

**PATTERN OF PRACTICE OF RADICAL RADIATION THERAPY FOR
OROPHARYNGEAL CANCERS: A RETROSPECTIVE REVIEW
FROM JANUARY 2009 TO DECEMBER 2012**

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A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfilment of the requirement for the degree of
Masters of Medicine in the branch of Radiation Oncology

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DECLARATION

I, Yastira Ramdas declare that this research report is my own work. It is being submitted for the degree of Masters of Medicine in Radiation Oncology in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

.....

Yastira Ramdas

Signed aton the.....day of2015

DEDICATION

I dedicate this dissertation to my family, who always encouraged me to keep my dreams alive, helped me understand to achieve anything requires faith and belief in oneself, vision, hard work, determination and dedication.

Your love, support and guidance will always allow me success.

For my guiding angel, my shining star from above, my late Father, Chithrangath George Ramdas (1949-2009). My inspiration, my mother, Pricilla Devi Ramdas. My believer, my brother, Danvir Ramdas.

And my greatest strength, who always provided me with endless support and the will to continue despite any adversity, my amazing husband Rinay Bhowanath.

ABSTRACT

Title

Pattern of practice of Radical Radiation Therapy of Oropharyngeal Cancer: A retrospective review from January 2009 to December 2012.

Background

Radiation therapy is a highly effective method of treating oropharyngeal carcinoma, either as a single modality treatment with concurrent chemotherapy or as an adjuvant treatment after surgical resection. There exists an association with human papillomavirus (HPV) and oropharyngeal cancer, dividing oropharyngeal carcinoma into HPV positive oropharyngeal carcinoma and HPV negative oropharyngeal carcinoma. Overall survival has been analysed in these two groups and have been shown to be 80-95% for HPV positive oropharyngeal carcinomas and 57-62% in HPV negative subgroup at 3 years respectively. This retrospective review was intended to analyse patient response to treatment, overall survival, local disease free survival and the difference between HPV positive oropharyngeal carcinoma and HPV negative oropharyngeal carcinoma at Charlotte Maxeke Johannesburg Academic Hospital: Department of Radiation Oncology.

Patients and methods

A retrospective descriptive study was conducted on patients having received radical radiation therapy, with or without chemotherapy, from January 2009 to December 2012 with a histologically confirmed diagnosis of squamous cell carcinoma involving oropharyngeal sites

only. The information obtained from records of forty-eight patients was captured on the prescribed data sheets designed for this study.

Results

Forty-eight eligible patients were accrued within this retrospective study. The median age of the patient group was 56 years (range 32-78) and comprised of 10 females and 38 males. The performance status was mainly Eastern Cooperative Oncology Group (ECOG) 1 (83%). The radiation therapy dose was within the range 60-70Gy, with majority patients completing 70 Gy (65%). Concurrent chemoradiation was given in 59% of patient group (28 patients). The most common site being the base of tongue (60%), followed by tonsil (36%), soft palate (2%) and posterior pharyngeal wall (2%). Eighty five percent of patients were stage IV oropharyngeal carcinoma. Only 6% of patients were tested for HPV-DNA PCR, and all were HPV positive. A total of 79% patients had a positive smoking history and 50% consumed alcohol regularly. Fifty six percent of patients tested negative for HIV, 14.6% tested positive for HIV and 29.3% had unknown HIV status.

At the time of the analyses (March 2014) only 7 (15%) of patients were alive. The 2 year overall survival was 13%, the local disease free survival at 2 years was 59%. None of the prognostic factors were predictive of overall survival using univariate and multivariate analysis.

Conclusion

Majority of patients present in stage IV lesions with commonest sites of involvement being Base of Tongue. The local disease free survival of 2 years was 59% and the overall survival of 15%. There was no impact of prognostic factors studied on overall survival.

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- To all our patients, without whom medicine and research would not be possible.

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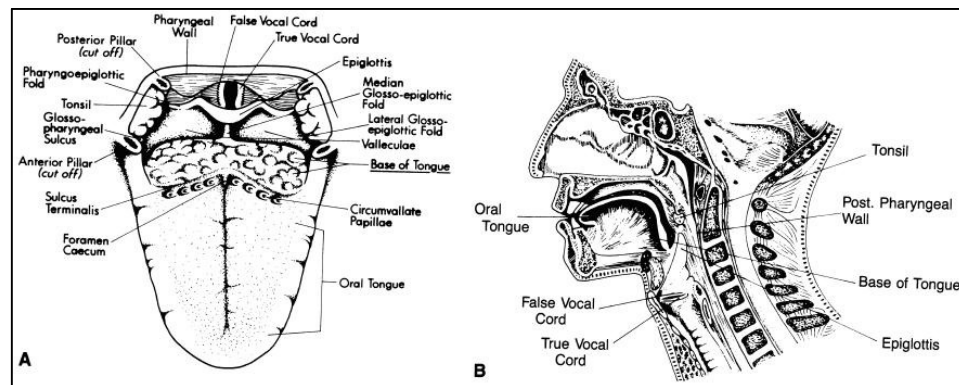
AJCC	American Joint Committee on Cancer
BOT	Base of tongue
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
DNA	Deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment Of Cancer
Gy	Gray (unit of radiation)
HIV	Human immunodeficiency virus
HPV	Human Papillomavirus
FDA	Food and Drug Administration
IMRT	Intensity modulated radiation therapy
PCR	Polymerase chain reaction
RB	Retinoblastoma
RTOG	Radiation Therapy Oncology Group
SCC	Squamous cell carcinoma
UICC	Union for International Cancer Control
2D	Two-dimensional
3DCRT	Three-dimensional radiation therapy
EGFR	Epidermal Growth Factor Receptor

1.0 INTRODUCTION

1.1 Background

A subset of tumours involving the mucosa of the base of tongue (BOT), palatine tonsils, soft palate and the posterior pharyngeal wall collectively make up oropharyngeal cancers^[1,2]. The proximal boundary is at the edge of the hard palate and it is distally bound by valleculae and hyoid bone as illustrated in Figure 1.1^[3]

Figure 1.1 The anatomy of the oropharynx^[3]



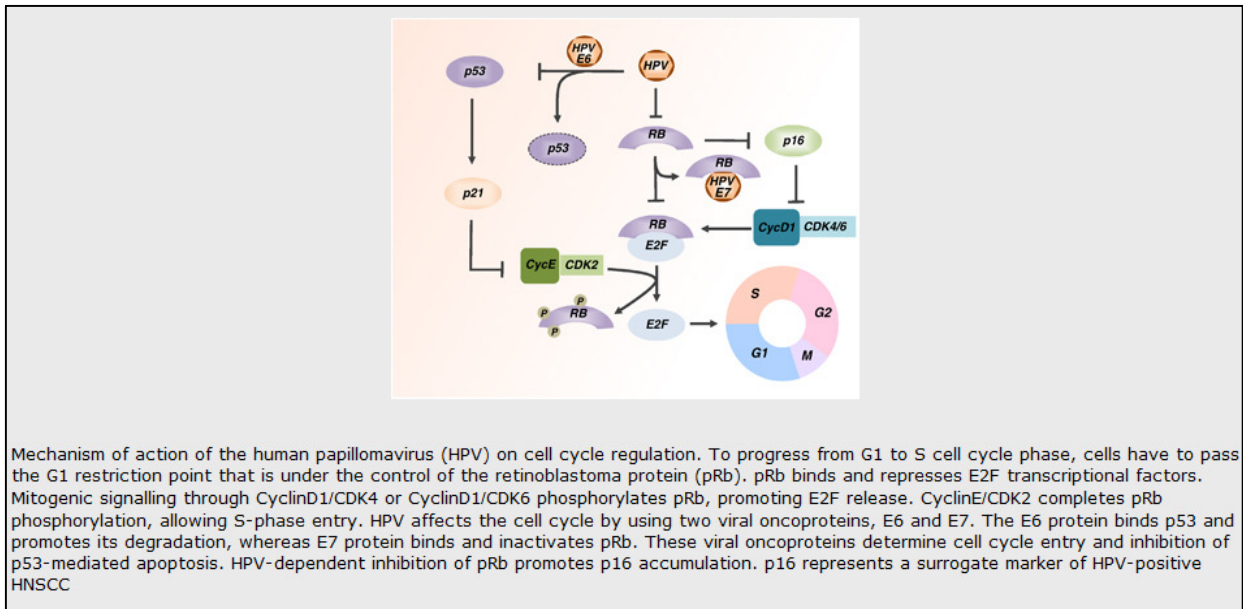
Worldwide squamous cell carcinoma (SCC) of the oropharynx is the twenty-second most common cancer^[4], with an annual incidence of 8-10 per 100000 population^[5].

Approximately 300-350 new cancers of the head and neck region are seen in the Department of Radiation Oncology at the Charlotte Maxeke Johannesburg Academic Hospital every year. Oropharyngeal cancers comprise approximately 2% of newly diagnosed head and neck cancers per annum.

HPV-related rates rose rapidly among the white men born since the mid-1940s, tripling among those aged 25-44 and recently surpassing the black male rate.^[6]

1.2 Aetiology

Figure 1.2 Mechanism of action of HPV on cell cycle regulation ^[7]



More than 80% of oropharyngeal cancers have been associated with HPV ^[8-11].

This virus is generally associated with changes in sexual practice such as increased number of sexual partners including oral sex partners, young age first sexual intercourse, human immunodeficiency virus infection (HIV) and repeated sexually transmitted diseases. HPV is a small non-enveloped Deoxyribonucleic acid (DNA) virus, which has high affinity to affect the skin and mucous membrane in humans. There are over 100 subtypes of HPV; the type associated with oropharyngeal carcinoma most notably is HPV type 16. The HPV contains two oncogenes E6 and E7 that are key factors in the carcinogenesis process as illustrated in Figure 1.2 ^[11, 12]. These oncogenes inactivate two important tumour suppressor genes, P53 and Retinoblastoma (RB), which regulate cell cycle growth and proliferation ^[11, 12]. Degradation (P53) and inactivation (RB) of tumour suppressor genes lead to genomic instability and ultimately HPV induced

oropharyngeal carcinoma ^[11, 12]. Modern trend of HPV positive oropharyngeal cancers are in the white male, younger age, higher socio-economic status, who demonstrate little or no history of smoking and or alcohol use.

Historically, tobacco smoking and alcohol use are long known well defined risk factors for HPV negative oropharyngeal cancers. These two substances either individually or together (synergistic effect) contribute to the field cancerization effect in the oropharynx. This cancerization effect is not seen in HPV positive oropharyngeal carcinoma. Cigarette smoking contains mutagens and carcinogens, which may act as promoters in the cancer process. In a separate pooled analysis, low intensity tobacco use over a longer period yielded a greater risk factor than high intensity use over a shortened period ^[13]. With alcohol use, this was reversed, with high intensity and shorter duration of its use-increased risk of acquiring cancer ^[13]. The consumption of alcohol and cigarette smoking has declined over the past several decades, which allowed a decrease risk of head and neck cancers and subsequently an expected decrease in HPV negative oropharyngeal cancers ^[14, 15]. Poor oral hygiene coupled with a low fruit and vegetable diets were associated with the development of oropharyngeal cancers.

HPV positive and HPV negative oropharyngeal carcinomas have different clinical, pathological, and molecular features that distinguish them from each other.

Table 1.1 Difference between HPV-positive and HPV-negative SCC ^[1, 12]

Characteristic	HPV-positive	HPV-negative
Age	Younger	Older
Socio-economic status	High	Low
Anatomic site	Tonsil and BOT	All site
Risk Factors	Sexual behaviour	Alcohol and tobacco use
Histology	Non-keratinized, basaloid	Keratinized
Molecular/pathological change ^[16,17]	TP53 wild type, p16 positive, No Epidermal Growth Factor Receptor (EGFR) over over-expressed.	TP53 mutated High EGFR expression
Survival	Improved	Worse
Second primary tumours/field cancerization	Negative	Positive

1.3 Natural History

Oropharyngeal cancers develop in the posterior aspect of the mouth. The subsites are the tonsillar complex, BOT, soft palate and the pharyngeal wall.

HPV-positive tumours, typically present with smaller primary tumours and a more advanced lymph-node stage, with the lymph node often having a cystic appearance ^[1, 18, 19].

