PATIENTS TREATED WITH RADICAL COURSE OF RADIATION THERAPY FOR CARCINOMA OF LARYNX AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Dr Tsholofelo Desiree Mutsoane

A research report submitted to the faculty of Health Sciences University of Witwatersrand, in partial fulfilment for the degree of Master of Medicine (M.Med) Radiation Oncology.

Supervisor: Professor R. Lakier

Academic head of department of Radiation Oncology University of Pretoria South Africa.

Co-Supervisor: Dr A. Bentley

Department of Internal Medicine Charlotte Maxeke Johannesburg Hospital

University of Witwatersrand

Johannesburg 2014

Declaration

I Tsholofelo Desiree Mutsoane declare that this research report is my own work except where otherwise acknowledged. It is being submitted for the degree of Master of Medicine in Radiation Oncology at the University of Witwatersrand Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

This study has received ethical approval from the University of Witwatersrand ethical committee for research of human subject. Protocol number / clearance certificate number: M10927.

Signed at: Johannesburg (Wits University), South Africa on the 12th of May 2014

Signed: 

Dedication

I dedicate this work to my mother Ruth Mutsoane for your support and for looking after my daughter whenever I needed you to while I was working on my dissertation. To my late father Abram Mutsoane for believing in me and always encouraging me with my studies in the most delicate years of my life, high school and “teenage hood”.

Most importantly I dedicate this work to my lovely husband George Maesela for your love, support, patience and encouragement and to my baby girl Kgalalelo Maesela for being such a sweet baby, not over demanding. Thank you.

Abstract

Title

PATIENTS TREATED WITH RADICAL COURSE OF RADIATION THERAPY FOR CARCINOMA OF THE LARYNX AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Background

Larynx preservation is the standard recommended treatment approach for cancer of the larynx. We looked at results of patient treated with larynx preserving approach at our institution.

Objectives

The study objectives included describing the demographics of the population in the study and comparing characteristics and outcomes for patients in the different treatment groups. We also assessed waiting time for treatment, treatment completion rates and overall treatment time for all the patients in the study group. Outcomes of patients at last follow up and survival for different stages of disease were described.

Materials and Methods

A retrospective study of patients with cancer of the larynx treated at Charlotte Maxeke Academic Hospital department of radiation oncology between the year 2007 and 2009. All patients who received radiotherapy including palliative and radical cases were assessed. Outcomes were measured from end of treatment to 1 year and 2 years follow up for survival.

Results

We identified 106 eligible patients. The mean age was 58.6 years (standard deviation of 10.051).Two thirds (67%) of the patients presented with stage IVa disease, 14% had stage IVb, 13% had stage III, and very few patients had stage I and II disease 4% and 2% respectively. One third of patients were treated with radical chemotherapy plus radiotherapy and majority of them received only 1 cycle of chemotherapy. The other 26 % of patients treated with radical intent received radiotherapy alone. A significant number of our patients (42 %) were treated with palliative intent of which 13 % were patients who had disease progression while awaiting treatment. The majority of patients (53%) had an improvement in symptoms while (5.7%) had died and (17%) were lost to follow-up.

Conclusion

Waiting time prior to radiotherapy is a major problem in our institution as our overall mean waiting time was 98.5 days. Patients who had disease progression as defined by change in the treatment intent from radical to palliative treatment (13%) had a mean waiting time of 187.9 days which was almost double our overall mean waiting time and significantly worse than that recommended by standard of care. Although this waiting time was not statistically significant when compared with other patients treated with radical intent, it is a concern for the department to have such long waiting time prior to therapy and is probably a reflection of inadequate statistical power.

Of the radical cases those treated with chemotherapy and radiotherapy very few (2.9%) completed 3 cycles of chemotherapy therefore we had low treatment completion rates. Some patients did not receive their 2^{nd} or 3^{rd} cycle of chemotherapy due to low creatinine clearance other patients reasons for not completing chemotherapy was not documentation in their medical records. Although concurrent chemotherapy plus radiotherapy is the standard of care

for larynx preservation, most of our patients received suboptimal treatment to the recommended schedule and a significant number of our patients were treated with palliative intent.

Chemotherapy was not administered in some patients because of low CD4 count value. Unfortunately this was not recorded systematically and HIV status was not an entry or exclusion factor so no comparisons could be made. The chemotherapy schedule was not given to many patients at the recommended schedule of 3 cycles so we were not able to compare this with the literature.

Resources constraints with regards to diagnostic and radiological facilities resulted in us not having measurable tumour volume increase to evaluate disease progression during waiting time and to evaluate response to treatment at follow-up.

We have identified that patients are receiving inadequate treatment at the Department of Radiation Oncology with waiting times in excess of that recommended in the literature. Several reasons have been tentatively identified.

Additional research in a form of prospective study is required in our department to assess if we could improve the number of patients treated with radical intent by giving induction chemotherapy during the waiting time for patients with advanced stage III & IV disease who have a good performance status. Protocols in our department need to be reviewed for patients with early disease to be treated with shorter regimen and a higher dose fractionation schedule of 2.25Gy as this will also reduce our overall treatment time and waiting time for treatment while improving local control.

Acknowledgement

1) Professor Roy Lakier Head of Radiation Oncology Steve Biko Academic Hospital for your supervision and not giving up on me, without you I would not have completed this work.
2) Dr Alison Bentley for your co-supervision and assistance with statistical analysis and availing yourself when I needed you most.
3) Dr Jeffrey Kotzen for giving me ideas and advice when I was preparing the proposal for my study.
4) My brothers Kgomotso Mutsoane and Mpho Mutsoane who helped with typing the dissertation and sharing their knowledge on computers, you are my heroes.
5) Miss Salome Liebenberg for helping with collection of patient files for my data collection and encouraging me to get done with the dissertation.
6) Louisa Sithole department secretary for your help whenever I needed it.
7) Irma Mare department research coordination for always availing yourself when I needed your assistance
8) Mrs Gloria Mokwatle of Medical Research Council for your support.
9) Department of Radiation Oncology filing office staff and Head and Neck clinic nurses for your cooperation and your patience with collecting and returning patients files to me while I was working on them.

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1. Introduction

This research report will briefly discuss the anatomy and pathology of the larynx and look at the risk factors for cancer of the larynx, staging and treatment with radiation therapy. It will detail the results of patients treated for cancer of the larynx at Charlote Maxeke Johannesburg Academic Hospital with radiation therapy discussing their treatment tolerability, completeness of treatment and outcome.

1.1.1 Anatomy of the larynx

The larynx is a very important organ of phonication also known as "Voice box". It is situated between the pharynx above and the trachea below. Apart from phonation, the larynx acts as a valve for preventing swallowed food and foreign bodies from entering the lower respiratory passage. It is divided into 3 regions i.e. supraglottic region, glottic region and subglottic (Figure 1.1.1).

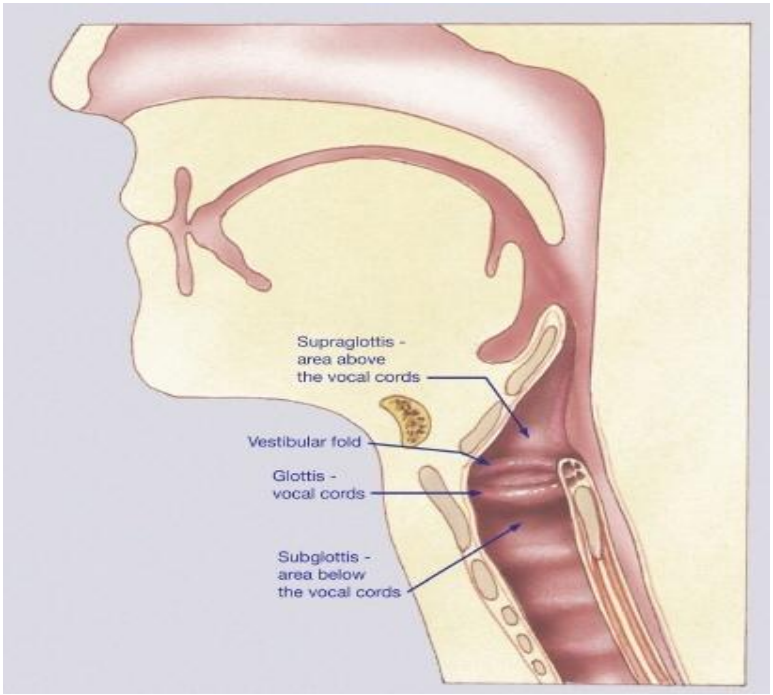

Figure 1.1.1 Anatomy of the larynx showing supraglottic, glottis and subglottic region. Credit to Miles Kelley art Library.

The supraglottic larynx consist of the epiglottis, false vocal cords, the ventricles and aryepiglottis folds including the arytenoids. The glottis region includes the true vocal cords and the anterior commissure, the subglottis is located below the vocal cords. The glottis is the part of the larynx most directly concerned with voice production (Moore KL, 1992). The shell of the larynx is formed by the hyoid bone, thyroid cartilage and the cricoid cartilage (Figure 1.1.2).

