT

Background: *Radiation therapy is a cornerstone in nasopharyngeal cancer treatment. However, it can induce acute and long-term adverse effects, such as acute mucositis and late submucosal fibrosis. Late toxicities could not only affect submucosa but also mucosal cells, determining long-term cytological changes.*

Objective: *Evaluation of delayed nasal cytological alterations in patients who underwent radiation therapy for nasopharyngeal carcinoma (NPC).*

Methods: *In this case-control study, we analyzed 30 healthy subjects and 30 patients treated with chemotherapy and radiotherapy for NPC between 2003 and 2011, with a median follow-up of 59 months. All subjects underwent symptoms anamnestic evaluation (rhinorrea, nasal obstruction), endoscopic fiber optic nasal examination, skin-prick tests, and nasal scraping for cytological exam.*

Results: *A higher percentage of rhinorrhea, nasal obstruction, mucosal hyperemia, and presence of nasopharyngeal secretions at fiber optic endoscopic exam was found in radiated subjects ($p < 0.05$). Nasal cytology analysis demonstrated a higher percentage of neutrophilic inflammation and squamous cell metaplasia and mucous cell metaplasia in treated patients ($p < 0.05$). No cytological atypia was seen. No statistically significant correlation between nasal cytological changes and objective findings, patients' age, tobacco smoking, and gastroesophageal reflux has been found in the radiotherapy group ($p > 0.05$).*

Conclusion: *Radiation therapy induces late nasal mucosal changes, which may be related to clinical consequences, such as abundant mucus production and its consequent endonasal stagnation. In the future, detailed knowledge of cytological changes in patients' nasal mucosa could represent a key prerequisite for the choice of effective interventions for late radiation-induced rhinitis.*

(Am J Rhinol Allergy 29, e41–e45, 2015; doi: 10.2500/ajra.2015.29.4156)

Nasopharyngeal carcinoma (NPC) is a rare tumor in Europe and the United States, whereas its incidence is higher in Eastern countries, such as China and Taiwan. According to International Agency for Research on Cancer, incidence of NPC in Europe was 0.3–0.4 men and 0.1–0.2 women/100,000 inhabitants in 2002.[1,2]

Radiation therapy represents standard of care for NPC in early and late stages, alone or in association with chemotherapy.

Irradiation fields for NPC involve nasal and oral mucous membranes and submucosa, inducing acute and long-term adverse effects, such as acute mucositis and late submucosal fibrosis.[3–6] However, late toxicities could not only affect submucosa but also mucosal cells, determining long-term cytological changes.

These effects mainly involve rapidly renewing cells, both neoplastic and healthy tissue stem cell. In the head and neck region mucosal proliferating cells are the more susceptible to radiation-induced mitotic deaths.

Decrease in oral epithelial cell density, cytological atypia, inflammatory infiltrate, and viral cytopathic effects are reported during chemotherapy and/or radiotherapy[7,8], but details of radiation effects on mucosa have not been studied as intensively as for skin and subcutaneous vasculoconnective tissue.

Aim of this case-control study is the evaluation of delayed nasal cytological alterations in patients who underwent radiation therapy for NPC.

MATERIALS AND METHODS

Between 2003 and 2011, 30 healthy subjects and 30 patients treated with chemo-radiation therapy for NPC at our Department were enrolled in this retrospective case-control study. Each patient underwent neoadjuvant, concomitant and/or adjuvant chemotherapy associated with radiotherapy and had a minimum follow-up of two years to evaluate stabilized late effects. All patients included in the study were disease free at the time of enrollment, and they had no clinically evident viral and/or bacterial diseases involving nasal cavities. Healthy subjects were patients with vocal fold nodules or polyps and without any clinical and endoscopic sign of sinonasal disease. Written informed consent was obtained in every case. Approvals of the Ethics Committee of the University of Turin and the Institutional Review Board were obtained.

Mean age was 52.35 ± 11.89 years (range, 42–76 years) for the control group and 53.53 ± 10.96 years (range, 37–75 years) for the treated group. Socio-demographic and clinical characteristics, such as age and gender distribution tobacco, alcohol consumption, previous exposure to irritant substances, gastroesophageal reflux and allergies, and tumor related factors, such as histologic type, TNM classification and stage, are reported in Table 1. There were no clinical or demographic differences between control group and treatment group ($p > 0.05$).