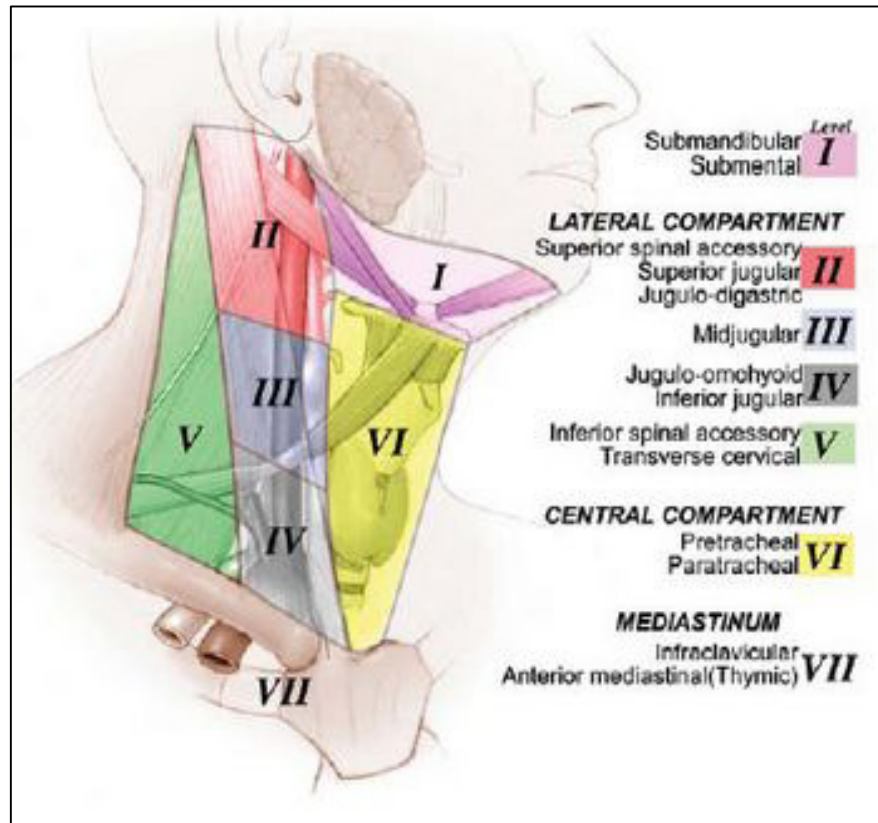
HPV-negative cancers have variable presentation. Tumours at the BOT present at a more advanced stage, with a high propensity to nodal spread and are often poorly differentiated ^[20]. Thirty to fifty percent of patients will present with

uncontrolled loco-regional cancers and will progress to the development of distant metastasis ^[21]. Common presenting symptoms are persistent sore throat and dysphagia.

A large proportion of oropharyngeal cancers occur in the tonsillar complex, initially asymptomatic, with more severe late symptoms of otalgia, bleeding, decreased mobility of oral tongue and trismus. These findings are suggestive of advanced disease.

Pharyngeal wall and soft palate tumours are relatively rare tumours.

Figure 1.3 Lymph node levels of the Neck ^[22]



The primary route of spread for oropharyngeal carcinomas are through direct extension, lymphatic spread and less commonly haematogenous metastases ^[20].

The most common lymph-node metastasis in oropharynx is ipsilateral level II ^[20] as illustrated in Figure 1.3^[22]. Lymph-node metastasis is related to primary tumour size and location. Nodal staging for oropharyngeal cancer is illustrated in Appendix 8.7

Distant metastatic spread is relatively uncommon, with lung parenchyma being the most common site, followed by osseous and hepatic metastases ^[20].

1.4 Preventative measures

Recently, interest has been growing for the development of a vaccine due to viral causation in the development of oropharyngeal cancers. Vaccines targeting the high-risk subtype of HPV (types 16 and 18) and the low risk type (type 6 and 11) are being developed. Two HPV vaccines have been approved by the Food and Drug Administration (FDA) for clinical use. Both are available in South Africa, Cervarix (bivalent vaccine, directed against HPV type 16 and 18) and Gardasil (Quadrivalent vaccine Merck, directed against HPV type 6, 11, 16 and 18) ^[23].

Other malignancies related to HPV namely cervical cancer for which the HPV vaccine was approved for the use in South Africa in 2008 ^[23].

In USA, the Advisory committee on Immunization Practises recommends the routine vaccination of all females aged 11-12 years; the vaccination of unvaccinated women between 13 years – 26 years (South Africa 9-26 years) and since 2011 the routine vaccination of boys ^[24,25].

It is envisaged that this vaccination will decrease the rate of HPV related premalignant lesions and cancers (including oropharyngeal cancers).

1.5 Staging

Staging of oropharyngeal carcinoma is based on the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) system. This clinical staging was based on available history, physical examination, endoscopic, and radiographic data.

Staging of oropharyngeal carcinomas are described in detail in Appendix 8.1.

1.6 Management of oropharyngeal cancers

The main aim for management of oropharyngeal cancer is the preservation of organ function with minimal toxicity. Most patients presenting at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) have advanced disease and are not candidates for surgery.

Based on the AJCC staging system patients are put into different stages ranging from, locally confined disease (stage I and II tumours) which are considered early stage disease, and locally advanced disease (stage III and IV) non-metastatic disease. This staging helps guide treatment decisions.

For all subsites, early stage disease are generally treated with a single modality, either radiation therapy or surgery. Locally advanced disease generally requires a multi-modality approach. This can be either:

- a) Surgery followed by radiation therapy with or without chemotherapy based on pathological risk factors or
- b) Radiation therapy given with chemotherapy.

Radiation can be given alone, as a definitive therapy, without chemotherapy due to medical co-morbidities, low CD4 count in Human immunodeficiency virus (HIV) positive patient or patient refusal.

The most common site and stage of oropharyngeal cancer seen was the BOT, stage IV. The management of stage IV BOT at CMJAH is concurrent chemoradiation. These patients are planned on virtual simulation. The planning process includes positioning of patient, placement of field borders, beam

arrangements with beam modifiers and dose prescription. Typical planning of a patient are as described below.

POSITIONING:

Patient's simulation and treat position is supine, in a mask and head on a headrest. The spine is straightened. The shoulders are immobilized by straps. The chin extended. The patient is CT scanned with 5mm slices from the base of skull to level of the carina.

BEAM ARRANGEMENTS:

Radiation therapy is delivered via a three field technique; through isocentric opposed-lateral fields (large fields) matched to a lower neck portal (anterior neck field).

Large fields (bilateral face and neck) are lateral parallel opposed photon fields to treat the primary tumour and the upper neck nodes.

Multi-leaf collimators are used to shape the field borders depending on the site lesion, and block out some of the oral cavity and the base of skull, including brain.

This field is treated up to 40Gy. Then an off cord field is planned, here all the field borders are the same except for the posterior border that moves completely

off the spinal cord, to around the anterior 1/3rd vertebral body for all lesion except post pharyngeal wall where it extends past 1/3rd vertebra. This is done to make sure the dose to the spinal cord is within radiation tolerance of the spinal cord. Off cord are treated to a further 30Gy.

Wedge pair fields (beam modifiers) are used in the large fields and in the off cord fields. The anterior neck field is usually used for irradiating the mid, lower neck and supraclavicular nodes. The superior border is matched to the inferior border of the lateral portals at the skin using asymmetric jaws. Inferior border is 2 cm below the clavicles. The lateral borders include the medial two-thirds of the clavicles.

A midline lead block is used from the beginning of treatment of the anterior neck field to block out spine. The block extends 1cm above the superior border of the field and 1cm below the inferior border of the field for divergence and to prevent leakage. The width of the block is 2cm.

RIGHT AND LEFT POSTERIOR NECK FIELDS:

A clinical mark is done to the patient while on the treatment bed. Electrons are used to treat this. A strip of skin is left to prevent oedema. The depths of the lymph nodes on each side are used to calculate the energy of the electron beam.

The large fields, off-cords and anterior neck fields are treated with 6MV photons.

1.7 Prognosis

Several studies have shown an over-all survival rate of 80-95% for HPV positive patients compared to 57-62% for HPV negative subgroup of oropharyngeal cancer at 3 years respectively ^[26].

The rate of curability in these patients depends on the extent of the primary tumour (stage and specific site). BOT cancer has a local control rate of approximately 85% for early lesions ^[3].

Tonsil carcinoma in a retrospective review displayed survival rates of 89% (stage I), 91% (stage II), 79% (stage III) and 52% (stage IV) ^[27].

In a retrospective review with SCC of the soft palate, the over-all survival was 80% at 2 years and dropped to 67% at 5 years ^[28].

Definitive radiation therapy given to SCC of pharyngeal wall resulted in cause specific survival rates at 89 % (stage I), 88 % (stage II), 44% (stage III) and 34 % (stage IV) ^[29].

1.8 Rationale for this study

At the CMJAH, approximately 80-85% of patients present with advanced disease and in a poor general condition (anaemia, low serum protein, low ECOG and poor general health). These patients are offered palliative radiation therapy and best supportive care.

The remaining 15-20% of patients are suitable for radical/curative treatment, either by surgery followed by adjuvant radiation therapy with or without

chemotherapy or definitive radiation therapy with or without chemotherapy. The radiation therapy dose ranges from 60-70Gy in 30-35 fractions given 5 days a week once daily treatments. The chemotherapy schedule used in the department of Radiation Oncology at CMJAH is Cisplatin 70mg/m² given every 21 days.

The objective of this study was to assess if the patients presented at CMJAH were able to receive the internationally recommended doses of radiation and chemotherapy and if the survival rates match those presented internationally.

With the emergence of HPV as a causative agent in oropharyngeal cancers and its excellent response to treatment, an additional outcome of this study was to assess a similar outcome and percentage positivity for HPV.

2.0 LITERATURE REVIEW

2.1 Radiation therapy treatment

Radiation therapy is a highly effective treatment of oropharyngeal cancers, as a single modality, with concurrent chemotherapy or as an adjuvant post-surgery.

It has emerged as the standard of care in definitive treatment of oropharyngeal carcinoma ^[30].

There has been significant evolution with radiation therapy in oropharyngeal cancers from two-dimensional treatment planning (2D), where standard treatment field delineation was based on bony landmarks, to more conformal techniques that based treatment planning on CT scan and a three-dimensional radiation therapy (3DCRT) to more modern intensity modulated radiation therapy (IMRT).

Much of the data regarding radiation therapy comes from trials using 2D conventional treatment. Optimal doses and fractionation schedules have largely been tested.

To best understand total dose and fractionation scheme, The European Organization for Research and Treatment of Cancer (EORTC) evaluated benefits of hyper fractionation (80.5Gy using 1.15Gy/fraction twice daily) compared with conventional fractionation (70Gy using 1.8Gy/fraction once daily) in the EORTC 22791 trial. The patients treated with hyper fractionation had improved loco-regional control (5 years, 59% vs. 40%; $P=0.02$). Additionally there was a trend toward improved over-all survival ($p=0.08$) particularly in stage III ^[31].

To further investigate optimal fractionation scheme, the Radiation Therapy Oncology Group (RTOG) enrolled patients on the RTOG 90-03, which, compared four different fractionation regimens:

- a) Conventional fractionation (70Gy using 2Gy/fraction once daily)
- b) Split course accelerated fractionation (67.2Gy using 1.6Gy/fraction twice daily with a two week break after 38,4Gy)
- c) Concomitant boost fractionation (72Gy using 1.8Gy/fraction in the mornings and 1.5Gy/fraction boost as a second daily treatment during the last 12days)
- d) Hyper fractionation (81.6Gy using 1.2Gy/fraction twice-daily).

Of the 1073 patients enrolled, 60% had oropharyngeal cancer. Patients treated with pure hyper fractionation and concomitant boost technique (c & d) had improved loco regional control and a trend towards improved Disease Free Survival (DFS) (37,6% vs. 31,7% and 39,3% vs. 31,7%), compared to the other two arms (conventional and split course); there were no differences in over-all survival. These improvements were associated with increased acute (mucositis and oesophagitis) and late toxicities (radiation myelitis) in all three accelerated arms ^[32].

A study done in the Danish Head and Neck Cancer Study Group compared the use of standard 5 fractions/week fractionation and accelerated 6 fractions/week fractionation; patients were treated to a dose of 66-68Gy at 2Gy/fraction. Patients treated with 6 fractions/week had improved 5 year rates of loco regional control

(70% vs. 60%; $p=0,0005$) and disease specific survival (73% vs. 66%; $p=0,01$), however there was no difference in overall survival ^[33].

From the studies mentioned above, altered fractionation schedule has a significant benefit in SCC, but with associated severe toxicities when delivered with conventional fractionation.