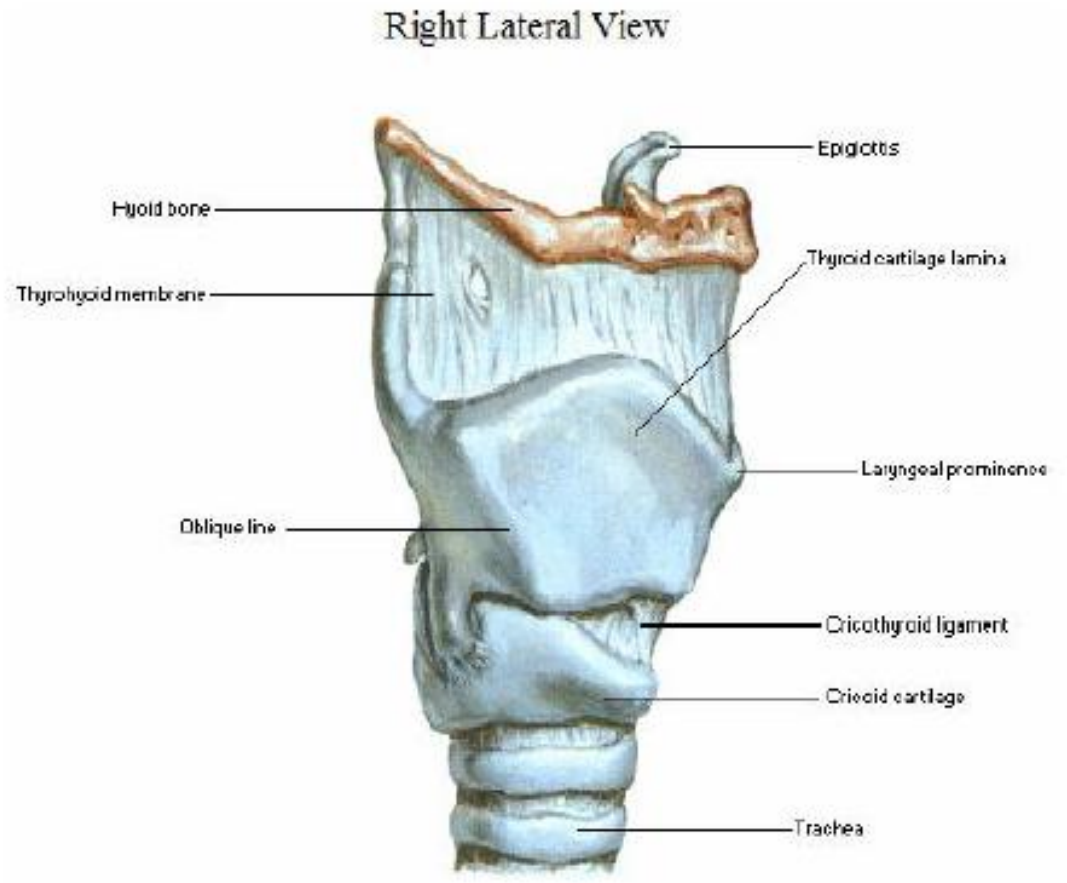

Figure 1.1.2The lateral view of the larynx, hyoid bone above, thyroid cartilage in the middle and cricoids cartilage below connecting to trachea. Credit to Netter's Atlas.

The supraglottic region has a rich capillary lymphatic plexus and initially drains to level II and then III and IV lymph nodes (Devita, 2008) Figure 1.1.3. There is essentially no capillary lymphatic of the glottis (true vocal cord) region. Lymphatic spread from cancer at the glottis only occurs if tumour extends to supraglottic or subglottic areas (Perez and Brady, 2008). The subglottic area has relatively few capillary lymphatics and spread is primarily to the pre-tracheal (delphian) nodes and the level IV nodes (Figure 1.1.3).

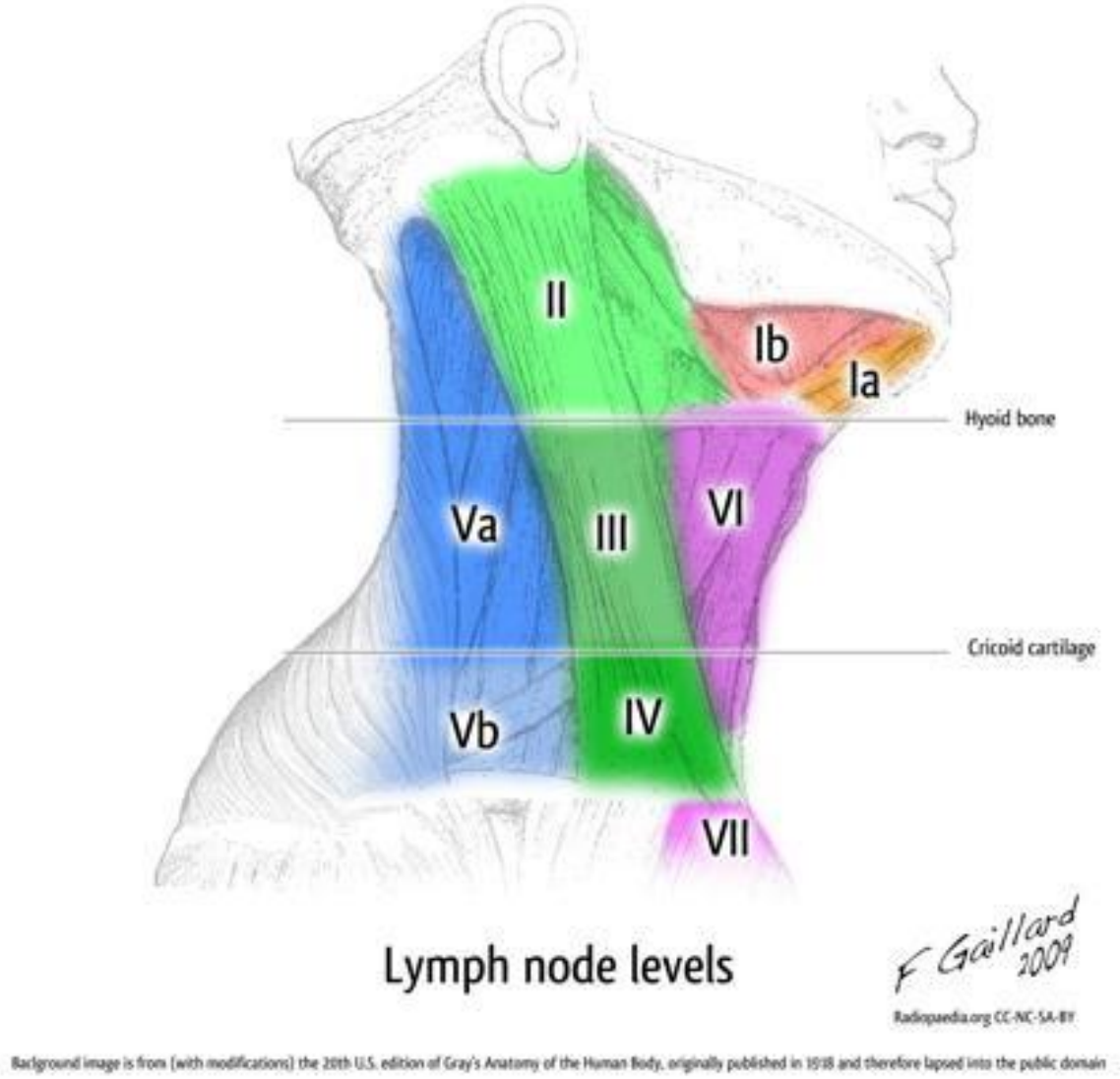

Figure 1.1.3 Picture showing anatomy of lymph node levels for head and neck. Credit to F. Gaillard.

Level I: Ia = submental, Ib = submandibular nodes.

Level II: upper deep cervical, extending from skull base to hyoid

Level III: mid deep cervical, extending from hyoid to cricoid

Level IV: lower deep cervical, extending from cricoids to clavicle

Level V: posterior cervical, bounded by sternomastoid, trapezius and clavicle

1.1.2 Laryngeal Pathology

The pathological disorders of the larynx include inflammatory e.g. laryngitis, epiglottitis commonly caused by infections such as H.Influenza or allergic reactions. Benign laryngeal polyps usually develop in singers and are sometimes called 'singers nodes'.

Tumours of the larynx may be benign e.g. papillomas or malignant mostly squamous cell carcinoma (Underwood J.C.E, 1996). Squamous cell carcinoma accounts for at least 95% of malignant cancers of the larynx and the other 5% of cancers comprise lymphomas, small cell carcinomas, soft tissue sarcomas and metastatic disease accounts for 5% of cancers of the larynx (Leibel and Phillips, 2010). Verrucous carcinoma is an uncommon but distinct variety of squamous cell carcinoma. It is a bulky, exophytic, papillomatous, low–grade squamous cell carcinoma (Leibel and Phillips, 2010).