Chemo-radiotherapy schemes are reported in Table 2. Cisplatin-based concurrent chemotherapy (CT) was 30 mg/m^2 administered weekly (one to three cycles) or 100 mg/m^2 administered once every three weeks (five to eight cycles); neoadjuvant CT schemes included cisplatin/fluorouracil or taxanes/cisplatin/fluorouracil (one to three cycles); and adjuvant CT was based on one or two cycles of cisplatin and fluorouracil. Radiotherapy was performed using two-dimensional, conformal three-dimensional, or intensity-modulated techniques. Only two patients underwent selective or type III modified radical neck dissection for persistent nodal disease.

All patients were immobilized with a thermoplastic mask. Radiation techniques are described elsewhere.[9,10]

In two-dimensional radiotherapy (five patients) and conformal three-dimensional radiotherapy (five patients) groups, nasopharynx and metastatic lymph nodes were treated up to 70.2 Gy (1.8 Gy daily fractions, five fractions per week) with a six Megavolt linear accelerator (Elekta SL-75, Stockholm, Sweden). Uninvolved nodal levels I–IV and retropharyngeal nodes were treated bilaterally with 45–64.8 Gy

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The authors have no conflicts of interest to declare pertaining to this article

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Original Article

Early prediction of acute xerostomia during radiation therapy for nasopharyngeal cancer based on delta radiomics from CT images

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Background: Acute xerostomia is the most common side effect of radiation therapy (RT) for head and neck (H&N) malignancies. Investigating radiation-induced changes of computed tomography (CT) radiomics in parotid glands (PGs) and saliva amount (SA) can predict acute xerostomia during the RT for nasopharyngeal cancer (NPC).

Methods: CT and SA data from 35 patients with stages I–IVB were randomly collected from an NPC clinical trial registered on the clinicaltrials.gov (ID: NCT01762514). All patients received radical treatment based on intensity-modulated RT (IMRT) with a prescription dose of 68.1 Gy in 30 fractions. The patients' ages ranged 24–72 years, and each patient had five CT sets acquired at treatment position: at the 0^{th}, 10^{th}, 20^{th}, 30^{th} fractions during the RT, and at 3-month later after the RT. The PGs for each CT set were delineated by a radiation oncologist and verified independently by another. Patients' saliva was collected every other 10 days during the RT. Acute xerostomia was evaluated based on the RTOG acute toxicity scoring and the SA. In total, 1,703 radiomics features were calculated for PGs from each CT set, including feature value at 0^{th} fraction (FV_{0F}), FV_{10Fs} and delta FV (ΔFV_{10F-0F}), respectively. Extensive experiments were conducted to achieve the optimal results. RidgeCV and Recursive Feature Elimination (RFE) were used for feature selection, while linear regression was used for predicting SA_{10F}. Four more patients were added for independent testing.

Results: Substantial changes in various radiomics metrics of PGs were observed during the RT. Eight normalized feature value (NFV), selected from NFV_{0F}, predicted SA_{10F} with a mean square error (MSE) of 0.9042 and a R^2 score of 0.7406. Fourteen NFV, selected from ΔNFV_{10F-0F}, NFV_{0F}, and NFV_{10F} to predict SA_{10F}, showed the best predictive ability with an MSE of 0.0569. The model predicted the level of acute xerostomia with a precision of 0.9220 and a sensitivity of 100%, compared to the clinical observed SA. For the independent test, the MSE of PSA_{10F} was 0.0233.

Conclusions: This study demonstrated that radiation-induced acute xerostomia level could be early predicted based on the SA and radiomics changes of the PGs during IMRT delivery. SA, NFV_{0F}, NFV_{10F} and especially ΔNFV_{10F-0F} provided the best performance on acute xerostomia prediction for individual patient based on RidgeCV_RFE_LinearRegression method of delta radiomics.