With advances in radiation therapy, a more conformal way of delivering radiation therapy with increased sparing of normal tissue and the prevention on late complications saw the development of IMRT. Several recent trials have been performed with IMRT, looking at loco regional control, functional outcome/toxicity and its role when given with chemotherapy. Data from these studies showed excellent loco regional control rates and improved toxicity outcomes as compared with conventional methods ^[34, 35]. The most notable outcome with IMRT was statistically significant reduction in xerostomia and improvements in quality of life ^[36].

At CMJAH, oropharyngeal cancers are treated with virtual simulation. This is similar to 2.5D planning and treatment where CT scan is being used for planning. Radiation doses used for this radical treatment range from 60Gy-70Gy in 30-35 fractions.

2.2 Chemotherapy

For locally advanced oropharyngeal cancers, concurrent chemoradiation is the standard of care, which is based on results of the meta-analysis of Chemotherapy in Head and Neck cancers (MACH-HC). Data was collected on greater than 16000 patients with head and neck cancers treated from 1965 to 2000 as part of 87 randomized trials; individual patient data were assembled and analysed with regards to the benefit of chemotherapy (neoadjuvant, concurrent and adjuvant). The common primary site was oropharynx (37% of all patients). The analysis showed a significant benefit in over-all survival with the use of chemotherapy, with a corresponding hazard ratio of death of 0,88 ($p < 0,0001$) and an absolute benefit of chemotherapy at 5 years of 4,5%. The timing of chemotherapy was also analysed, and concurrent chemotherapy was found to be superior to neoadjuvant or adjuvant chemotherapy ^[37].

Cisplatin based chemotherapy demonstrated most significant benefit when given concurrently, due to its potent radiosensitizing effect.

Chemoradiation has emerged as standard of care in locally advanced SCC cancer of head and neck; however, it is associated with increased toxicity. An analysis of three RTOG trials (RTOG 91-11, 97-03 and 99-14) Machtay and colleagues ^[38] noted that 43% of patients treated with concurrent chemoradiation developed severe late toxicities. The French Groupe d' Oncologies Radiotherapie Tete et Cou (GORTEC) trial ^[39] patients treated with concurrent chemoradiation had a rate of severe late toxicity (grade 3 and 4) of 56% vs. 30% in radiation only arm

This data has shown an increased efficacy with concurrent chemotherapy, at the cost of increased acute and late toxicities.

2.3 Surgery

The historical approach to surgery for oropharyngeal carcinoma involved extensive surgery at the cost of poor cosmesis and quality of life due to the functional impairment. Majority of the patients that had surgery done in the study group would have ultimately required radiation with or without chemotherapy. Indications for post-operative radiation therapy are close margins, T3 or T4 primary cancer, perineural invasion, multiple positive lymph nodes, and lymphovascular space invasion. Indications for postoperative chemotherapy are positive margins and extra capsular extension.

There has been an evolution in surgical techniques with the development of computer-assisted surgical technique ^[40].

Although, improvement of surgical techniques have been made the future of treatment of oropharyngeal cancer is still in radiation and chemoradiation.

3.0 PATIENTS AND METHODS

This analysis was a retrospective descriptive study involving the review of patient case records. It was undertaken at the Department of Radiation Oncology at CMJAH. The Protocol for the study was approved by the Postgraduate Committee of the Department of Radiation Sciences, Faculty of Health Sciences, University of Witwatersrand (Appendix 8.3). The ethical clearance was obtained from the Human Research Ethics Committee at the University of Witwatersrand (Clearance certificate number M140234) (Appendix 8.5).

3.1 Patient characteristics

A retrospective study of patients with the diagnosis of SCC of the oropharynx was conducted at CMJAH. Ninety oropharyngeal cancer patients received treatment at the head and neck clinic over a 4-year period (1 January 2009 to 31 December 2012). Of this patient group, only 48 patients were candidates for radical/curative radiation therapy and therefore the analysis was limited to these 48 patients. Permission to view these files was obtained from the Chief Executive Officer (CEO) of CMJAH (Appendix 8.3).

All patients fulfilled the following inclusion criteria:

- Oropharyngeal cancers (Tonsil, BOT, Soft palate, Pharyngeal wall) only.
- Age of patients >18 years old.
- SCC histology only.
- Patients accepted for radical/curative treatment.

Exclusion Criteria:

- Other head and neck tumour sites (Nasopharynx, Hypopharynx, and oral cavity).
- Distant metastasis.
- Histology other than Squamous carcinoma

The following information was, obtained from the files and captured on a data capture sheet/performa (Appendix 8.6):

- Demographics: Age, gender and race.
- Date of first consultation
- Site of tumour with the oropharynx
- Histological subtype
- Stage of disease
- HIV status
- HPV status
- Smoking history
- Alcohol history
- ECOG status (Appendix 8.2)
- Date of start and completion of treatment
- Management: dose of radiation therapy received, chemotherapy history
- Response to treatment
- Status patient last seen

This data were entered into a Microsoft Excel 2013 spreadsheet.

Table 3.1 Patient and tumour characteristics

Characteristics	Number patients (n=48)
Age Group	
31-40 years	2 (4%)
41-50 years	8 (17%)
51-60 years	22 (46%)
61-70 years	12 (25%)
71-80 years	4 (8%)
Mean	56.23 years
Median	57 years
Tumour site	
BOT	29 (60%)
Tonsil	17 (36%)
Soft palate	1 (2%)
Pharyngeal wall	1(2%)
Tumour stage	
Stage I	0
Stage II	1 (2%)
Stage III	6 (13%)
Stage IV	41 (85%)
HIV status	
Positive	7 (14,6%)
Negative	27 (56,3%)
Unknown	14 (29,2%)
HPV status	
Positive	3 (6%)
Negative	0
Unknown	45 (94%)
Smoking	
Yes	38 (79%)
No	4 (8%)
Ex-smoker	6 (13%)
Alcohol	
Yes	24 (50%)
No	11 (23%)
Ex-alcohol consumer	13 (27%)
ECOG performance status	
0	0 (0%)
1	40 (83%)
2	7 (15%)
3	1 (2%)

All 48 patients received radical radiation therapy with doses ranging from 60-70Gy. Some patients received Cisplatin 70mg/m² concurrent chemoradiation. Patient selection for concurrent chemoradiation was based on the tumour stage, ECOG status, the creatinine clearance rate, and the overall general condition of patient.

These patients were monitored during treatment as well as routinely post-treatment.

Table 3.2 Treatment characteristics

Characteristic	Number of patients (n=48)
Radiation therapy	
60Gy	1 (2%)
62Gy	1 (2%)
64Gy	1 (2%)
66Gy	12 (25%)
68Gy	2 (4%)
70Gy	31 (65%)
Chemotherapy	
None	19 (40%)
Unknown	1 (2%)
1 cycles	16 (33%)
2 cycles	12 (25%)

Table 3.1 outlines the patient and tumour characteristics whereas table 3.2 shows patient treatment characteristics.

3.2 Statistical analysis

Statistical analysis was done using SPSS 21 package, a computerised statistical program. The mean values of the parameters such as age were compared using paired sample t-tests. The local control and disease free survival was calculated from the 1st day of treatment to the 1st day of local failure.

The over-all survival calculated from the 1st day of treatment to the date of death or last day of follow up, using the Kaplan Meier analysis and long rank test.

Multivariate analysis using the Cox regression model was performed to assess the significance of various parameters such as median/mean age, sex, stage of disease, site of lesion on the disease free and overall survival.

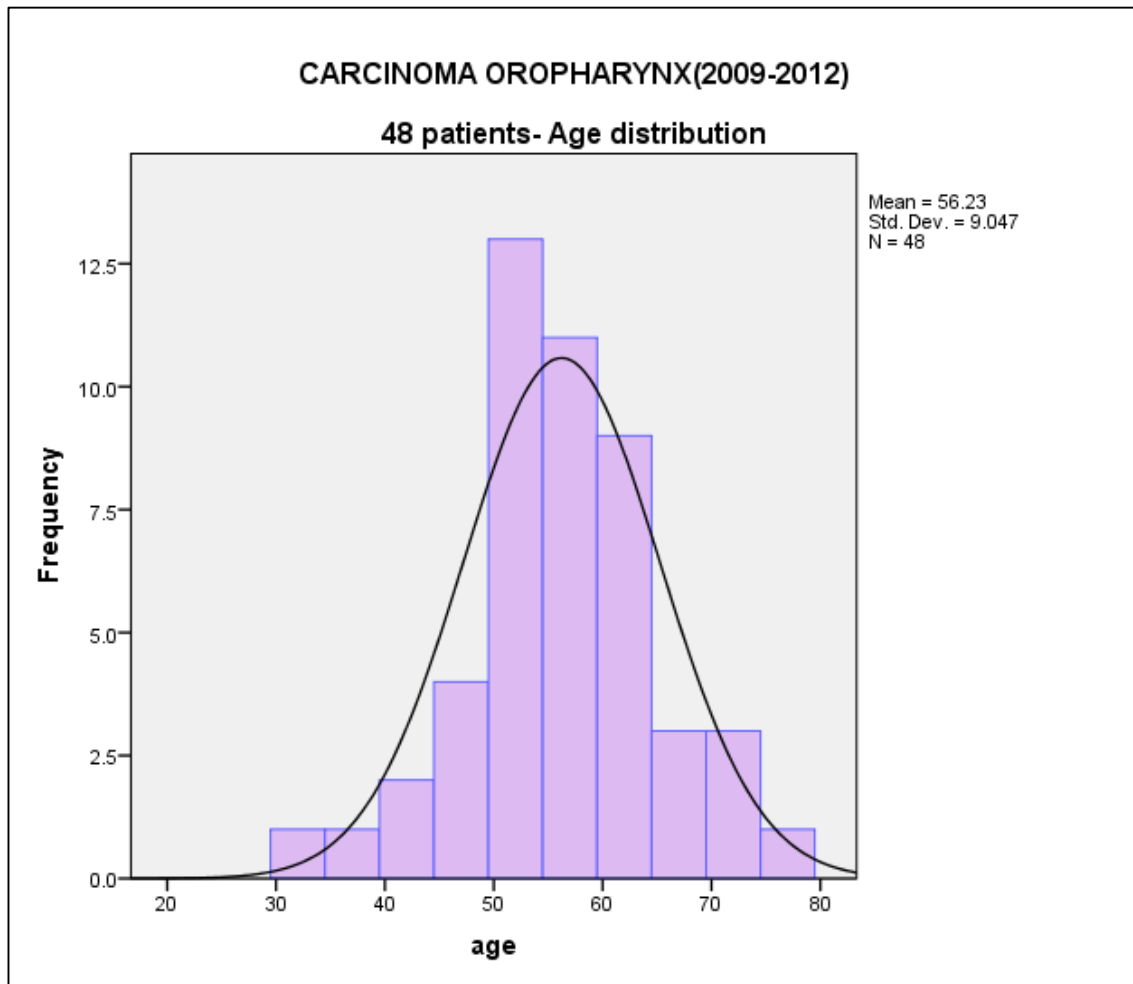
3.3 Beam Arrangements

Radiation therapy is delivered via a three field technique; through isocentric opposed-lateral fields (large fields) matched to a lower neck portal (anterior neck field).

4.0 RESULTS

A total of 48 patients were retrospectively analysed in this study, of which 38 were males and 10 were female. The race/ethnicity was not analysed in this study. The median age was 56 years (range: 32 – 78 years).