Carcinomas arising from true vocal cords are usually well differentiated or moderately differentiated whereas carcinomas of the supraglottis and subglottis are less differentiated (Leibel and Phillips, 2010). Carcinoma in situ (CIS) occurs in vocal cords but is rare in the supraglottis.

Carcinoma of the larynx represents about 2% of total cancer risk and is the most common head and neck cancer. About 51% of cancer of the larynx remains localized, 29% have regional spread and 15% have distant metastasis at the time of diagnosis (Perez and Brady, 2008). Cancer of the larynx is strongly related to cigarette smoking and is more prevalent in

males than females (Perez and Brady, 2008).The contribution of smoking and alcohol is greater for supraglottic cancer than glottis cancer. Other rare risk factors include exposure to asbestos, diesel fumes, rubber and wood dust. People who employ their voices extensively also appear to be at higher risk of developing larynx cancer (Leibel and Phillips, 2010).

1.1.3 Clinical Presentation

The most common presenting symptom is hoarseness of voice if cancer affects the glottis region (true vocal cord) but it may not be prominent feature if the tumour is in the supraglottic or subglottic region unless it becomes quite extensive (Perez and Brady, 2008). Other common symptoms are sore throat or a feeling of a 'lump in the throat' or earache where pain is referred to the ear by the vagus nerve. Late symptoms include dysphagia, weight loss, foul breath and airway obstruction and aspiration (Perez and Brady, 2008).

Initial evaluation of patients with laryngeal cancer includes careful history and physical examination as these patients may have other co-morbidities associated with smoking e.g. chronic obstructive pulmonary disease (COPD), pulmonary tuberculosis, or other primary tumours.

1.1.4 Investigations and Staging

The important investigations for diagnosis and staging include flexible fibre optic laryngoscopy which complements the laryngeal mirror as the procedure can be performed in the office. As the scope is inserted through the nose it is particularly useful in more difficult cases (Perez and Brady, 2008).The extent of tumour invasion and mucosal spread can be assessed as well as the mobility of the vocal cords for staging as fixed or partially mobile

cords are suggestive of a more advanced lesion (Perez and Brady, 2008). Biopsy of the lesion can also be taken during the examination.

Rigid Direct Laryngoscopy requires anaesthesia but allows better visualization and is the most valuable and essential step in the diagnosis and staging of cancer of the larynx (Leibel and Phillips, 2010). CT scan with contrast enhancement and / or MRI are useful in providing information about extra-laryngeal spread of disease, cartilage invasion and nodal metastases. The relative usefulness of CT scan versus MRI remains controversial and in many cases the two modalities are complementary (Leibel and Phillips, 2010). These studies are preferably performed before biopsy as post biopsy oedema may cause overestimation of tumour extent.

Metastatic work up includes chest X-ray and lab tests(FBC, LFT) to check liver function and if test are abnormal then liver ultrasound scan and bone scan are indicated. Anaemia is important to diagnose as it may be a negative prognostic factor for patients with cancer of the larynx who receive radiation therapy (Leibel and Phillips, 2010).

After investigations are completed the cancer is staged using the American Joint Committee on Cancer (AJCC-TNM) staging system (Appendix 1) which describes T1-T4 for the 3 different regions of the larynx i.e. supraglottis, glottis and subglottis region.

Tis= tumor in situ/ carcinoma in situ, T= invasive tumor extent, N= Nodal involvement and M= Metastases (see appendix 1 for the T-N-M stage)

The AJCC also developed the stage grouping which groups the TNM stage into stage 0 to stage IVC shown below. Group stage 1 and 2 are considered early stage carcinoma while group stage 3 and 4 are advanced cancer of the larynx.

Table 1.1 Group staging for cancer of the larynx

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

AJCC: American Joint Committee on Cancer stage grouping (Hansen EK; Roach M, 2010).

1.2 Treatment overview for cancer of the larynx

The choice of treatment modality depends on tumour stage, performance status, co-morbidity, functional outcome, and survival rate. Assessment in a multidisciplinary clinic is essential The goal of treatment for laryngeal cancer is to cure with the best functional results and the least risk of serious complications.

1.2.1 Role of Surgery

a) Stripping or CO2 laser

Lesions diagnosed as carcinoma in situ may be treated by stripping the vocal cord or excision using CO2 laser (Perez and Brady, 2008). It is however difficult to exclude the possibility of micro-invasion on the specimen therefore recurrences are frequent. The vocal cord may become thickened with repeated stripping and leading to hoarse voice (Perez and Brady, 2008)

b) Cordectomy

Cordectomy is an excision of the vocal cord and may be performed by transoral approach usually with a laser or externally by a thyrotomy (Perez and Brady, 2008). Its use is usually confined to small lesions of the middle third of the cord, early T1 lesions. After cordectomy a pseudo cord is formed and the patient is left with a useful somewhat harsh voice.

c) Vertical Partial Laryngectomy (Hemilaryngectomy)

One entire vocal cord with as much as a third of the opposite cord and adjacent thyroid cartilage is the maximum cord involvement suitable for this surgery in men. Women have smaller larynx usually only one vocal cord may be removed without compromising the airway (Perez and Brady, 2008).Hemilaryngectomy is contraindicated if tumor extends to the epiglottis, false vocal cords or both arytenoids.

d) Supracricoid Partial Laryngectomy

Supracricoid partial laryngectomy is used for selected T2 & T3 glottic carcinomas and entails removal of both the true and false vocal cords and the entire thyroid cartilage. The cricoid is sutured to the epiglottis and hyoid (cricohyoidoplexy) (Perez and Brady 2008).

e) Total Laryngectomy

Total laryngectomy with or without neck dissection is the operation of choice for advanced lesion and as a salvage procedure for radiation therapy failures in lesions that are not suited for conservation surgery. The entire larynx is removed and the pharynx is reconstructed.

1.2.2 Management of early stage I & II cancer of the larynx

Early stage I & II cancer of the larynx can effectively be treated with surgery or radiation therapy. Treatment guidelines emphasize that every effort should be made to avoid combining surgery and radiotherapy because functional outcomes may be compromised (Leibel and Phillips, 2010). Patients who are considered not reliable enough for close follow up may benefit from upfront surgery (Leibel and Phillips, 2010)

Radiotherapy is the preferred larynx preserving treatment for early stage cancer of the larynx with surgery reserved for salvage after radiation failure (Perez and Brady 2008). Larynx

preservation is achieved in 78-95% patients treated with radiotherapy for T1 lesion and 71-88% with T2 lesion (Leibel and Phillips, 2010).

(Mittal B et al, 1983) retrospectively analysed survival, tumour control, voice preservation and complications in patients with early T1/T2 laryngeal cancer treated with radiotherapy. Their 5 and 10 year survival rates were 97% and 95%, respectively. The tumour was ultimately controlled in 97% of patients and voice was preserved in 93% of their patients.

(Mendenhall WM et al, 2001) analysed patient related and treatment related parameters that may influence the likelihood of cure in patients with T1-T2 laryngeal cancer treated with radiotherapy and found that the major treatment related parameter that influenced cure was overall treatment time. They found that radiotherapy cured a high percentage of patients with T1-T2 cancer of larynx and had a low rate of severe complications.

In a retrospective study by (Cellai E et al, 2005) where they looked at results of 1087 patients with T1N0 cancer of the glottis treated with radical radiotherapy from two Italian radiation oncology centres. They found that the 3, 5 and 10 years local control rate was 86%, 84% & 83% respectively while the overall survival rate was 86%, 77% and 57% respectively.

(Johansen L.V et al, 1990) analysed primary radiotherapy for T1 squamous cell carcinoma of the larynx in 478 patients treated from 1963- 1985. Their 10 year survival for supraglottis and glottis tumours were 67% and 94%. They found that the major problems were new primary cancers which within 20 years occurred in 34 % of patients for supraglottis and 23% for glottis patients.

(Yamazaki H et al, 2006) also found that shorter overall treatment time showed superior local control for patients with T1N0M0 cancer of larynx treated with radiation therapy. In their randomised prospective study they compared local control for two fractionation regimens of

2Gy and 2.25Gy and the 5 year local control rate was 77% for the 2Gy arm and 92% for the 2.25Gy arm. No significant differences were found between the two arms in terms of adverse reactions.

American Society of Clinical Oncology (ASCO) convened an Expert Panel under the auspices of the Health Services Committee to develop recommendations regarding the appropriate application of larynx-preservation therapies (Pfister D.G et al, 2006). They recommend that all patients with T1 or T2 laryngeal cancer, with rare exception, should be treated initially with intent to preserve the larynx.

The incidence of lymph node involvement for T1 lesion is close to zero and for T2 lesion is 2% (Perez and Brady, 2008) therefore the treatment field is usually a small portal covering the primary lesion only, lymph nodes are not included as shown in Figure1.2.1below. Commonly used dose fractionation schedules at many institutions for early cancer of the larynx T1-T2 lesion is 66Gy/33# (2Gy per fraction) daily (Perez and Brady, 2008). Evidence suggests that increasing the dose per fraction may improve the likelihood of local control as shown in the study by (Yamazaki H et al, 2006).