Keywords: Acute xerostomia; delta radiomics; saliva amount prediction

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CLINICAL INVESTIGATION **Head and Neck**

XEROSTOMIA AND QUALITY OF LIFE AFTER INTENSITY-MODULATED RADIOTHERAPY VS. CONVENTIONAL RADIOTHERAPY FOR EARLY-STAGE NASOPHARYNGEAL CARCINOMA: INITIAL REPORT ON A RANDOMIZED CONTROLLED CLINICAL TRIAL

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Purpose: To compare directly the effect of intensity-modulated radiotherapy (IMRT) vs. conventional radiotherapy (CRT) on salivary flow and quality of life (QoL) in patients with early-stage nasopharyngeal carcinoma (NPC).

Methods and Materials: Fifty-one patients with T2, N0/N1, M0 NPC took part in a randomized controlled clinical study and received IMRT or CRT. Stimulated whole (SWS) and parotid (SPS) saliva flow were measured and Medical Outcomes Short Form 36 (SF-36), European Organization for Research and Treatment of Cancer (EORTC) core questionnaire, and EORTC head-and-neck module (QLQ-H&N35) were completed at baseline and 2, 6, and 12 months after radiotherapy.

Results: Forty-six patients (88%) were in disease remission 12 months after radiotherapy. At 12 months postradiotherapy, 12 (50.0%) and 20 patients (83.3%) in the IMRT group had recovered at least 25% of preradiotherapy SWS and SPS flow respectively, compared with 1 (4.8%) and 2 patients (9.5%), respectively, in the CRT group. Global health scores showed continuous improvement in QoL after both treatments ($p < 0.001$). However, after 12 months subscale scores for role-physical, bodily pain, and physical function were significantly higher in the IMRT group, indicating a better condition ($p < 0.05$). Dry mouth and sticky saliva were problems in both groups 2 months after treatment. In the IMRT group, there was consistent improvement over time with xerostomia-related symptoms significantly less common than in the CRT group at 12 months postradiotherapy.

Conclusions: IMRT was significantly better than CRT in terms of parotid sparing and improved QoL for early-stage disease. The findings support the case for assessment of health-related QoL in relation to head-and-neck cancer using a site-specific approach. © 2006 Elsevier Inc.

Nasopharyngeal carcinoma, Radiotherapy, Parotid sparing, Quality of life, Randomized controlled clinical trial.

INTRODUCTION

Radiotherapy (RT) is the primary treatment modality for nasopharyngeal carcinoma (NPC) because the tumor is highly radiosensitive and surgical access to the nasopharynx is difficult. After conventional RT (CRT), the 5-year local relapse-free survival rate for NPC is reported to be 75–95% for stages T1–2 (1) and 45–80% for stages T3–4, with overall survival of 50–70% for all stages (2, 3). Although the locoregional control rate is high, particularly for early-stage disease, complications related to irradiation of sensitive normal structures adjacent to the nasopharynx and in the path of the irradiation are substantial and frequently irreparable (4–6). The most common complication is hyposalivation as a consequence of permanent damage to the salivary glands, particularly the parotids. The resultant xerostomia is considered to be the most common side effect of conventional head-and-neck irradiation and leads to substantial impairment of patient quality of life (QoL) (7–10).

Salivary gland-sparing intensity-modulated radiotherapy (IMRT) is becoming a key treatment approach in the management of head-and-neck cancer because of its capacity for achieving improved target irradiation while limiting radiation dose to normal tissues and thereby reducing treatment side effects that lead to functional and psychosocial morbidity (11–14). Dosimetric studies have shown that IMRT for head-and-neck cancer may spare the parotids from ex-

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RESEARCH ARTICLE

Temporal Evolution of Parotid Volume and Parotid Apparent Diffusion Coefficient in Nasopharyngeal Carcinoma Patients Treated by Intensity-Modulated Radiotherapy Investigated by Magnetic Resonance Imaging: A Pilot Study

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Abstract

Purpose

To concurrently quantify the radiation-induced changes and temporal evolutions of parotid volume and parotid apparent diffusion coefficient (ADC) in nasopharyngeal carcinoma (NPC) patients treated by intensity-modulated radiotherapy by using magnetic resonance imaging (MRI).