Figure 4.1 Patient age distribution

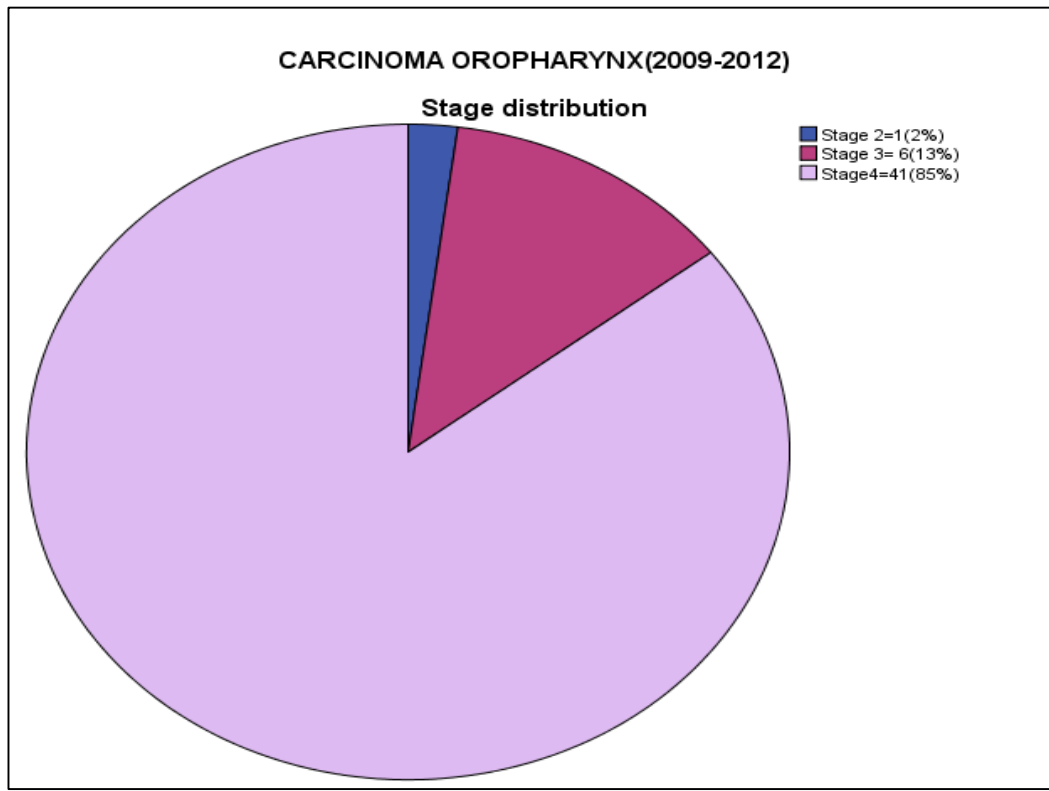


As illustrated in Figure 4.1, majority of patients in this study were between the ages of 50-65 years.

The bulk of patients in this study had good ECOG performance score of 1 (83%) and 2 (15%). Only one patient had an ECOG performance score of 3 and was included in this radical treatment group of patients. 79% of the patients were current smokers and 50% of patients regularly consumed alcohol.

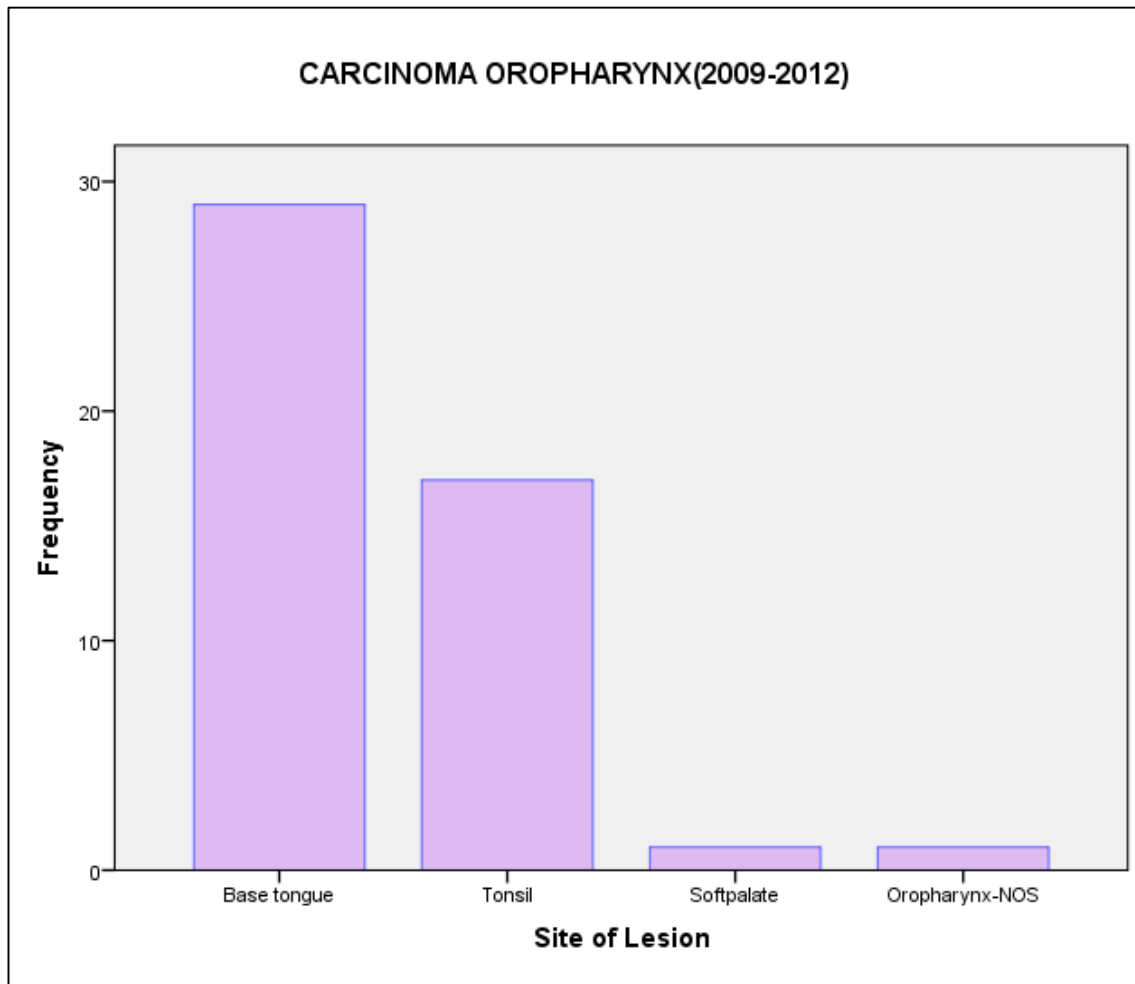
Gender had no prognostic significance when analyzed on both multivariate and univariate analysis.

Figure 4.2 Patient cancer stage distributions



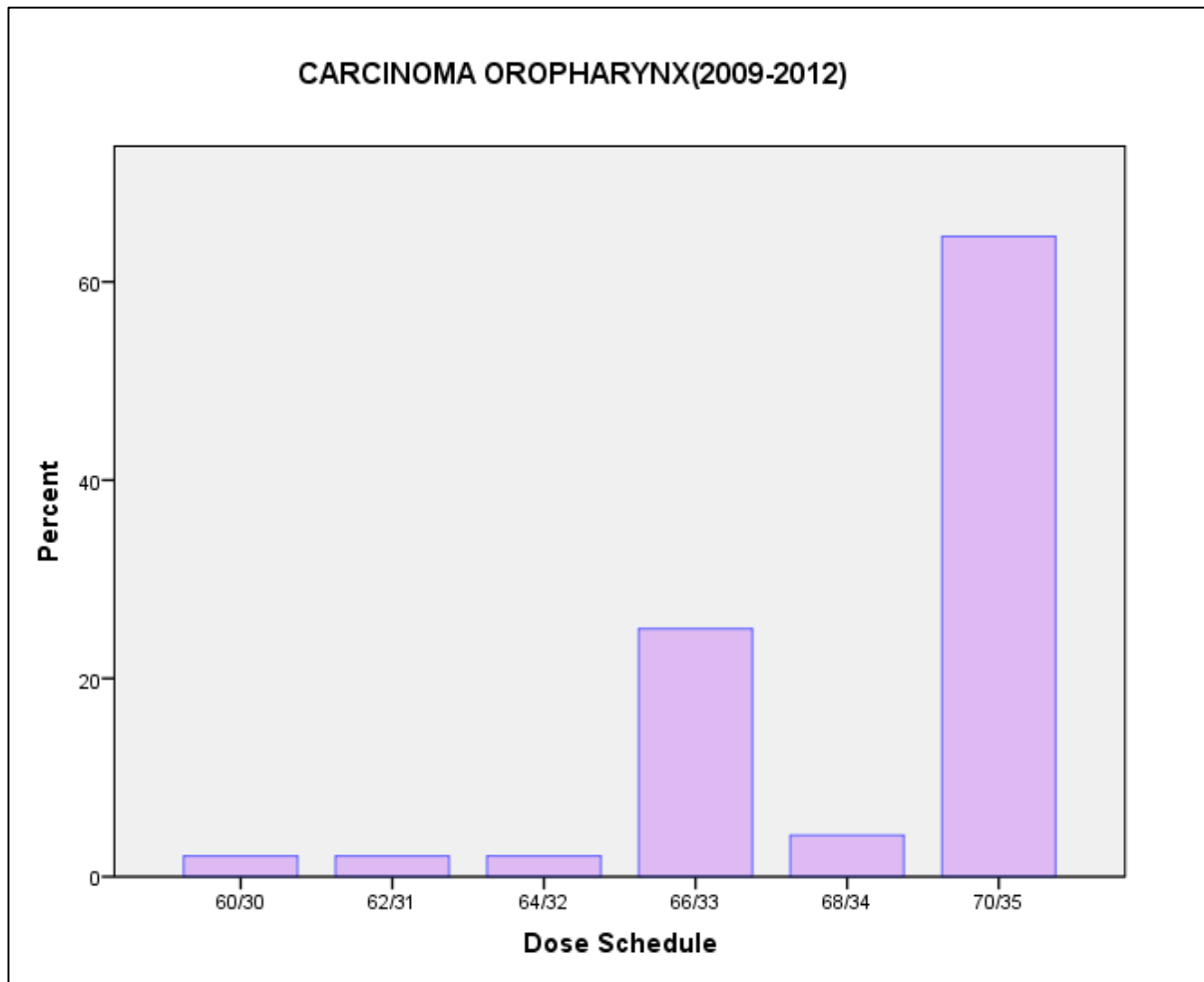
The patients in this study were staged according to the AJCC/UICC system. They were grouped according to their tumour extent (T), lymph-node status (N) and presence or absence of distant metastasis (M). Most of the patients in the analysis had locally advanced primary tumour, with nodal disease, categorizing them as IV shown in Figure 4.2.

Figure 4.3 Patient Lesion sites



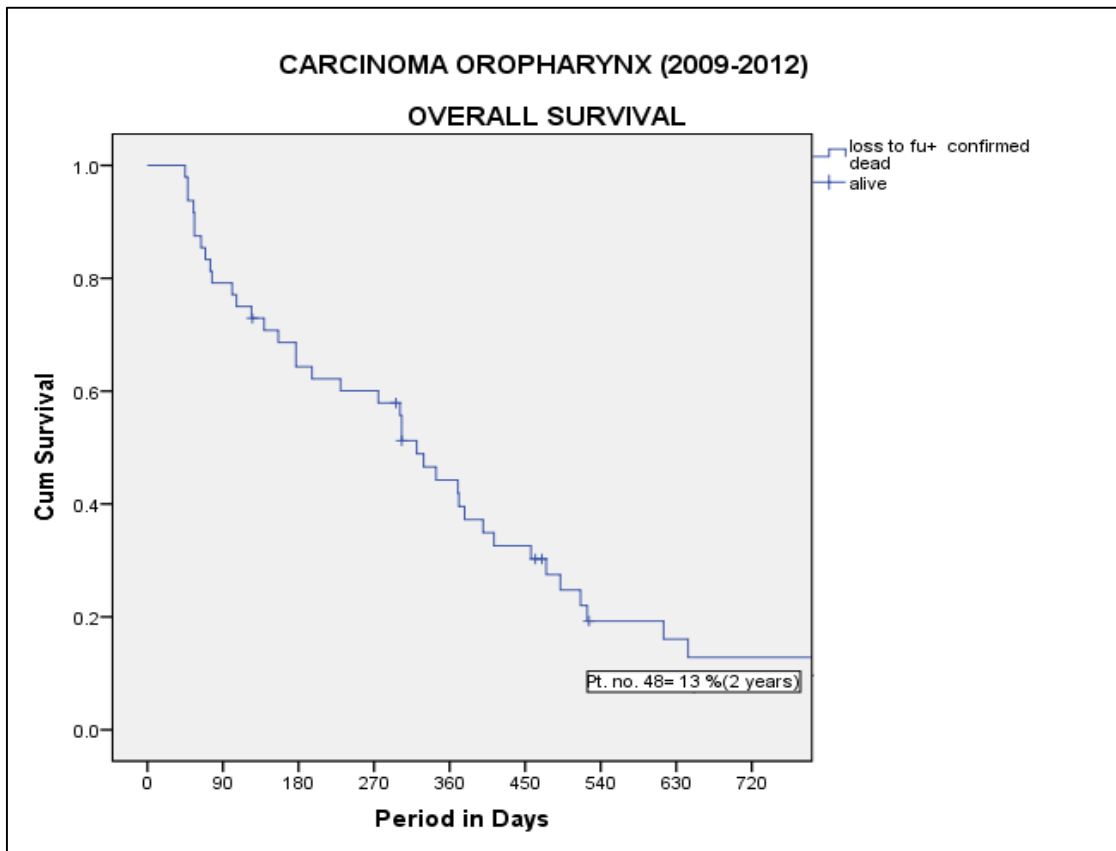
As illustrated in figure 4.3 different subsites were treated. The most common presenting site of disease was the BOT, followed by the tonsil. Since most of the patients presented with locally advanced disease and due to the close proximity of these sites, the tumour sometimes involved more than one site. Treatment fields for radiation therapy included the entire oropharynx, with a margin for microscopic extension.