A study of modest size fixed field radiotherapy approach for clinically node-negative supraglottic carcinoma of the larynx showed that treating a modest size fixed field to a high biologically effective dose is highly effective and enables preservations of larynx with acceptable regional control and no loss of survival compared to whole neck radiotherapy regimes (Sykes A.J et al, 2000).

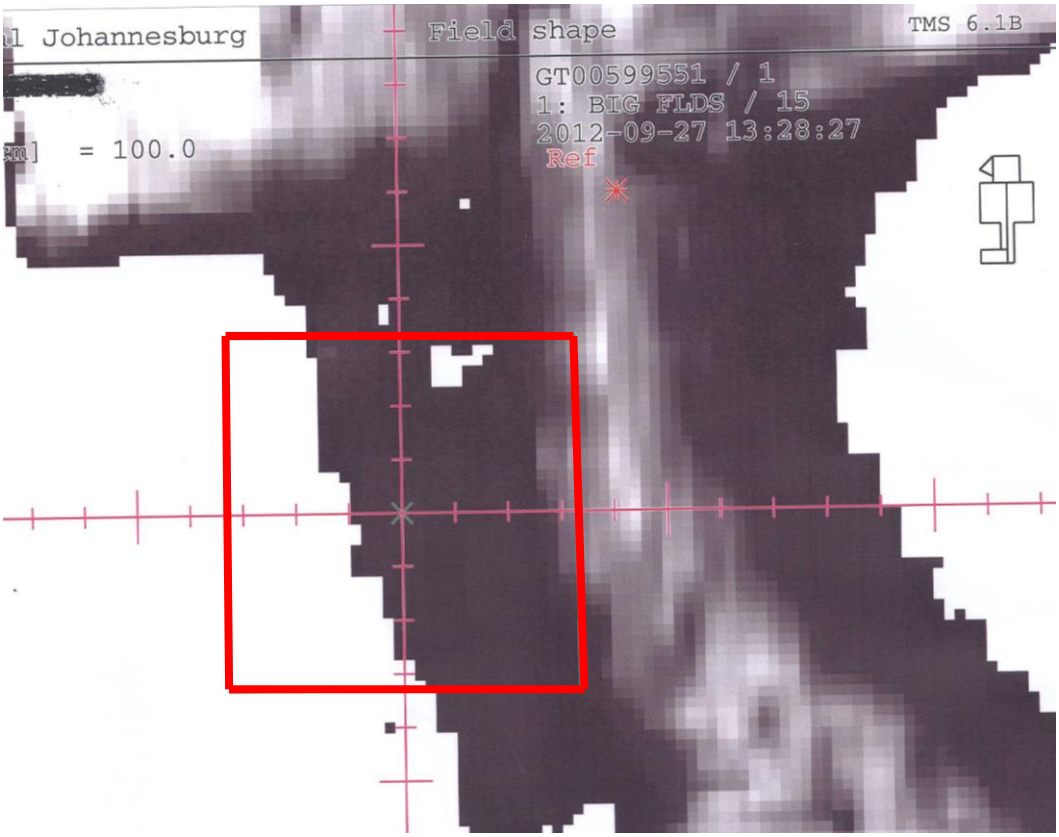

Figure 1.2.1 Treatment portal for early stage cancer of the larynx. Extent of field indicated by bold red line, field size usually 6x6 cm). Digitally reconstructed radiographs (DRR's) from Charlotte Maxeke Johannesburg Academic Hospital.

1.2.3 Management of advanced stage III & IV cancer of the larynx

In the 1980's total laryngectomy was the standard treatment for locally advanced stage III & IV cancer of the larynx. Postoperative radiation was often needed in these patients if surgical margins were positive, tumour extended into soft tissues, subglottic extension > 1cm, cartilage invasion, perineural invasion, multiple positive lymph nodes & extracapsular invasion (Pfister D.G et al, 2006). Partial laryngectomy and radiation therapy were the recommended therapeutic options for selected patients, hoping to avoid total laryngectomy (Pfister D.G et al, 2006).

Definitive radiation therapy alone was reserved for medically inoperable patients (Perez and Brady, 2008).The results of radiation alone proved to be suboptimal when compared with radiation therapy given after surgery in the long term follow up study of RTOG 73-03 (Tupchong L et al, 1991).This phase 3 study of preoperative (50.0Gy) versus postoperative radiation therapy (60.0Gy) for supraglotitc larynx and hypopharynx primaries showed 78% of loco-regional failure occurring in the first two years when considering only supraglottic larynx. Preoperative patients had 31% local failure rate within two years versus 18% of postoperative patients. After two years distant metastases and second primaries became predominant failure pattern especially in postoperative radiation therapy patients. The study showed no advantage in absolute survival for postoperative patients and the rates of severe surgical and radiation therapy complications where similar between the two arms (Tupchong L et.al, 1991).

Total laryngectomy in patients with stage III or IV cancer of the larynx currently is reserved as salvage therapy for local failures after larynx preserving non surgical treatment approach or for patients with extensive cartilage involvement.

(Webber R S et.al, 2003) looked at the outcome of salvage total laryngectomy (TL) following organ preservation therapy. The study evaluated the incidence of morbidity, mortality and disease control for patients requiring salvage total laryngectomy following organ preservation therapy from 1992 to 2000. It concluded that laryngectomy following organ preservation therapy was associated with acceptable morbidity. Peri-operative mortality was low but up to one third of patients developed a pharyngocutaneous fistula, locoregional control following salvage TL was good more than 74% and survival was not influenced by the initial organ preservation treatment.

a) Larynx preserving treatment approach for stage III and IV cancer

In 1991 the landmark Veterans Affairs (VA) laryngeal cancer study first established the role of chemotherapy as part of a larynx preserving treatment strategy for advanced laryngeal cancer stage III and IV disease (Wolf et al, 1991). This trial provided the best initial evidence to support cisplatin based induction chemotherapy as part of a larynx preserving treatment approach. They randomised patients with stage 3 or 4 laryngeal cancer to primary surgery followed by post operative radiotherapy versus 3 cycles of induction chemotherapy followed by radiation therapy if patients showed response to chemotherapy after 2 cycles. Those patients who had no response or showed disease progression after chemotherapy were treated with surgery (total laryngectomy) instead of radiation therapy. Surgery was also reserved for patients who relapsed after radiation as salvage therapy. The chemotherapy and radiotherapy arm yielded survival rates comparable to those achieved with primary surgery and two thirds of the patients retained their larynx function.

The EORTC Head and Neck Cancer Cooperative Group in 1996 further supported the principles of the VA trial. The prospective study aimed at comparing larynx preserving treatment (induction chemotherapy plus definitive radiation therapy in patients who showed complete response or surgery in those who did not) with conventional treatment (total laryngectomy with radical neck dissection and post-operative radiation) Lefebvre JL et al, 1996. The study showed a median duration of survival of 25 months in the immediate surgery arm and 44 months in the induction chemotherapy arm resulting in the treatments being judged to be equivalent. The 3 and 5 years estimate of retention of a functional larynx in patients treated in the induction chemotherapy arm was 42% and 35% respectively. In conclusion larynx preservation without jeopardising survival is feasible with the use of induction chemotherapy followed by radiotherapy (Lefebvre JL et al, 1996).

A randomized trial of induction chemotherapy with cisplatin (P) and 5-fluorouracial (F) with or without docetaxel for larynx preservation suggested that docetaxel (T) may add to the efficacy of PF(Pointreau Y et.al, 2009).The objective of this trial was to determine whether adding T to PF could increase the laryngeal preservation rate. Results showed that in patients with advanced larynx and hypopharynx carcinomas, TPF induction chemotherapy was superior to the PF regimen in terms of overall response rate. These results suggest that larynx preservation could be achieved for a higher proportion of patients (Pointreau Y et.al, 2009).

The primary objective of combining chemotherapy with radiation therapy (concurrent chemo-irradiation) was to achieve an improved therapeutic result which could be evaluated as a function of enhanced tumour response or reduced normal tissue toxicity (Leibel and Phillips, 2010).Chemotherapeutic agent e.g. cisplatin act as both radiosensitizers and also provide additive cytotoxicity (Perez and Brady, 2008). Four mechanisms were described by (Steel GG et al, 2000) in which combined modality therapy i.e. chemotherapy plus radiation could improve therapeutic outcome: 1) spatial cooperation, 2) toxicity independence, 3) protection of normal tissue, 4) enhancement of tumour response

The Radiation Therapy Oncology Group (RTOG) Study 91-11undertaken in collaboration with head and neck intergroup and published in 2003 established the use of concurrent chemotherapy with radiation as the superior non surgical larynx preserving strategy (Forastiere A.A et al, 2003). The study demonstrated that patients with advanced laryngeal cancer receiving concurrent cisplatin and radiation had a better larynx preservation rate of 84% at a median follow up of 3.8 years compared to that afforded either by radiation alone (67%) or by induction cisplatin / 5FU followed by radiation (72%) Forastiere AA et al,2003.