Materials and Methods

A total of 11 NPC patients (9 men and 2 women; 48.7 ± 11.7 years, 22 parotid glands) were enrolled. Radiation dose, parotid sparing volume, severity of xerostomia, and radiation-to-MR interval (RMI) was recorded. MRI studies were acquired four times, including one before and three after radiotherapy. The parotid volume and the parotid ADC were measured. Statistical analysis was performed using SPSS and MedCalc. Bonferroni correction was applied for multiple comparisons. A *P* value less than 0.05 was considered as statistically significant.

Results

The parotid volume was 26.2 ± 8.0 cm^3 before radiotherapy. The parotid ADC was 0.8 ± 0.15 × 10^{-3} mm^2/sec before radiotherapy. The parotid glands received a radiation dose of

Original Article

Effectiveness of oxygen nebulization at preventing radiotherapy - induced mucositis in patients with nasopharyngeal cancer

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ABSTRACT

Purpose: To evaluate the effectiveness of oxygen nebulization at preventing radiotherapy-induced mucositis in patients with nasopharyngeal cancer.

Methods: Sixty patients with nasopharyngeal cancer treated with simultaneous integrated boost intensity-modulated radiotherapy were randomly assigned to oxygen nebulization or ultrasonic nebulization groups; treatment was once daily for 20 minutes. All patients received routine oral care. We compared saliva pH and volume, food intake, and change in oral mucosa during radiotherapy, and dry mouth and sore throat after radiotherapy between the two groups.

Results: There were significant differences in the incidence of grade III or IV mucositis, saliva volume and pH, and dry mouth and sore throat between the two groups when the total dose was 33 Gy ($P < 0.05$ or $P < 0.01$).

ORIGINAL ARTICLE

Prospective Evaluation of Quality of Life and Nutrition Before and After Treatment for Nasopharyngeal Carcinoma

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Objective: To prospectively assess quality of life in patients undergoing chemoradiation therapy for nasopharyngeal cancer. Concurrent chemoradiotherapy is standard for advanced nasopharyngeal cancer; however, the toxic effects of this treatment are substantial.

Design: Prospective evaluation of quality of life and nutritional status before and after treatment for nasopharyngeal carcinoma.

Patients and Intervention: A cohort of 14 patients, treated with concurrent chemoradiotherapy for 7 weeks, completed the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire and Head and Neck Module before and 3, 6, 12, and 24 months after treatment. Changes in score were analyzed and correlated with the toxic effect grade.

Results: Quality of life issues during the 24 months of follow-up included poorer global health ($P=.01$), fatigue ($P=.01$), appetite loss ($P<.001$), swallowing difficulties ($P=.002$), sense problems ($P=.03$), difficulty with social eating ($P=.005$), dental problems ($P=.045$), trismus ($P=.001$), xerostomia ($P<.001$), sticky saliva ($P=.001$), cough ($P=.02$), and feeling ill ($P=.03$). Pain ($P=.004$) and emotional functioning ($P<.001$) significantly improved from the pretreatment rating. The median weight loss was 7 kg, with most weight loss occurring during treatment, despite nutritional support with gastrostomy feeding tubes. One patient still required percutaneous endoscopic gastrostomy feeding at 2 years after treatment. Physician-scored toxic effects correlated poorly with quality-of-life scores.

Conclusions: Quality of life and functional assessment should be important end points in the follow-up of patients with nasopharyngeal cancer who receive chemoradiotherapy. This study supports the need for ongoing support and rehabilitation in a multidisciplinary setting.

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NASOPHARYNGEAL CARCINOMA (NPC) is a relatively uncommon malignancy in Australia with an incidence of about one thirtieth of that reported in China and Southeast Asia.[1] Concurrent chemoradiotherapy is now accepted as standard treatment for stages III and IV NPC, and many patients will achieve long-term cure despite advanced locoregional disease.[2] Although the addition of platinum-based chemotherapy improves disease control, it is associated with considerable early and late toxic effects. Hence, subjective measures such as health-related quality of life and functional status are important end points and should be incorporated into the evaluation of therapies with substantial adverse effects.

Quality of life may be defined as a patient's appraisal of and satisfaction with his or her current level of functioning compared with what is perceived to be possible.[3] Evidence regarding quality of life provides patients with a comprehensible measure of the functional consequences that result from the complex interaction between disease and treatment. In addition, it gives the clinician an unbiased measure that can be used to balance the gain in disease control against the effects of treatment. The aim of this study was to evaluate prospectively the changes in quality of life during a 2-year period in patients undergoing chemoradiotherapy for NPC at a single tertiary care institution.