Figure 4.4 Patient dose schedules



All the patients received radical radiation therapy doses (range 60-70 Gy) shown in figure 4.4. The majority completed treatment in 7 weeks, with a small fraction having split treatment due to acute skin toxicities. Fifty-eight percent of patients received concurrent chemotherapy, with 16 (33%) receiving one cycle and 12 (25%) receiving two cycles.

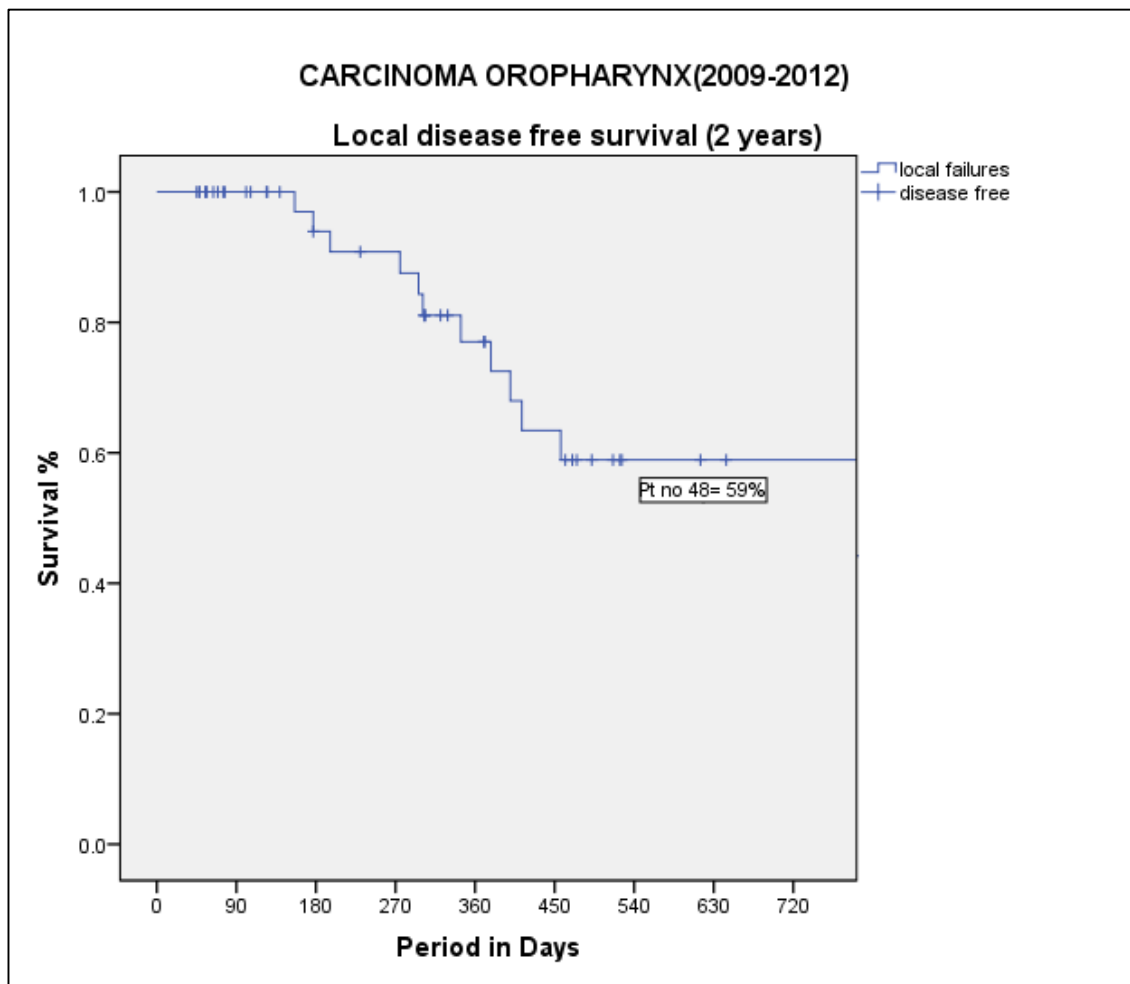
Figure 4.5 Overall survival graph for patient group with lost to follow-up patients added to dead patients



When the lost to follow up was added to the dead patients and the alive censored, the overall survival at 2 years was 13 % Figure 4.5.

At the time of this analysis, 7 (15%) patients were alive, 20 (42%) were dead and 21 (43%) lost to follow up. The overall survival at 2 years was 50 %, with the lost to follow-up added to the alive patients.

Figure 4.6 Patient local disease free survival results



The local disease free survival at 2 years was 59%, as illustrated in Figure 4.6. Local treatment failure occurred in 13 (27%) patients.

Table 4.1 Tabulated p-values results by using multivariate and univariate method

Prognostic factors	p-values multivariate	p-value univariate
Age $\geq$ 55 years 26 patients < 55 years 22 patients	0,744	1,00
ECOG	0,218	1,00
Smoking	0,889	1,00
Sex	0,799	1,00
HIV status	0,603	1,00
AJCC stage	0,605	1,00
Site	0,389	1,00
Chemotherapy	0,714	1,00

On multivariate and univariate analysis using Cox regression analysis, none of the prognostic factors were predictive for over-all survival as shown in table 4.1.

Late toxicities in the patient group could not be analysed due to the no documentation of at follow evaluations.

5.0 DISCUSSION

In advanced oropharyngeal carcinoma, the main goal of therapy was local disease control, organ function preservation and improving the patient's quality of life. Oropharyngeal cancer affects speech, swallowing, degustation, and psychological well-being. All these factors must be considered when managing this cancer.

Combination modality treatment, with concurrent chemoradiation has shown to improve local control rates and over-all survival in patients with locally advanced stage III-IV oropharyngeal cancer ^[30, 37, 41]. In the recent years, there has been improvement in the prognosis of oropharyngeal carcinoma due to advances in radiation therapy delivery, addition of concurrent chemotherapy and the high prevalence of HPV virus ^[26, 42].

Numerous studies have shown that HPV positive oropharyngeal carcinoma has a higher overall survival rate than HPV negative oropharyngeal cancer, and a better prognosis regardless of the treatment modalities used ^[26,43]. HPV status was independently associated with improved outcomes. The Eastern Cooperative Oncology Group, Trans-Tasman Radiation Oncology Group, Radiation Therapy Oncology Group and Danish Head and Neck Cancer study groups have shown over-all survival rates between 62%-95% (HPV positive oropharyngeal cancers) and 26%-77% (HPV negative oropharyngeal cancers).

Most oropharyngeal carcinomas are diagnosed at advanced stages and with a higher incidence of lymph-node metastasis, most likely related to the rich lymphatic supply of the oropharynx.

The primary endpoint of this retrospective review was to assess response to treatment, overall survival, disease free survival and the difference between HPV positive and negative oropharyngeal carcinoma with patients having received radical treatment. The treatment modalities used were radical dose radiation therapy (60-70Gy), with or without concurrent chemotherapy (cisplatin 70mg/m²).

These treatment modalities did not show an improvement in over-all survival or the disease free survival. At the time of analysis (March 2014), only 7 (15%) patients were alive, 20 (42%) patients were dead and 21 (44%) patients were lost to follow-up. The overall survival at 2 years was 50%, when all lost to follow-up and alive was censored. Overall survival was 13% when only alive patients were censored. These results had no correlation with current literature, demonstrating a poorer overall survival. The HPV-DNA Polymerase chain reaction (PCR) test was only performed routinely in three patients out of the forty-eight making it difficult to analyse the difference between the HPV positive and negative patients. The local disease free survival at the 2nd year was 59%, which correlated with the current literature. The log rank univariate and multivariate analysis of prognostic factors were not predictive for over-all survival.

An analysis conducted by Ang et al. (2011) reported overall survival on stage III and IV positive and negative oropharyngeal carcinoma. 3 year overall survival rate was 82,4% (HPV positive) compared to 57,1% (HPV negative). Loco-regional failure remains common in HPV negative tumours, with 15-35% of locally advanced disease developing local recurrence within 3 years ^[26].

GORTEC reported a multi-institutional randomized prospective trial comparing radiation therapy plus concurrent chemotherapy with radiation alone in patients with stage III and IV oropharyngeal cancer. The three year overall survival was 51% vs. 31%, 3 year disease free survival was 42% vs. 20% and loco-regional control 66% vs. 42% respectively ^[30].

A retrospective review conducted at the Department of Radiation Oncology at the University of Texas M.D Anderson Cancer Center evaluated patients with locally advanced oropharyngeal cancers (stage III and IVb SCC) treated with modern therapy approaches from 2000-2007. This review demonstrated relatively high survival rates in the locally advanced oropharyngeal cancer treated with non-surgical techniques. The 5-year actuarial overall survival, recurrence-free survival and local-regional control rates for the entire cohort were 78%, 77%, and 87% respectively. The study also concluded increasing T-stage and smoking were associated with higher rates of local-regional recurrence and poor survival ^[43].

An important aspect of this retrospective review was a large number of patients that were lost to follow up (21 patients-44%). Another significant factor was the bulk of patients having received treatment, formed part of the low socio-economic populous of the greater Johannesburg area. Majority of patients were lost to follow-up. This factor has highlighted the lack of comprehensive patient biographic information accrual which must be developed and recorded in an effective database. Patients must provide at the minimum three different contact numbers as well as next of kin before treatment can be initiated. Designated officials must follow-up with patients absconding from appointments. Additional attempts need to be made through social workers and the Home

Affairs Department of South Africa (ID checks, death registration etc.). Proper control of patients can lead to better management of early recurrence, poor nutritional status and treatment related toxicities. The initial counselling of patients must be intensive and comprehensive. The importance of treatment and follow up care must be explained and patients must be reassured and helped if complications arise during treatment.

The limitations of this retrospective analysis were sample size per treatment group, poor recording at pre-treatment evaluation and at follow-up in most patients, and a large number of patients were lost to follow-up (21 patients 44%). As only 3 patients had HPV-DNA PCR tests done, comparison between HPV positive and negative oropharyngeal cancer could not be done.

Late toxicities in this patient group could not be analysed due to the poor follow up documentation. Gender had no prognostic significance when analyzed on both multivariate and univariate analysis.

Further suggestions for improvement of patient follow-up are:

- Have a designated person for patient follow-up (research co-ordinator/ State entity / Out-patient-department oncology nurse or social worker).
- Proper document check at record filing office at the time of registration (Identity document check).
- Regular training of new and updating knowledge of existing staff regarding the importance of high quality record keeping.
- Full residential information and contact details.
- Follow-up records should be checked at least once every six months.
- Patient must provide at least 3 reachable telephone numbers.

6.0 CONCLUSION

In this retrospective pattern of care analysis for radical radiation therapy with or without concurrent chemotherapy for oropharyngeal carcinoma, found that the mortality rate at 2 years was significantly high. Majority of patients were lost to follow up with unknown reasons. Intensive and comprehensive pre-counselling is vital for the success treatment and follow up outcomes. Only three patients in this study were routinely tested for HPV virus in an HPV causing cancer.

Majority of patients present in stage IV lesions with commonest sites of involvement being Base of Tongue. The local disease free survival of 2 years was 59% and the overall survival of 15%. There was no impact of prognostic factors studied on overall survival.

Literature suggests better outcomes in patients with HPV positive oropharyngeal cancer. The routine testing of HPV-DNA PCR should be implemented so as to distinguish between the two groups. There are ongoing trials looking at reducing treatment doses in the HPV positive, which can ultimately reduce treatment toxicities.

Advanced radiation therapy techniques have emerged in the last decade. 3DCRT delivery of treatment was limited to traditional geometric fields until the development of IMRT. IMRT is considered standard of care in most countries for patients with oropharyngeal carcinoma, because of its significant tissue sparing effect leading to improved quality of life. Although, improvement of surgical techniques have been made the future of treatment of oropharyngeal cancer is still in radiation and chemoradiation.