Chemotherapy concurrently with radiation therapy in head and neck cancers showed survival benefits in the Meta-Analysis of chemotherapy in head and neck cancer group (MACH-NC)

Pignon JP et al, 2007. The study identified that the addition of chemotherapy to loco-regional treatment provides a modest overall improvement in survival (4% at 5years) for patients with loco-regionally advanced head and neck cancer. There was a (8%) benefit with the use of concomitant chemotherapy and radiotherapy with no significant benefit for the use of induction or adjuvant chemotherapy (Pignon JP et.al, 2007).

In a phase 2 trial of chemo-radiotherapy as the primary therapy for locally advanced head and neck cancers, cisplatin, infusional fuorouracil and hydroxyurea were used along with radiation therapy twice daily at 1.5 Gy/fraction on days 1-5 (total dose-15 Gy). Five days of treatment were followed by 9 days of rest, during which time patients received granulocyte colony-stimulating factor. At a median follow-up of 38 months, the 3 year progression-free survival was 72%, loco-regional control 92%, systemic control was 83%, and overall survival 55%. Toxicities included mucositis (grade 3= 45%; 4= 12%), neutropenia (grade 4= 39%), and thrombocytopenia grade 4= 53% (RTOG appendix 3). They concluded that intensive concomitant chemotherapy plus radiotherapy leads to high loco-regional control and survival rates with organ preservation and a reversal of the historical pattern of failure (distant > loco-regional) Vokes E.E et.al,2000.

There has been growing interest in identifying molecular markers to predict disease outcome. Cetuximab a monoclonal antibody against EGFR (epidermal growth factor receptor) has been used to enhance cytotoxic effect of radiation therapy for head and neck cancers. This drug has not been directly compared with cisplatin but may be considered for patients who have co-morbidities that contra-indicates cisplatin use (Perez and Brady).

There is renewed interest in the role of induction chemotherapy as part of sequential treatment in the concurrent chemotherapy with radiotherapy schedule for advanced larynx cancer (Leibel and Phillips, 2010). Results of ongoing randomised trials comparing induction

chemotherapy followed by chemotherapy plus radiotherapy versus chemotherapy plus radiotherapy alone are awaited (Leibel and Phillips, 2010).

b) Radiation Therapy technique for advanced stage III & IV disease

For advanced stage lesions the incidence of lymph node involvement increases to 20-30% therefore fields are larger to cover lymph nodes which include the jugulodigasric (level IIA & IIB nodes) and middle jugular lymph nodes (level III nodes) shown in Figure1.1.3 above. The treatment fields are depicted in the DRR's (Digitally Reconstructed Radiographs) from CMJAH **figure1.2.2** (large lateral field) and **figure 1.2.3** (lateral off-cord field) the posterior border is moved forward after 40Gy/20# radiation dose to come off the spinal cord. The inferior jugular nodes (level IV nodes) are included in a separate low neck portal **figure1.2.4** (anterior neck field). Lead (Pb) shield is introduced in the centre after 40Gy/20# radiation dose to shield the spinal cord **figure1.2.5.** Dose fractionation schedule for T3/T4 lesion is 70Gy/35# (2Gy per fraction) daily (Perez and Brady).

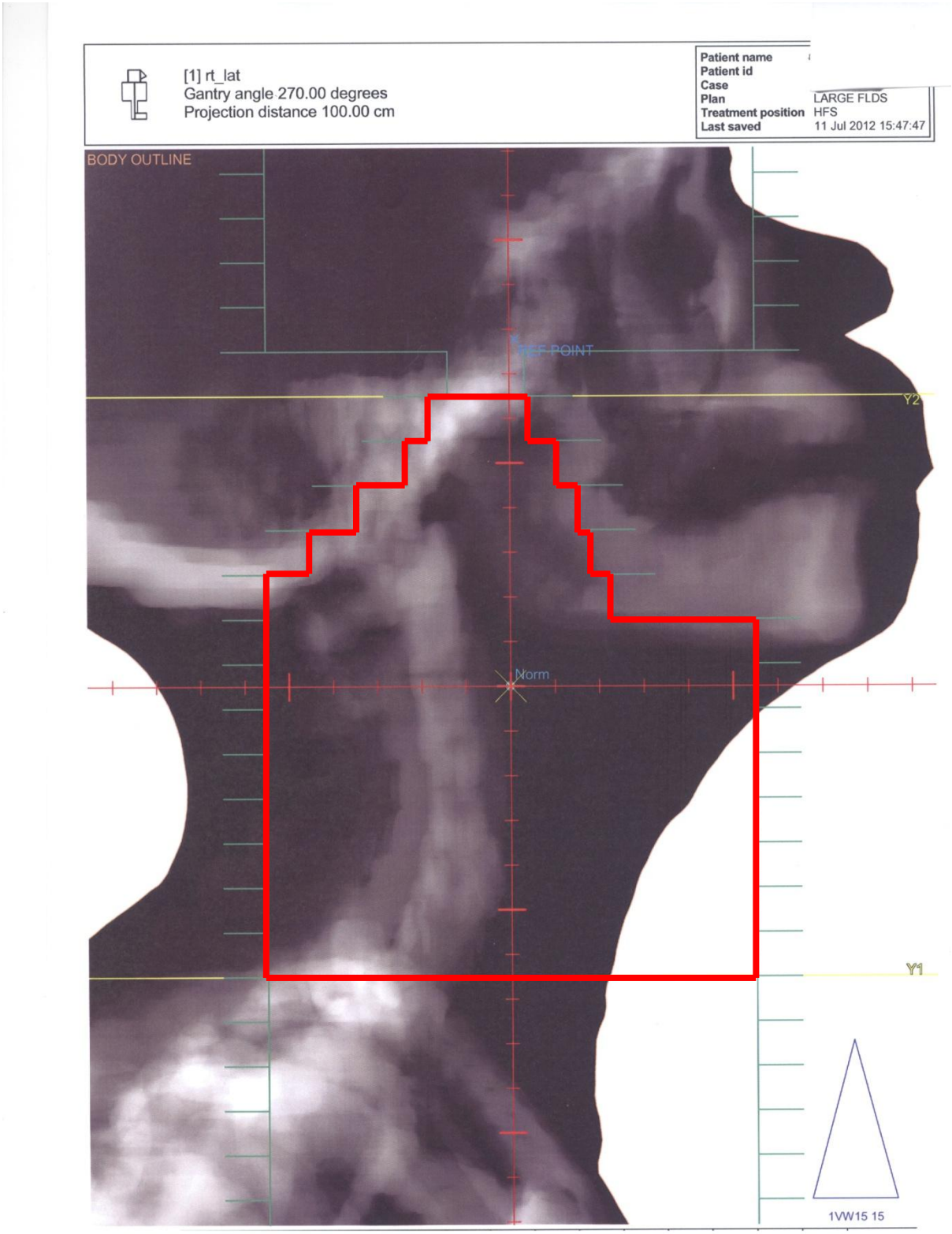

Figure 1.2.2 Lateral large field for treating advanced stage cancer of the larynx. Extent of field indicated by bold red line.