Author Affiliations: Sydney Head and Neck Cancer Institute (Mss Oates, Read, and Reeves; Drs Clark and O'Brien; and Mr Gao) and Departments of Radiation Oncology (Dr Jackson) and Medical Oncology (Dr Boyer), Sydney Cancer Centre, Royal Prince Alfred Hospital and University of Sydney, Sydney, Australia.

METHODS

POPULATION AND TREATMENT

After institutional ethics approval and patient consent were obtained, data were prospectively collected for all patients with NPC who presented to the Sydney Head and Neck Cancer

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Intensity-Modulated Radiation Therapy With or Without Chemotherapy for Nasopharyngeal Carcinoma: Radiation Therapy Oncology Group Phase II Trial 0225

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose

To investigate the feasibility of intensity-modulated radiation therapy (IMRT) with or without chemotherapy, and to assess toxicities, failure patterns, and survivals in patients with nasopharyngeal carcinoma (NPC).

Patients and Methods

Radiation consisted of 70 Gy given to the planning target volumes of primary tumor plus any N+ disease and 59.4 Gy given to subclinical disease, delivered over 33 treatment days. Patients with stage T2b or greater or with N+ disease also received concurrent cisplatin (100 mg/m^2) on days 1, 22, and 43 followed by adjuvant cisplatin (80 mg/m^2) on day 1; fluorouracil (1,000 mg/m^2/d) on days 1 through 4 administered every 4 weeks for three cycles. Tumor, clinical status, and acute/late toxicities were assessed. The primary objective was to test the transportability of IMRT to a multi-institutional setting.

Results

Between February 2003 and November 2005, 68 patients with stages I through IVB NPC (of which 93.8% were WHO types 2 and 3) were enrolled. Prescribed IMRT (target delineation) was given to 89.8%, whereas 64.9% received chemotherapy per protocol. The estimated 2-year local progression-free (PF), regional PF, locoregional PF, and distant metastasis–free rates were 92.6%, 90.8%, 89.3%, and 84.7%, respectively. The estimated 2-year PF and overall survivals were 72.7% and 80.2%, respectively. Acute grade 4 mucositis occurred in 4.4%, and the worst late grade 3 toxicities were as follows: esophagus, 4.7%; mucous membranes, 3.1%; and xerostomia, 3.1%. The rate of grade 2 xerostomia at 1 year from start of IMRT was 13.5%. Only two patients complained of grade 3 xerostomia, and none had grade 4 xerostomia.

Conclusion

It was feasible to transport IMRT with or without chemotherapy in the treatment of NPC to a multi-institutional setting with 90% LRPF rate reproducing excellent reports from single institutions. Minimal grade 3 and lack of grade 4 xerostomia were encouraging.

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INTRODUCTION

Although rare among whites, nasopharyngeal carcinoma (NPC) is rather common among Asians.[1] Standard treatment for NPC is radiotherapy (RT) for early-stage lesions or chemoradiotherapy for more advanced lesions.[2,3] Historical local control (LC) rates for patients who undergo conventional RT range from 64% to 95% for T1-2 tumors but decrease to 44% to 68% in T3-4 lesions.[4-9] Modern series, including recent phase II/III trials have shown an improvement in LC (up to 95%), which is likely attributed to major advances in imaging, radiation techniques, and the incorporation of chemotherapy into standard management.[2,10-13]

Retrospective studies that used RT alone for NPC suggest a correlation between LC and the dose delivered to the tumor.[8,14] One study showed that LC was significantly improved when greater than 67 Gy were delivered to the tumor. In another retrospective series, improved LC was also attributed to improvements in technical accuracy. Because the nasopharynx is surrounded by normal critical structures, accuracy in dose delivery is essential in any dose-escalation studies.