Clinicians must tailor treatment of patients, based on age, ECOG status, co-morbidities, HPV status and compliance of patients. Optimal management ultimately depends on a multidisciplinary evaluation.

Implementation of these strategies may allow for comparable overall survival, disease free survival and compliance data to international data.

7.0 REFERENCES

1. Skinner HD, Holsinger FC, Beadle BM. Oropharyngeal Carcinoma. *Curr Probl Cancer*. 2012;36:334-415.
2. Panwar A, Batra R, Lydiatt WM, Ganti AK. Human papilloma virus positive oropharyngeal squamous cell carcinoma: A growing epidemic. *Cancer treatment reviews*. 2014;40:215-219.
3. Mendenhall WM, Werning JW, Pfister DG. *Treatment of head and neck cancer*. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001.
4. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray, F. *Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11* [Internet]. Cancer; 2014 [cited 2015 April 14]. Available from: <http://globocan.iarc.fr>
5. Licitra L, Bernier J, Grandi C, Merlano M, Bruzzi P, Lefebvre JL. Cancers of the Oropharynx. *Critical Reviews in Oncol/Hemato*. 2002;41:107-122.
6. Brown LM, Check DP, Devesa SS. Oropharyngeal cancer incidence trends: diminishing racial disparities. *Cancer Causes Control*. 2011;22:753-63.
7. Suh Y, Amelio I, Urbano TG, Tavassoli M. Clinical Update on Cancer: Molecular Oncology of Head and Neck Cancer. *Cell Death and Disease*. 2014;5:1018-1038.
8. Marklund L, Hammarstedt L. Impact of HPV in Oropharyngeal Cancer. *J Onco*. 2011;10:1-6.
9. D'Souza G, Kreimer AR, Viscidi R, Pawlita M, Fakhry C, Koch WM, Westra WH, Gillison ML. Case control study of human papillomavirus and oropharyngeal cancers. *N Eng J Med*. 2007;356:1944-1956.

10. Kreimer AR, Clifford GM, Boyle PL. Human papillomavirus type in head and neck squamous cell carcinomas worldwide: a systemic review. *Cancer Epidemiol Biomarkers Prev.* 2005;14:467-75.
11. Feller L, Wood NH, Khammissa RAG, Lemmer J. Human papillomavirus-mediated carcinogenesis and HPV-associated oral and oropharyngeal squamous cell carcinoma. Part 1: Human papillomavirus-mediated carcinogenesis. *Head & face med.* 2010;6:14.
12. Urban D, Corry J, Rischin D. What is the best treatment for patients with human papillomavirus-positive and negative oropharyngeal cancers? *Cancer.* 2014;0:1-9.
13. Lubin JH, Purdue M, Kelsey K, Zhang ZF, Winn D, Wei Q, Talamini R, Szeszenia-Dabrowska N, Sturgis EM, Smith E, Shangina O, Schwartz SM, Rudnai P, Neto JE, Muscat J, Morgenstern H, Menezes A, Matos E, Mates IN, Lissowska J, Levi F, Lazarus P, Vecchia CL, Koifman S, Herrero R, Franceschi S, Wünsch-Filho V, Fernandez L, Fabianova E, Daudt AW, Maso LD, Curado MP, Chen C, Castellsague X, Brennan P, Boffetta P, Hashibe M, Hayes RB. Total exposure and exposure rate effects for alcohol and smoking and risk of head and neck cancers: a pooled analysis of case control studies. *Am J Epidemiol.* 2009;170:937-947.
14. Sturgis EM, Ang KK. The epidemic of HPV-associated oropharyngeal cancer is here: it is time to change our treatment paradigms? *J Natl Compr Cancer Netw.* 2011;9:665-73.
15. Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, Jiang B, Goodman MT, Sibug-Saber M, Cozen W, Liu L, Lynch CF, Wentzensen N, Jordan RC, Altekruse S, Anderson WF, Rosenberg PS, Gillison ML. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. *J Clin Oncol.* 2011;29:4294-4301.

16. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancers. *Nat Rev Cancer*. 2010;11:9-22.
17. Young RJ, Rischin D, Fisher R, McAuthur GA, Fox SB, Peters LJ, Corry J, Lim A, Waldeck K, Solomon J. The relationship between epidermal growth factor receptor status, p16INK4A, and outcome of head and neck squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1230-1237.
18. Hafkamp HC, Manni JJ, Haesevoets A, Voogd AC, Schepers M, Bot FJ, Hopman AHN, Ramaekers FCS, Speel EJM. Marked difference in survival rate between smokers and non-smokers with HPV 16-associated tonsillar carcinoma. *Int J Cancer*. 2008;122:2656-2664.
19. Goldenburg D, Begum S, Westra WH, Khan Z, Sciubba J, Pai SI, Califano JA, Tufano RP, Koch WM. Cystic lymph-node metastasis in patients with head and neck cancers: an HPV-associated phenomenon. *Head Neck*. 2008;30:898-903.
20. Gunderson LL, Tepper JE. 3rd edition. Philadelphia: Elsevier Saunders; 2012.
21. Lin DT, Cohen SM, Coppit GL, Burkey BB. Squamous cell carcinoma of the oropharynx and hypopharynx. *Otolaryngol Clin North Am*. 2005;38:59-74.
22. TNM Staging of Oropharyngeal Cancer [internet] 2011 August 4 [cited 2014 May]. Available from:
<http://dentallecnotes.blogspot.com/2011/08/t-stage-depends-on-anatomical-location.html>
23. Herbst MC. Fact sheet on Human Papilloma Virus Infection and Cancer [internet] 2014 June [cited 2015 April 14]. Available from:
<http://www.cansa.org.za/files/2014/06/Fact-Sheet-Human-Papilloma-Virus-Infection-Cancer-June-2014.pdf>

24. FDA licensure of bivalent human papillomavirus vaccine (HPV2, Cervarix) for use in females and update HPV vaccination recommendations from the Advisory Committee on Immunization Practices (ACIP). CDC. MMWR Morb Mortal Wkly Rep. 2010;59:626-9.
25. Recommendations on the use of quadrivalent human papillomavirus vaccines in males- Advisory Committee on Immunization practice (ACIP). CDC. MMWR Morb Mortal Wkly Rep. 2011;60:1705-8.
26. Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, Westra WH, Chung CH, Jordan RC, Lu C, Kim H, Axelrod R, Silverman C, Redmond KP, Gillison ML. Human papillomavirus and survival of patients with oropharyngeal cancer. *New Eng J Med*. 2010; 363:24–35.
27. Galati LT, Myers EN, Johnson JT. Primary surgery as treatment for early squamous cell carcinoma of the Tonsil. *Head Neck*. 2000;3:294-296.
28. Weber RS, Peters LJ, Wolf P, Guillaumondwqui O. Squamous cell carcinoma of the soft palate, uvula and anterior faucial pillar. *Otolaryngol Head and Neck Surg*. 1988;99:16-23.
29. Hull MC, Morris CG, Tannehill SP, Werning JW, Amdur RJ, Hinerman RW, Villaret DB, Mendenhall WM. Definitive radiotherapy alone or combined with a planned neck dissection for squamous cell carcinoma of the pharyngeal wall. *Cancer*. 2003;98:2224-2231.
30. Forastiere AA, Trotti A. Radiotherapy and concurrent chemotherapy: a strategy that improves locoregional control and survival in oropharyngeal cancer. *J Natl Cancer Int*. 1999;91:2065-2066.
31. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, Gardani G, Van Den Bogaert W, Danzak S, Bolla M. Hyperfractionation versus conventional

- fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol.* 1992;25:231-241.
32. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, Garden AS, Ridge JA, Cooper JS, Ang KK. A radiation therapy Oncology Group (RTOG) phase III randomised study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 90-03. *Int J Radiat Oncol Biol Phys.* 2000;48:7-16.
 33. Overgaard J, Hansen HS, Specht L, Overgaard M, Grau C, Andersen E, Bentzen J, Bastholt L, Hansen O, Johansen J, Andersen L, Evensen JF. Five compared with six fractions per week of conventional radiotherapy of squamous cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. *Lancet* 2003;362:933-940.
 34. Eisbruch A, Harris J, Garden AS, Chao CK, Straube W, Harari PM, Sanquineti G, Jones CU, Bosch WR, Ang KK. Multi-institutional trial of accelerated hypofractionated intensity-modulated radiation therapy for early stage oropharyngeal cancer (RTOG 00-22). *Int J Radiat.* 2009;76:1333-1338.
 35. Daly ME, Le QT, Maxim PG, Loo BW Jr, Kaplan MJ, Fischbein NJ, Pinto H, Chang DT. Intensity-modulated radiotherapy in the treatment of oropharyngeal cancer: clinical outcome and patterns of failure. *Int J Radiat Oncol Biol Phys.* 2010;76:1339-1346.
 36. Nutting CM, Morden JP, Harrington KJ. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase III multicentre randomised controlled trial. *Lancet Oncol.* 2011;12:127-136.
 37. Pignon JP, le Maitre A, Maillard E, Bourhis J. Meta-analysis of chemotherapy in head and neck cancers (MACH-NC): an update on 93 randomized trials and 17,346 patients. *Radiother Oncol.* 2009;92(1):4-14.

38. Machtay M, Moughan J, Trotti A, Garden AS, Weber RS, Cooper JS, Forastiere A, Ank KK. Factors associated with severe late toxicity after concurrent chemoradiation for locally advanced head and neck cancer: an RTOG analysis. *J Clin Oncol.* 2008;26:3582-3589.
39. Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Calais G. Final results of the 94-01 French head and neck Oncology and Radiation Group randomized trial comparing radiation alone with concomitant radiochemotherapy in advanced stage oropharynx carcinoma. *J Clin Oncol.* 2004;22:69-76.
40. Cheong D, Letson GD. Computer-assisted navigation and musculoskeletal sarcoma surgery. *Cancer Control.* 2001 Jul; 18(3):171-176.
41. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P, Rhein B, Tortochaux J, Oudinot P, Bertrand P. Randomized trial of Radiation therapy vs. concomitant chemotherapy and radiation therapy for advanced-stage oropharyngeal carcinoma. *J Natl Cancer Inst.* 1999;91:2081-2086.
42. Lee NY, de Arruda FF, Puri DR, Wolden SL, Narayana A, Mechalakos J, Venkatraman ES, Kraus D, Shaha A, Shah JP, Pfister DG, Zelefsky MJ. A comparison of intensity-modulated radiation therapy and concomitant boost radiotherapy in the setting of concurrent chemotherapy in locally advanced oropharyngeal carcinoma. *Int J Radiat Oncol Phys.* 2006;66:966-974.
43. Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, Forastiere A, Gillion ML. Improved survival of patients with human papilloma-positive head and neck squamous cell carcinoma in a prospective clinical trial. *J Natl Cancer Inst.* 2008;100:261-269.