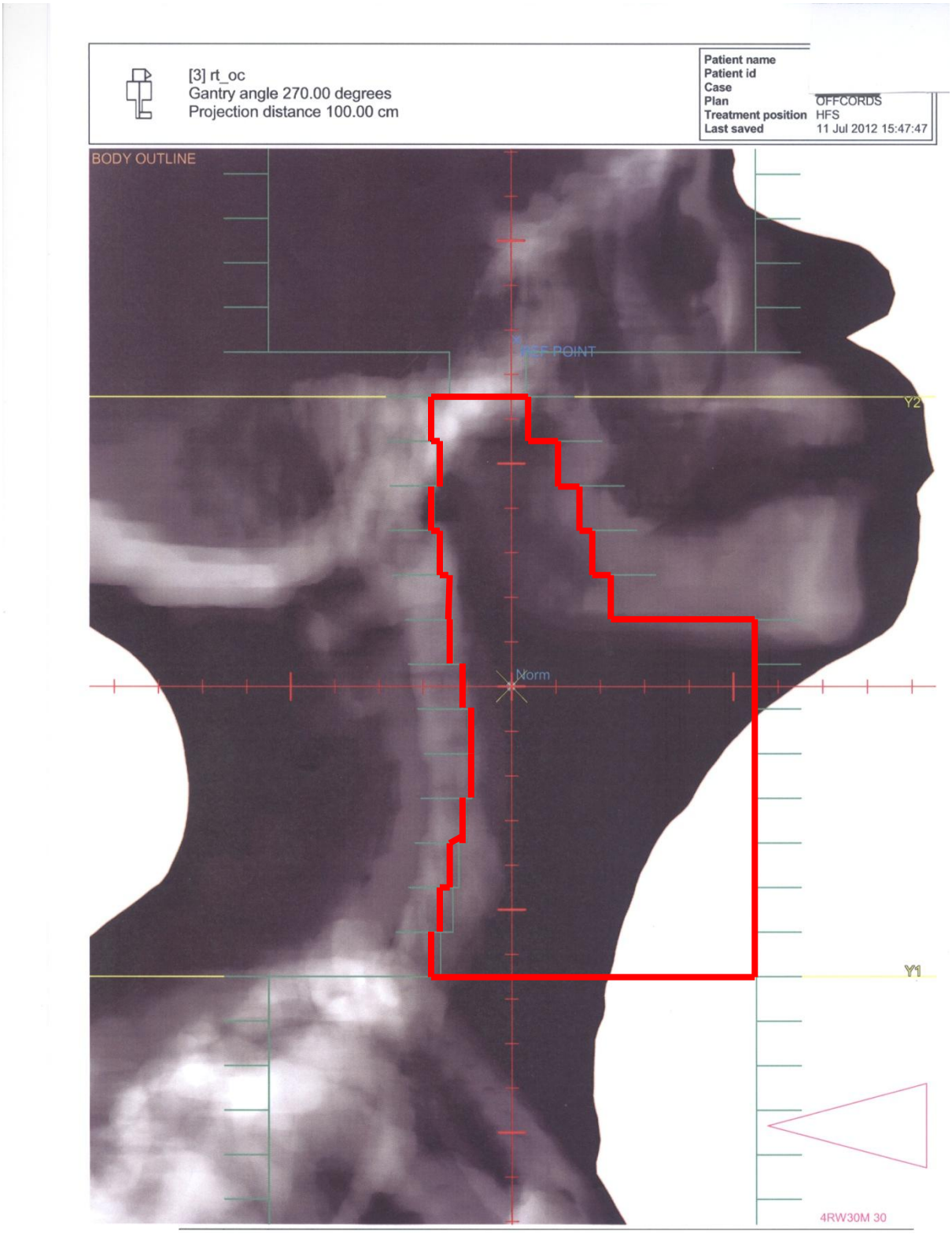

Figure 1.2.3 Lateral off-cord field (bold red line). The posterior border is moved forward to come off the spinal cord.

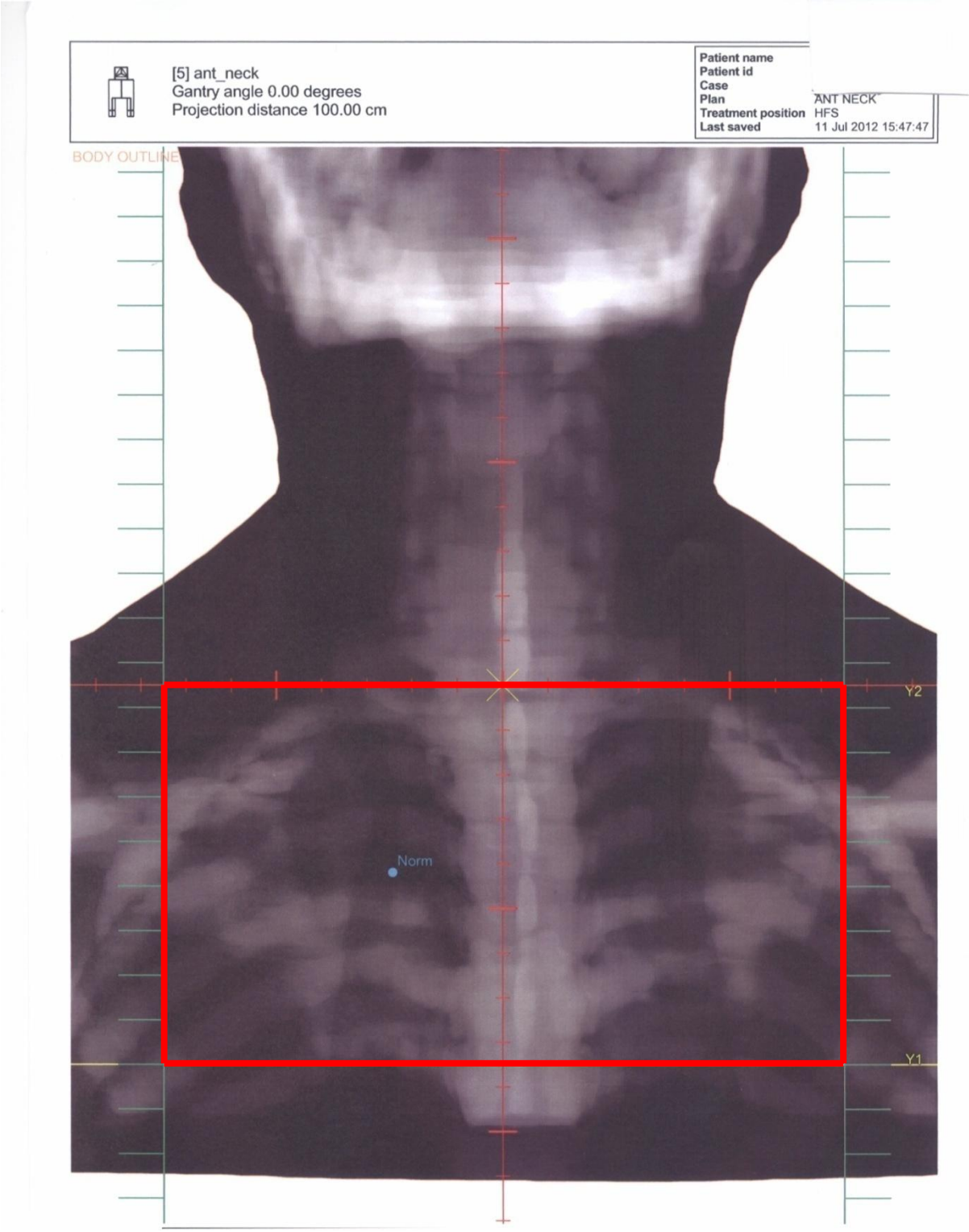

Figure 1.2.4 Anterior neck field for advanced cancer of the larynx. Superior border is matched to lateral fields shown in Figure 1.2.2 & Figure 1.2.3 above. Extent of field indicated by bold red line.

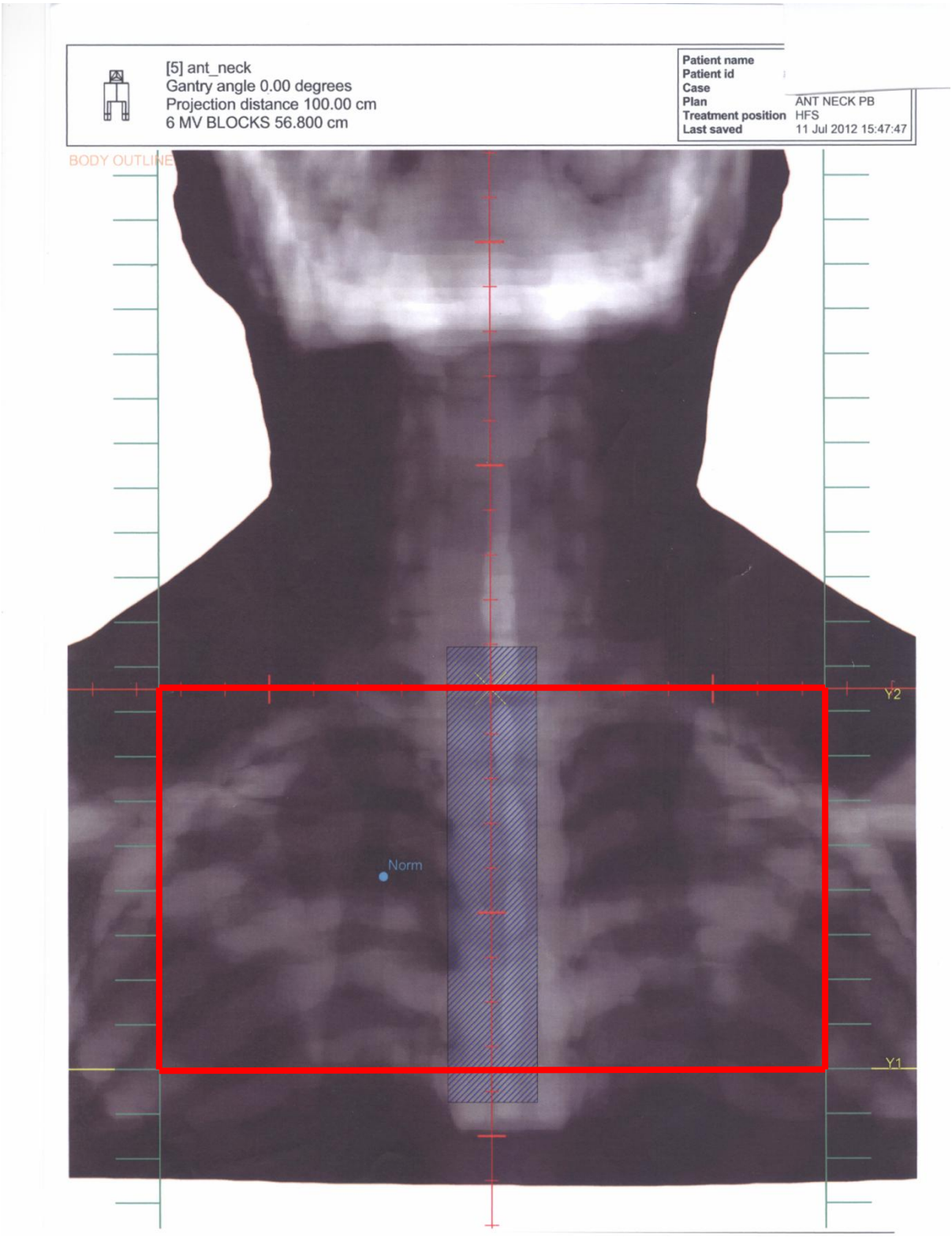

Figure 1.2.5 Anterior neck field with lead (Pb) shield in the centre. Extent of field indicated by bold red line.