Intensity-modulated RT (IMRT) modulates the radiation beams so that a high dose can be delivered to the tumor while the dose to the normal tissues is reduced.[15] Investigators compared dosimetric plans of IMRT with conventional

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Prospective Randomized Study of Intensity-Modulated Radiotherapy on Salivary Gland Function in Early-Stage Nasopharyngeal Carcinoma Patients

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ABSTRACT

Purpose

This randomized trial compared the rates of delayed xerostomia between two-dimensional radiation therapy (2DRT) and intensity-modulated radiation therapy (IMRT) in the treatment of early-stage nasopharyngeal carcinoma (NPC).

Patients and Methods

Between November 2001 and December 2003, 60 patients with T1-2bN0-1M0 NPC were randomly assigned to receive either IMRT or 2DRT. Primary end point was incidence of observer-rated severe xerostomia at 1 year after treatment based on Radiotherapy Oncology Group /European Organisation for the Research and Treatment of Cancer late radiation morbidity scoring criteria. Parallel assessment with patient-reported outcome, stimulated parotid flow rate (SPFR), and stimulated whole saliva flow rate (SWSFR) were also made.

Results

At 1 year after treatment, patients in IMRT arm had lower incidence of observer-rated severe xerostomia than patients in the 2DRT arm (39.3% *v* 82.1%; $P = .001$), parallel with a higher fractional SPFR (0.90 *v* 0.05; $P < .0001$), and higher fractional SWSFR (0.41 *v* 0.20; $P = .001$). As for patient's subjective feeling, although a trend of improvement in patient-reported outcome was observed after IMRT, recovery was incomplete and there was no significant difference in patient-reported outcome between the two arms.

Conclusion

IMRT is superior to 2DRT in preserving parotid function and results in less severe delayed xerostomia in the treatment of early-stage NPC. Incomplete improvement in patient's subjective xerostomia with parotid-sparing IMRT reflects the need to enhance protection of other salivary glands.

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INTRODUCTION

Incidental irradiation of the parotid glands with consequent long-term xerostomia is a well-recognized problem after radiation therapy for head and neck cancers. A number of studies have shown that intensity-modulated radiation therapy (IMRT) could minimize radiation dose to the parotid glands without compromising tumor dose.[1-4] Nonrandomized clinical studies also suggest that xerostomia was less common after IMRT compared with conventional two-dimensional radiotherapy (2DRT).[5-16]

Salivary function protection is particularly difficult in the treatment of nasopharyngeal carcinoma (NPC) because the clinical target encompasses the parapharyngeal region and upper neck on both sides. Despite the use of IMRT, successful parotid sparing may only be safely performed in early-stage disease, but even so, the degree of benefit over 2DRT is still unclear, short of evidence from a randomized study. The objective of this randomized study was to compare salivary function in early-stage NPC patients after treatment with 2DRT and IMRT.

PATIENTS AND METHODS

Study Population and Design

Patients eligible for accrual had histologically proven NPC (WHO type II/III) with either T1, T2a or unilateral T2b disease (unilateral parapharyngeal extension), and N0 or N1 nodal status (American Joint Committee on Cancer staging classification, 1997). All underwent computed

ORIGINAL ARTICLE

INFLUENCE OF INTENSITY-MODULATED RADIATION THERAPY TECHNIQUE ON XEROSTOMIA AND RELATED QUALITY OF LIFE IN PATIENTS TREATED WITH INTENSITY-MODULATED RADIATION THERAPY FOR NASOPHARYNGEAL CANCER

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Abstract: *Background.* The purpose of this study was to compare 5-field and 7-field intensity-modulated radiation therapy (IMRT) techniques in terms of xerostomia and related quality of life in patients with nasopharyngeal cancer.

Methods. Eight and 23 patients were treated with 5-field (group I) and 7-field (group II) techniques, respectively. The xerostomia was evaluated using the Radiation Therapy Oncology Group (RTOG) scale, stimulated and unstimulated salivary flow (SSF/USF), and xerostomia-related questionnaires (XQs). The assessments were done before and at 3, 6, 12, 18, and 24 months after radiotherapy.

Results. The mean parotid dose was 45.7 Gy and 29.9 Gy and the ≥G3 toxicity at 24 months was 25% and 19% in group I and II, respectively. Sixty-three percent and 93% of patients recovered at least 25% of SSF pretherapy values. The XQ scores of both groups improved over time but more so in group II.