44. Garden AS, Kies MS, Morrison WH, Weber RS, Frank SJ, Glisson B, Gunn GB, Beadle BM, Ang KK, Rosenthal DI, Sturgis EM. Outcomes and patterns of care of patients with locally advanced oropharyngeal carcinoma treated in the 21st century. *Rad Onc.* 2013;8:21.
45. Oropharyngeal Cancer Treatment (PDQ®) [internet]. National Cancer Institute at the National Institutes of Health: 2014 April [cited 2014 June]. Available from:
<http://www.cancer.gov/cancertopics/pdq/treatment/oropharyngeal/Patient/page2>
46. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655,
47. Lymph node levels of Neck [internet] 2014 May 13 [cited 2014 June]. Available from:
<http://epomedicine.com/medical-students/lymph-node-levels-of-neck>

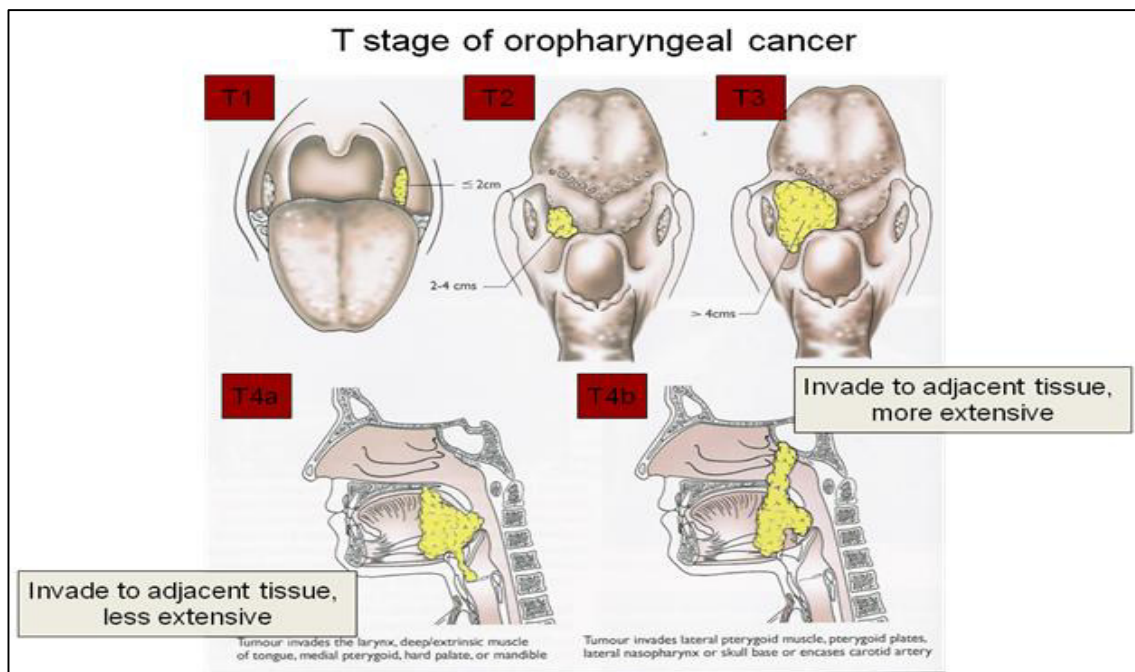
8.0 APPENDICES

8.1 Stages of Oropharyngeal Carcinoma

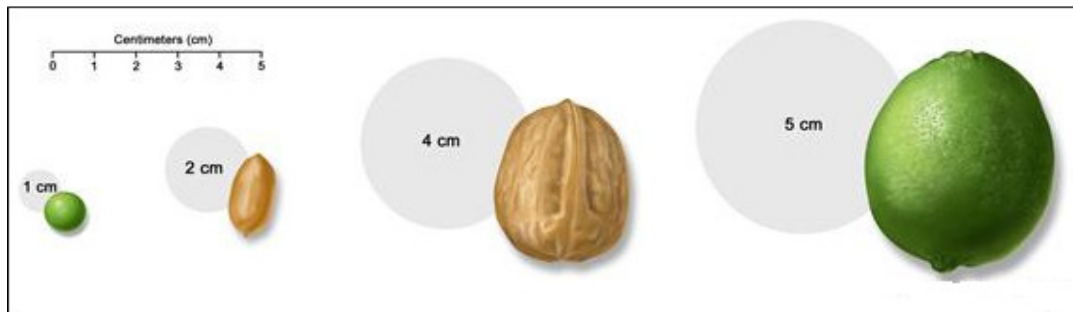
The following stages are used for oropharyngeal cancer ^[43]:

Stage 0 (Carcinoma in Situ)

In stage 0, abnormal cells are found in the lining of the oropharynx. These abnormal cells may become cancer and spread into nearby normal tissue. Stage 0 is also called carcinoma in situ.



The different T-stages of oropharyngeal cancer are shown above ^[22].



Pea, peanut, walnut, and lime show tumour sizes shown above ^[45].

Stage I

In stage I, cancer has formed and is 2 centimeters or smaller and is found in the oropharynx only.

Stage II

In stage II, the cancer is larger than 2 centimeters but not larger than 4 centimeters and is found in the oropharynx only.

Stage III

In stage III, the cancer is either:

- 4 centimeters or smaller; cancer has spread to one lymph node on the same side of the neck as the tumour and the lymph node is 3 centimeters or smaller; or
- Larger than 4 centimeters or has spread to the epiglottis (the flap that covers the trachea during swallowing). Cancer may have spread to one lymph node on the same side of the neck as the tumour and the lymph node is 3 centimeters or smaller.

Stage IV

Stage IV is divided into stage IVA, IVB, and IVC as follows:

- In stage IVA, cancer:
 - Has spread to the larynx, front part of the roof of the mouth, lower jaw, or muscles that move the tongue or are used for chewing. Cancer may have spread to one lymph node on the same side of the neck as the tumour and the lymph node is 3 centimetres or smaller; or
 - Has spread to one lymph node on the same side of the neck as the tumour (the lymph node is larger than 3 centimetres but not larger than 6 centimetres) or to more than one lymph node anywhere in the neck (the lymph nodes are 6 centimetres or smaller), and one of the following is true:
 - Tumour in the oropharynx is any size and may have spread to the epiglottis (the flap that covers the trachea during swallowing); or
 - Tumour has spread to the larynx, front part of the roof of the mouth, lower jaw, or muscles that move the tongue or are used for chewing.
- In stage IVB, the tumour:
 - Surrounds the carotid artery or has spread to the muscle that opens the jaw, the bone attached to the muscles that move the jaw, nasopharynx, or base of the skull. Cancer may have spread to one or more lymph nodes which can be any size; or
 - May be any size and has spread to one or more lymph nodes that are larger than 6 centimeters.
- In stage IVC, the tumour may be any size and has spread beyond the oropharynx to other parts of the body, such as the lung, bone, or liver.

8.2 ECOG Performance Status Scale^[46]

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

8.3 Protocol Study Approval



GAUTENG PROVINCE

HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

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Date: 27th March 2014

Dr. Y. Ramdas
Department of Radiation Oncology
Charlotte Maxeke Johannesburg Academic Hospital

Dear Dr. Ramdas

RE: "Pattern of practice of radical radiation therapy for Oropharyngeal Cancer: A retrospective Review form January 2009 to December 2012"

Please note that permission to conduct the above mentioned study is provisionally approved. Your study can only commence once ethics approval is obtained. Please forward a copy of your ethics clearance certificate as soon as the study is approved by the ethics committee for the CEO's office to give you the final approval to conduct the study.

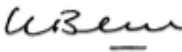
~~Approved~~ not approved

Ms. G. Bogoshi

Chief Executive Officer

Date: 28/03/2014

8.4 Masters of Medicine Approval

	Faculty of Health Sciences Private Bag 3 Wits, 2050 Fax: 027117172119 Tel: 02711 7172040
Dr Y Ramdas 84 Hawk Street Kharwastan 4092 South Africa	Reference: Ms Thokozile Nhlapo E-mail: thokozile.nhlapo@wits.ac.za 02 April 2014 Person No: 675553 PAG
Dear Dr Ramdas	
Master of Medicine: Approval of Title	
We have pleasure in advising that your proposal entitled <i>Pattern of Practice of radical radiation therapy for oropharyngeal cancers: A retrospective review from January 2009 to December 2012</i> has been approved. Please note that any amendments to this title have to be endorsed by the Faculty's higher degrees committee and formally approved.	
Yours sincerely	
	
Mrs Sandra Benn Faculty Registrar Faculty of Health Sciences	

8.5. Ethics Clearance Certificate



R14/49 Dr Yastira Ramdas

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M140234

NAME: Dr Yastira Ramdas
(Principal Investigator)

DEPARTMENT: Radiation Oncology
Charlotte Maxeke Johannesburg Academic Hospital

PROJECT TITLE: Pattern of Practice of Radical Radiation Therapy for
Oropharyngeal Cancers: A Retrospective Review
from January 2009 to December 2012

DATE CONSIDERED: 28/02/2014

DECISION: Approved unconditionally

CONDITIONS:

SUPERVISOR: Prof Vinay Sharma

APPROVED BY: 
Professor P Cleaton-Jones, Co-Chairperson, HREC (Medical)

DATE OF APPROVAL: 09/04/2014

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature _____

Date _____

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

8.6 Patient Data Capture Form/Performa

PERFORMA FOR OROPHARYNGEAL CANCERS

CODE NUMBER:

DATE OF REGISTRATION:

DXT NUMBER:

SITE OF OROPHARYNGEAL CANCER

- 1 = TONSILLAR COMPLEX
- 2 = BASE OF TONGUE
- 3 = SOFT PALATE
- 4 = PHARYNGEAL WALLS

HIV STATUS

- 1 = POSITIVE
- 2 = NEGATIVE

HPV STATUS

- 1 = POSITIVE
- 2 = NEGATIVE
- 3 = NOT TESTED

HISTOLOGY SUBTYPE

- 1 = SQUAMOUS CELL CARCINOMA

ECOG STATUS:

- 1 = ECOG1
- 2 = ECOG2
- 3 = ECOG3

SMOKING

- 1 = NEVER SMOKED
- 2 = EX-SMOKER
- 3 = CURRENT SMOKER

ALCOHOL USE:

- 1 = NEVER DRANK
- 2 = EX-DRINKER
- 3 = DRINKER

TNM STAGE:

RADIATION DOSE RECEIVED:

- 1 = 60 Gy
- 2 = 66 Gy
- 3 = 70 Gy

CONCOMITANT CHEMOTHERAPY:

- 1 = YES
- 2 = NO

NO OF CYCLES CHEMOTHERAPY RECEIVED:

START DATE TREATMENT:

COMPLETION DATE OF THERAPY:

DATE OF PROGRESSION:

DATE OF DEATH:

DISEASE FREE SURVIVAL (MONTHS):

OVER-ALL SURVIVAL (MONTHS):

8.7 Nodal Staging for Oropharyngeal Cancer

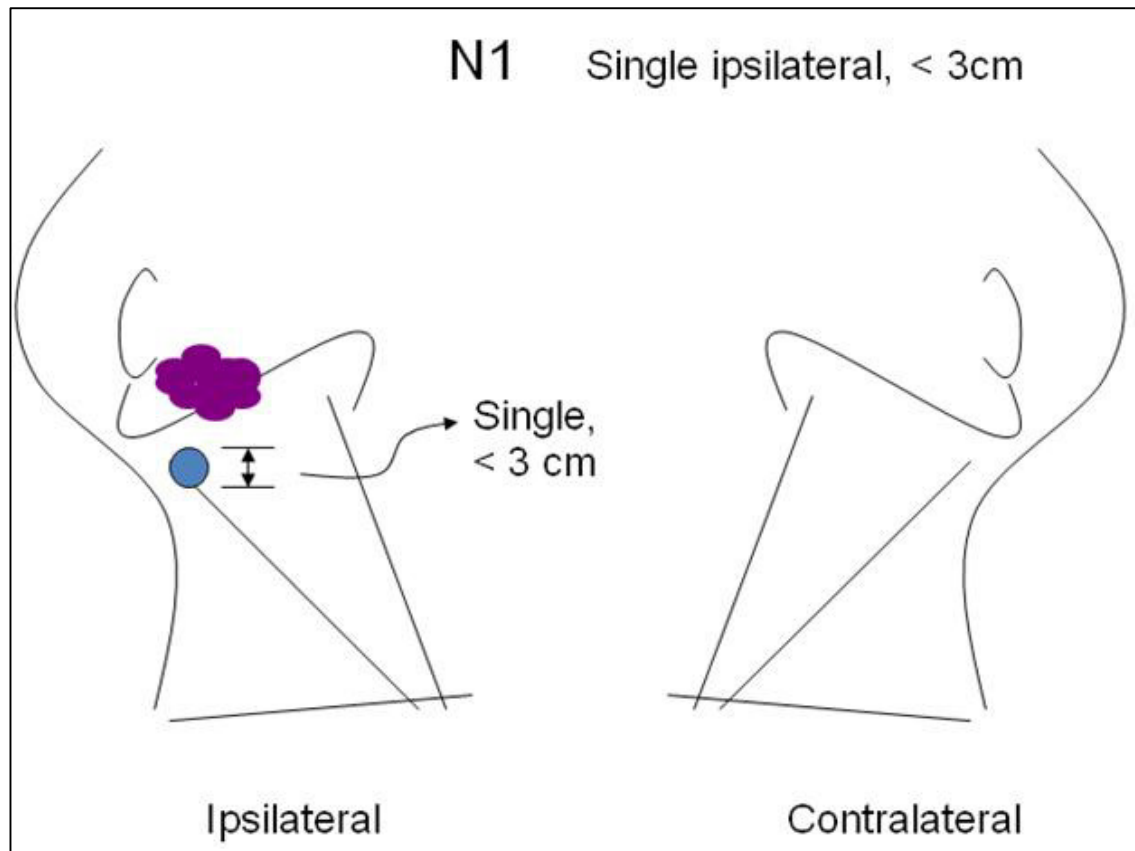


Figure 8.7.1 Nodal Staging^[47]