1.3 Factors that negatively influence treatment outcome

Overall treatment time is a very important factor determining outcome of head and neck cancers treated with radiotherapy. Head and neck cancers are fast growing tumours with rapid proliferation and treatment with radiation can trigger surviving cells (clonogens) in the tumour to divide faster than before i.e. accelerated repopulation (Hall EJ, 2000). The clonogen repopulation accelerates at about 28 days after initiating radiotherapy and local control is reduced by about 0.4 to 2.5 % for each day that the overall treatment time is prolonged (Hall EJ, 2000).

The influence of the number of fractions and overall treatment time on local control and late complication rate in advance T3/T4 (N0M0) squamous cell carcinoma of the larynx was retrospectively assessed by (Hliniak A et.al, 1983). After a minimum of 3 years follow-up 310 patients were assessed by the same laryngologists .Local control was achieved in 50% of patients and 21 patients who had tumour control, developed severe late complications such as necrosis or laryngeal oedema during the follow-up period. Overall treatment time was the predominant factor as patients with longer overall treatment time had more late complications and poorer local control.

(Overgaard J et.al, 1998) also compared conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx in 308 patients treated to 57Gy or 60Gy. Results showed that split-course was associated with a significantly reduced therapeutic ratio and did not improve tumour control while the severity of late complications increased. The 3-week pause in the radiation therapy did not reduce late complications, and the tumour response did not improve despite a 12-Gy increase in total dose. This indicates a significant repopulation and increase of number of clonogenic tumour cells during the pause. It is evident from these

studies that splitting treatment and increasing overall treatment time lead to poorer tumour control and increased late complications.

Waiting time prior to radiotherapy is a major problem in many radiotherapy centres and has a negative impact especially for rapidly growing head and neck cancers.(Jensen A.R et al, 2007) looked at tumour progression in waiting time for radiotherapy in head and neck cancer. They assessed the change in tumour volume on CT scans done during the waiting time and found that within an average of 4 weeks the majority of patients developed significant signs of tumour progression, 62% had measurable increase in tumour volume, 20% developed new lymph nodes and 10% progressed in TNM stage.

Effects of treatment delay on outcome of patients with early stage head and neck carcinoma receiving radical radiotherapy were assessed in a retrospective study by (Fortin A et al, 2002). They found that treatment delay of more than 40 days was significantly associated with increased risk of local and neck failure and poorer survival relative to patients treated in less than 30 days. They concluded that radiotherapy for squamous cell carcinoma of the head and neck should be started preferably within 20-30 days after evaluation by radiation oncologist.

(Hansen O et al, 2005) assessed the relationship between the duration of symptoms before the start of radiotherapy and treatment outcome in stage I – III glottis cancer. They found that one month delay from onset of symptoms to start of radiotherapy was equivalent to a 4.5 % decrease in recurrence free survival.

1.4 Palliative Radiotherapy

A proportion of patients with head and neck cancers are not candidates for curative therapy because of advanced stage of disease, medical comorbidities, performance status e.g. ECOG performance status (appendix 2) or a combination of these factors. Although the prognosis for these patients is poor, palliative radiotherapy has been widely used to provide symptom relief.

(Christiaan M et al 2011), retrospectively analysed palliative radiotherapy in newly diagnosed head and neck carcinoma and found that 82 % of their population had treatment response to palliative radiotherapy, 12 % had no response or progressive disease while 6 % had mixed responses. Delivered radiation dose was the only statistically significant predictor of treatment response and overall survival. In this study the median radiation dose was 50Gy and the median fraction number was 20.

Laryngeal cancer even in advanced stages has a relatively high cure rate if managed appropriately hence there's limited data on palliative treatment for laryngeal cancer.

2. CURRENT STUDY

2.1 Background

Most of the studies that demonstrated the feasibility of larynx preservation with chemotherapy plus radiotherapy for advanced cancer of the larynx were done in more developed countries than South Africa where resources are readily available. At the time we started the treatment it was not known how patients in our institution Charlotte Maxeke Johannesburg Hospital (CMJAH) would tolerate the recommended concurrent chemotherapy plus radiation therapy.

Most of our patients are of low socio-economic background as there is increasingly high unemployment rate of 25.2% (Statistics South Africa, 2013) they have poor nutritional support. In South Africa resources are limited as one radiation oncology centre in Johannesburg serves more than 10 hospitals for treatment of all types of cancer (personal communication with Miss Salome Liebenberg -departmental database collector).Patients travel long distances for radiation therapy from different hospitals e.g. patients from as far as Mafikeng (292km) in the north west province referred by Klerksdorp Hospital to CMJAH for radiation therapy (Map data ©2013 AfriGIS (Pty) Ltd, Google).

Resource constraints within the hospital as there are no dedicated oncology facilities, oncology patients have to wait with medical and surgical patients for investigations such as pathology and imaging. This can delay the preparation, staging and planning of therapy and the time needed to complete treatment for each patient of +/- 6 weeks also lead to long waiting times before treatment can be commenced.

In view of all the problems identified in our department of Radiation Oncology at CMJAH, this study was done to assess how patient's treatment is affected.

2.2 Study Objectives

- To describe the demographics of the population
- To compare characteristics of patients in the different treatment groups
- To assess waiting times, treatment completion rates and overall treatment time for all patients in the study group.
- To describe outcomes of patients at last follow up and survival for different stages of disease.

2.3 Material and Methods

The study was done at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) department of Radiation Oncology. The hospital is a tertiary academic institution that receives referrals from primary and secondary health institutions around Gauteng.

The department of Radiation Oncology at CMJAH sees about 70-80 new patients with cancer of the larynx each year (personal communication with Miss Salome Liebenberg - departmental database collector). Patients treated with radiotherapy for cancer of the larynx with or without chemotherapy between the year 2007 and 2009 were retrospectively assessed. Males and female patient were included in the study. Early, stage I and stage II disease and advanced, stage III and stage IV disease were assessed.

The sample included patients who were treated with radical intent which included:
(1) concurrent chemotherapy plus radiotherapy, (2) radical radiotherapy alone,
and patients treated with palliative intent which included: (3) patients with disease progression ‘treatment intent changed from radical to palliative’ and, (4) patients with

advanced disease i.e. on first assessment at the multidisciplinary meeting with ENT surgeons were deemed unfit to undergo radical treatment.

Some patients at initial assessment were planned for radical treatment but their condition or ECOG (appendix 2) performance status deteriorated while they wait for treatment and their treatment is changed to palliative. The waiting time was calculated from the date when patient was first seen in the radiation oncology department to the date that treatment was started. All patients were staged using the AJCC 2002 cancer staging manual 6th edition (Hansen EK; Roach M, 2010) as the patients in the study were assessed before the new AJCC 2010 manual 7th edition (Hansen EK; Roach M, 2010).

The AJCC 2002 (TNM and Group staging) was republished with no changes in the AJCC 2010 manual 7th edition (Hansen EK; Roach M, 2010) as well as the group staging shown in table 1.1.

Since radiation therapy is given daily Monday to Friday patient's treatment charts were looked at to see if there was a gap in treatment dates. If a gap was found then the doctor's notes on that date were checked to see if the patient's treatment was split because of treatment toxicity (RTOG/EORTC) radiation toxicity grading system (appendix 3).

Patients who did not have treatment interruption due to toxicity were excluded from the analysis of toxicity. All files were checked to see if treatment was completed as prescribed and the total dose administered was noted, for radical cases chemotherapy cycles given were noted. Follow-up time was calculated from the date of last treatment to the date last seen in the clinic for review. Outcome of patient when last seen (whether symptoms improved or not or patient demised) was documented. Patients who were not seen at our clinic since completion of treatment were entered as lost to follow-up.

2.3.1 Exclusion criteria

1) Patients who had surgery more than just a tracheostomy e.g. partial or total laryngectomy prior to radiation therapy as the study only assessed larynx preserving treatment approach.
2) All patients with cancer of the larynx who were seen at our clinic during the time period year 2007-2009 but never received any radiotherapy.

2.3.2Treatment Protocol CMJAH

Radiation Therapy

- Treatment and side effects thereof are explained to the patient and informed consent is obtained.
- All patients treated with radical intent were sent for dental assessment and clearance prior to treatment
- Patients are immobilised in a mask in supine position and neck in extension.
- CT scan of head and neck is done with patient in treatment position
- Fields are delineated according to extent of disease as in figure 2.1 for early stage I & II disease and figures 2.2 to 2.5 above for locally advanced stage III & IV disease
- Photons energy of 6MV (Megavoltage) used
- The posterior neck is boosted with electrons 10Gy in 5 fractions
- If patient had a tracheostomy the stoma is boosted with 20Gy in 10 fractions.
- The total radiation dose for T1/T2 disease is 62Gy/31# to 66Gy/33# and for T3/T4 disease is 70Gy/35#. During radiation therapy patients were assessed for treatment toxicity which is graded using the RTOG/EORTC radiation toxicity grading system (appendix 3).