Conclusion. The 7-field technique decreases the mean parotid dose, reducing xerostomia assessed by the RTOG/XQ score. © 2011 Wiley Periodicals, Inc. *Head Neck* **34:** 328–335, 2012

Keywords: nasopharyngeal carcinoma; intensity modulated radiation therapy; parotid sparing; salivary flow; quality of life

Nasopharyngeal cancer, despite its radiosensitivity, has long been a challenge for radiation oncologists because of its proximity to critical normal structures, such as the brain stem, spinal cord, and parotid glands, which restricts the dose levels that are required for local tumor control. Intensity-modulated radiation therapy (IMRT) is an important technical advance that offers the possibility of highly conforming the dose around the target, whereas sparing surrounding normal tissue.[1,2] Due to better target identification and coverage, mono-institutional experiences and a recent multi-institutional study have reported very promising outcomes in the treatment of nasopharyngeal cancer with IMRT.[3–7]

Such results bring particular attention to late toxicities such as xerostomia, even if non–life-threatening xerostomia significantly impacts the patient's quality of life. The lack of saliva negatively influences the ability to chew, swallow, talk, sleep, and general social interaction and well-being of the patient.

Decreasing parotid gland toxicity is particularly challenging in patients with nasopharyngeal cancer despite IMRT. The primary tumor is centrally located and, in a high percentage of patients, presents bilateral nodal involvement in regions that are adjacent to the parotid glands.

Several studies of xerostomia in patients treated for head and neck cancer have been published.

The purpose of this study was to focus on 1 of the most difficult challenges in head and neck cancer, that is, the delivery of curative treatment in patients with nasopharyngeal cancer.

In particular, the article aims to quantify the decrease in salivary gland toxicity based on stimulated salivary flow (SSF) and unstimulated salivary flow (USF), dosimetric data, radiobiological calculation, and quality of life comparing the different IMRT techniques.

MATERIALS AND METHODS

A prospective study to evaluate salivary gland toxicity in patients with nasopharyngeal cancer treated with IMRT was started in March 2003. The study protocol was approved by the institutional ethics committee. Informed consent was obtained from all patients after a detailed explanation of the procedures.

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Review

EXPERT REVIEWS

Outcomes of xerostomia-related quality of life for nasopharyngeal carcinoma treated by IMRT: based on the EORTC QLQ-C30 and H&N35 questionnaires

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The aim of this study was to review the published literature addressing the question of whether intensity-modulated radiotherapy (IMRT) resulted in an improvement of quality of life (QoL), especially xerostomia-related QoL of all nasopharyngeal carcinoma patients as time progressed. A literature search of PubMed, Embase and Google Scholar was performed, only reports containing original data of the QoL scores after treated by IMRT were included. Two independent reviewers extracted information of study design, study population, interventions, outcome measures and conclusions for each article. The inclusion criteria were met by 14 articles covering outcomes based on the questionnaires treated by IMRT. Data from same questionnaires (European Organization of Research and Treatment of Cancer QLQ-C30 and H&N35 questionnaires) were exacted and we analyzed four items (global health status, dry mouth and sticky saliva, swallowing, social eating and social contact), which have a close relationship with xerostomia-related QoL. Results indicated that a maximal deterioration of most QoL scales including global health status developed during treatment or at the end of the treatment course and then followed by a gradual recovery to 1 year, 1–2 years after IMRT, compared with their baseline level, some specific head and neck items, most in the EORTC QLQ H&N35, remained worse for the surviving patients. In conclusion, the published data reasonably support the benefits of IMRT in improving QoL, but xerostomia-related items still had a significantly negative effect in 2 years to impact a survivor's QoL.

Keywords: European Organization of Research and Treatment of Cancer QLQ-C30 and H&N35 questionnaires • intensity-modulated radiotherapy • nasopharyngeal carcinoma • quality of life • xerostomia

Nasopharyngeal carcinoma (NPC) is an endemic disease within specific regions in the world. The highest incidence is found among Southern Chinese (~25–30 per 100,000 persons per year) population, whereas among Caucasians from North American and other Western countries it is sporadic, with the incidence under 1 per 100,000 persons per year [1]. Unlike other head and neck carcinomas (HNC), NPC is seen in a relatively young age group and has a close relationship with the Epstein–Barr virus. As the tumor is located in close proximity to base of the skull and important vital structures, the primary treatment of NPC is radiotherapy (RT) alone or combined with chemotherapy, depending on stage of the disease and surgery is generally not an initial option [2].