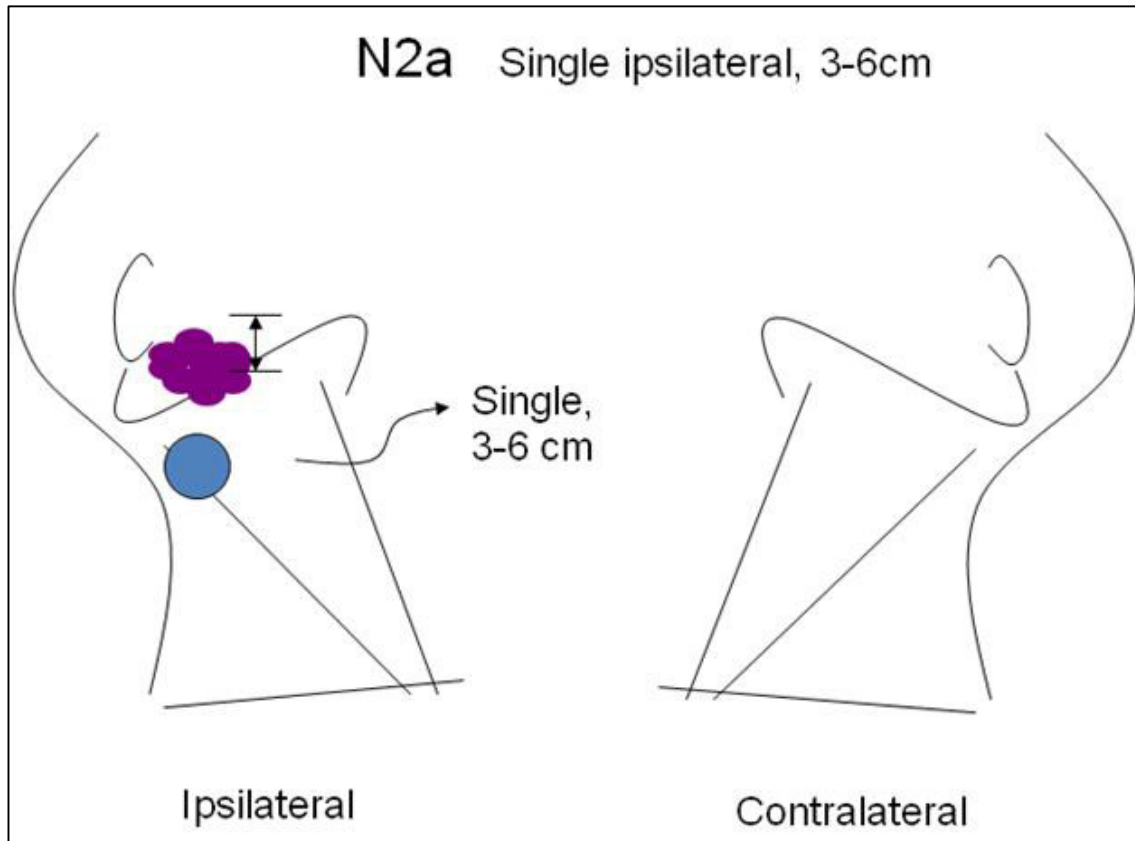


Figure 8.7.2 Nodal Staging^[47]

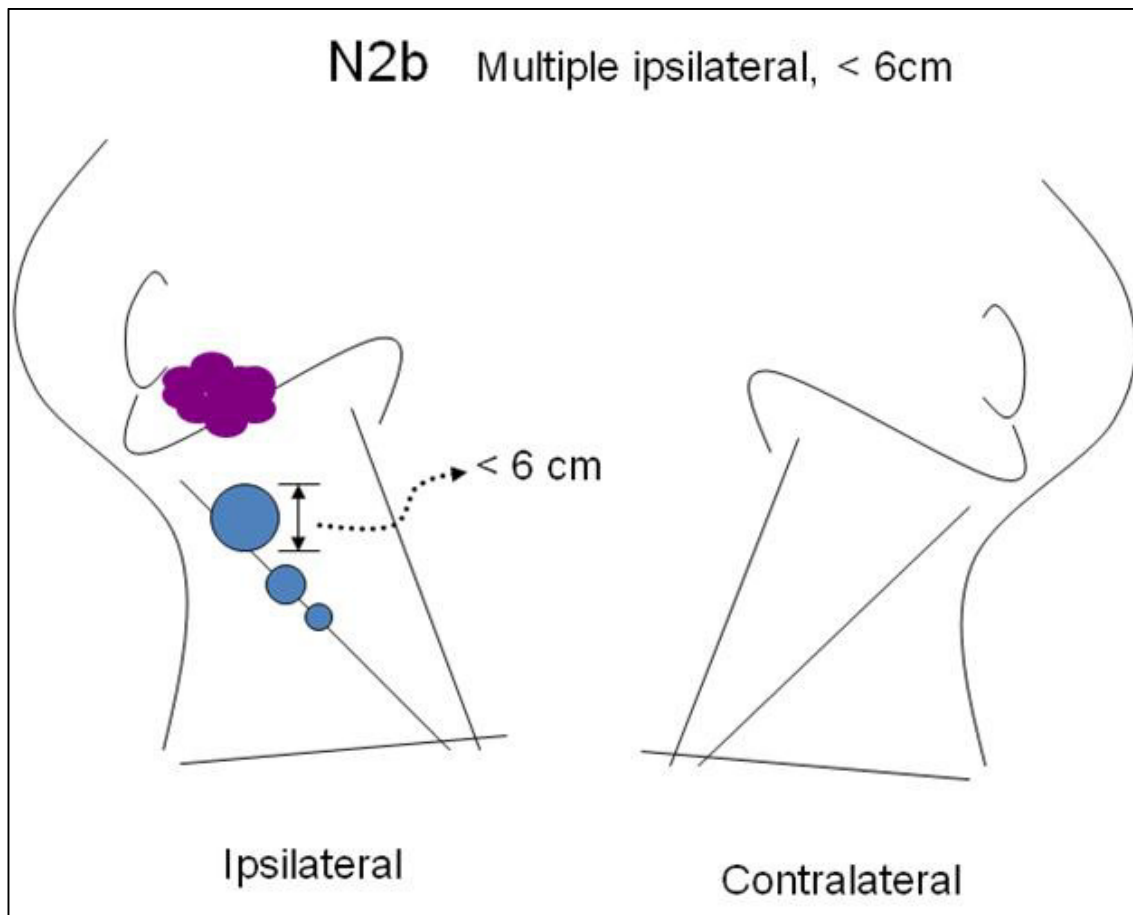


Figure 8.7.3 Nodal Staging ^[47]

N2c Bilateral or contralateral, < 6cm

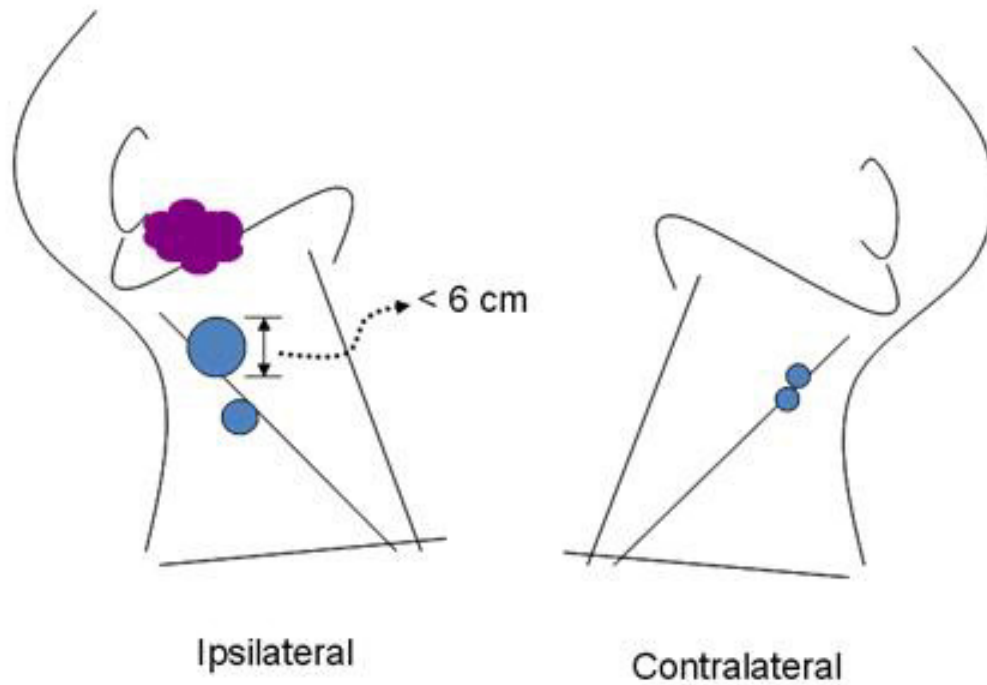


Figure 8.7.4 Nodal Staging ^[47]

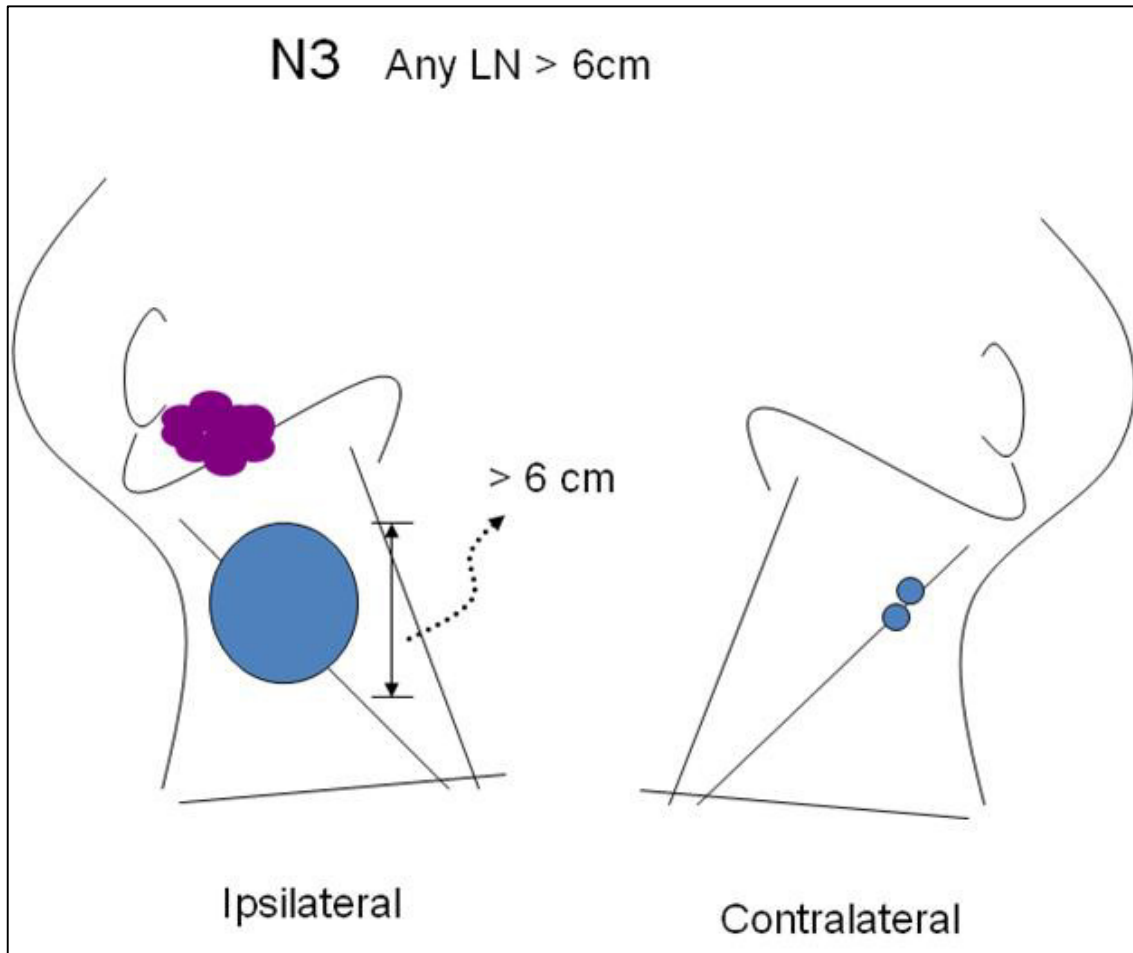


Figure 8.7.5 Nodal Staging ^[47]

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