Over the past 20 years, intensity-modulated radiation therapy (IMRT) has been implemented for routine clinical use. With multiple beams from different directions in which at least some of the beams are intensity-modulated, each beam intentionally delivers a non-uniform

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Tinjauan Pustaka

EFEK DASAR RADIASI PADA JARINGAN

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Informasi Artikel

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Abstrak / Abstract

Dalam pengobatan kanker menggunakan radioterapi, paparan radiasi ke jaringan normal harus menjadi pertimbangan karena efek samping kemudian akan membatasi pengobatan kanker. Efek atau respon jaringan normal terhadap radiasi dapat lebih mudah dipahami dengan mengetahui perbedaan tipe organisasi/struktur jaringan. Pada jaringan, terdapat mekanisme homeostasis sebagai respon kehilangan sel akibat cedera. Homeostasis menjamin repopulasi kelompok sel matur fungsional yang bertanggung jawab pada fungsi suatu organ. Sel matur fungsional relatif tidak terpengaruh oleh radiasi dan akan mati sesuai usia biologisnya. Manifestasi klinis timbul saat terjadi kegagalan repopulasi kelompok sel ini oleh sel pada lapisan prekusor. Efek radiasi pada beberapa jaringan tubuh secara umum dapat dijelaskan dengan prinsip yang sama.

Kata kunci : paparan radiasi, jaringan normal, homeostasis, sel matur, sel prekusor

In cancer treatment by radiotherapy, radiation exposure to normal tissue should be a consideration since its side effects are the major factors which limit radiation therapy. Normal tissue response to radiation can be more easily comprehended by knowing the various type of organization/structure of the tissue. In tissue, there is homoestatic mechanim of cell loss in response to injury. Homeostatic mechanism ensures repopulation of functional mature cells which are responsible for function of an organ. Fungsional mature cells are relatively unaffected by radiation and will die according to their biological age. Clinical manifestation occurs when precursor cells fail to repopulate. Radiation effects in some tissues of the body can generally be described with the same principle.

Key word: radiation exposure, normal tissue, homeostatic, mature cell, precursor cell

Pendahuluan

Saat ini kanker sebagai salah satu penyebab kematian di seluruh dunia. Tujuan pengobatan kanker adalah eradikasi kelompok sel kanker (tumor) secara utuh. Prinsip pengobatan ini dapat dipenuhi baik dengan tindakan operasi, pemberian kemoterapi, dan radiasi, atau dengan kombinasi diantara modalitas tersebut.

Modalitas radioterapi, prinsip utamanya yaitu menggunakan radiasi pengion untuk merusak materi genetik dari sel kanker (DNA), menyebabkan sel mengalami kematian atau kehilangan kemampuan proliferasinya. Dalam penggunaan radioterapi sebagai modalitas pengobatan, paparan radiasi ke jaringan normal harus menjadi pertimbangan. Seluruh bentuk pengobatan genotoksik berefek ke jaringan normal dengan derajat kerusakan yang bervariasi, dan efek samping inilah yang kemudian dapat membatasi pengobatan kanker.[1,2]

Respon Radiasi pada Tingkat Sel

Jaringan normal pada tingkat sel lebih terorganisir dan mempunyai kemampuan memperbaiki kerusakan dari radiasi, sedang kebanyakan sel kanker memiliki cacat pada sistem regulasi sel, pada umumnya mengakibatkan gangguan repair, dan mengakumulasikan kerusakan tersebut. Salah satu target utama dari radiasi adalah DNA pada inti sel, yang kemungkinan terjadi berupa *single strand brake* atau *double strand brake*.[3] Kerusakan DNA memicu aktivasi mekanisme tertentu dari siklus sel. Salah satunya adalah aktivasi p-53, yang kemudian menginduksi mekanisme tertahannya siklus sel atau mekanisme apoptosis.[1]

Pengaruh perawatan radioterapi pada pasien kanker nasofaring terhadap perubahan saliva dan kelenjar saliva

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