Chemotherapy

Cisplatin 70mg/m2 is given 3 weekly to patients treated with radical intent. Before administration bloods are taken for FBC (WCC>3.000 cells/µl, HB=12g/dl as long as not < 10g/dl, Plt >100 cells/µl), urea and creatinine, magnesium, calcium. Creatinine clearance is calculated using the Cockcroft and Gault formula and if >60mils/min chemotherapy continues, if < 60mils/min chemotherapy is not given.

Cockcroft and Gault formula (O.O. Faluyi et.al)

- **140-age(years) x weight(kg) x 1.23 / creatinine (mmol)** for males
- **140-age (years) weight(kg) x 1.04 / creatinine (mmol)** for female

Each patient is given pre-hydration using normal saline calcium, magnesium and potassium prior to chemotherapy. Anti emetic drugs including: 5-hydroxytryptamine-3 (5HT3) receptor antagonist, i.e. Granisetron or Ondansetron which significantly reduces acute cisplatin-induced emesis are given. One week after chemotherapy the above mentioned blood tests are repeated and electrolytes are corrected. The department has a dietician who assists and monitors nutritional status of patients and provide nutritional support during treatment.

2.4 Data Analysis

Data was analysed using descriptive statistics with frequencies + percentages for categorical data and means or medians and standard deviations or ranges for numerical values. The comparison of waiting times amongst treatments was done using the independent sample test. The equality of variances assumption was tested using the Levene's test for equality of variances before the waiting time comparison was made. Survival was calculated using the Kaplan-Meier method.

3. STUDY RESULTS

The department of Radiation Oncology at CMJAH saw 203 new patients with cancer of the larynx between the year 2007 and 2009. Only 106 patients were eligible for analysis as other patients were excluded. Sixteen patients were excluded because they had partial /total laryngectomy prior to radiotherapy and the other 81 patients were excluded because did not receive radiotherapy.

Males made up the majority of the population 91.5% versus 8.5% for females. The mean age at presentation was 58.6 years (standard deviation of 10.05). Of the 106 patient included in the study the majority 67% presented with stage IVa disease, 14% of patients had stage IVb, 13% had stage III, and very few had stage I and II disease 4% and 2% respectively (Figure 3.1).

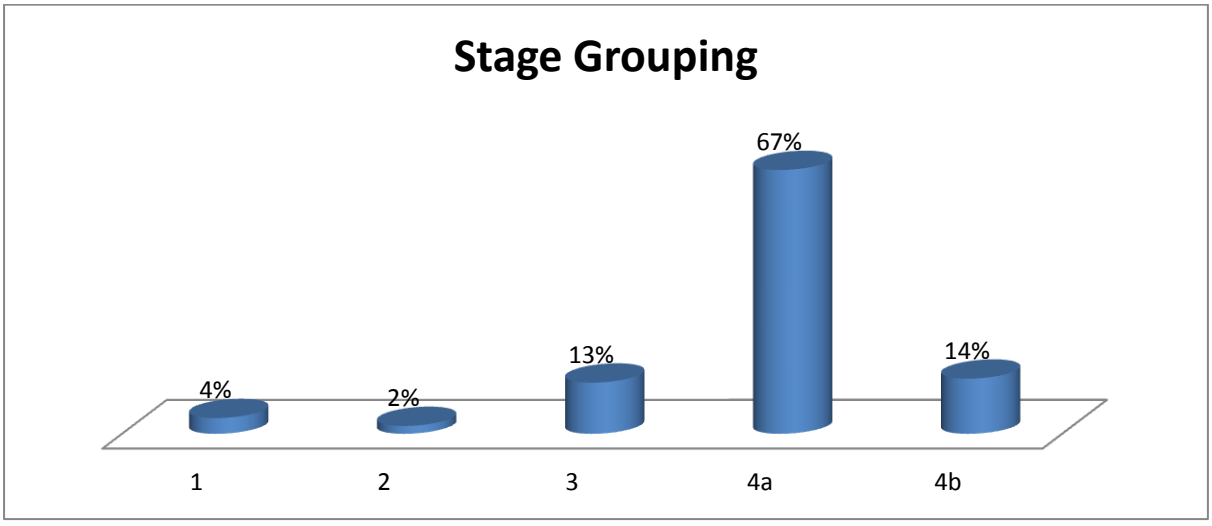

Figure 3.1 Distribution of subjects in the study with respect to the stage of disease.

In our department we have two main treatment groups based on the treatment intent i.e. Radical (curative) intent or Palliative intent. When assessing characteristics of patients in these two treatment groups we discovered that both groups were further divided into two groups which gave a total of four treatment groups.

The patients treated with radical intent were divided into Radical radiotherapy with concurrent chemotherapy and Radical radiotherapy alone. The characteristics of patients treated with palliative intent further divided this group into patients who had disease progression while awaiting treatment, therefore their treatment intent changed from radical to palliative and those who presented with advanced disease at first visit and required palliation from the start. Figure 3.2 shows the four different treatment groups and the percentage of patients treated.

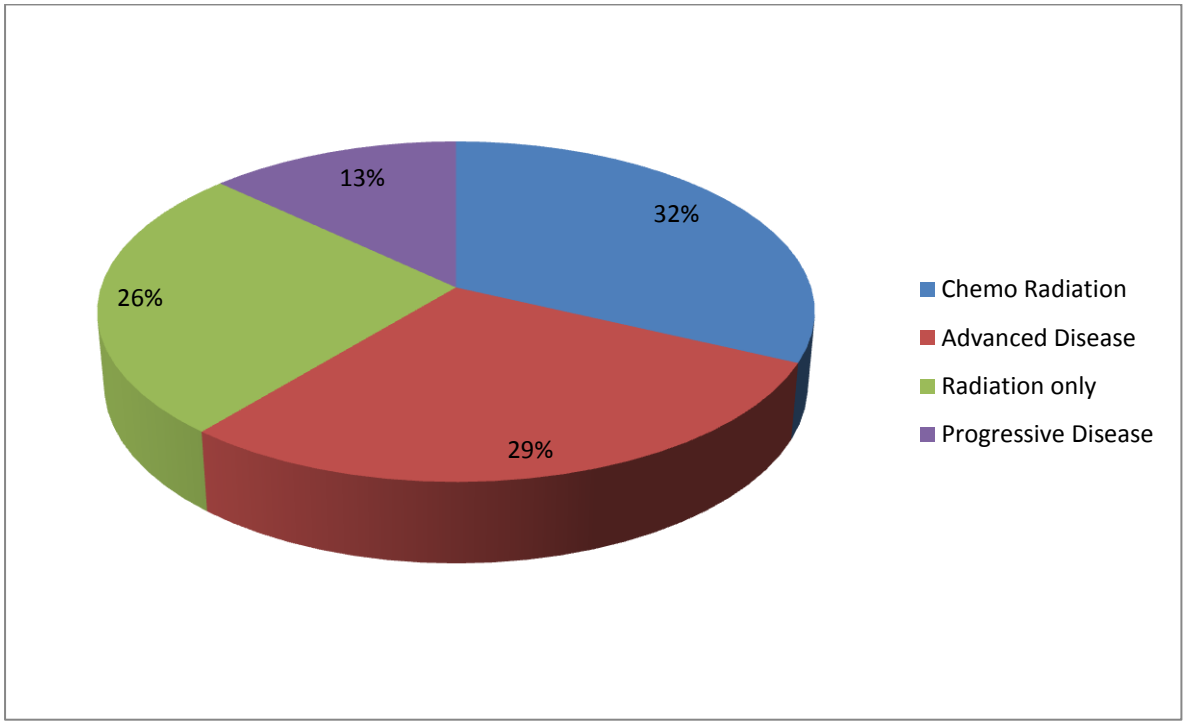

Figure 3.2 Treatment groups and percentage of patients treated

A total of 42.5% of the patient population were treated with palliative radiotherapy divided between those with progressive disease (13%) and those with advanced disease (29%) at initial assessment.

Most (57.5%) of the population were treated with a radical course of radiotherapy with an almost equal split between those receiving concurrent chemotherapy and radiotherapy and those receiving radical radiotherapy alone.

Table 3.1 Demonstration of Stages of disease between the four treatment groups.

		Treatment				
		Chemo/Rt	Palliative (advanced disease)	Radical Rt only	Palliative (disease progress)	Total (pt no) & %
Group Stage	I	0	0	4	0	4 (4%)
	II	0	0	2	0	2 (2%)
	III	4	2	7	1	14 (13%)
	IVA	27	20	13	11	71 (67%)
	IVB	3	9	1	2	15 (14%)
TOTAL (pt no)		34	31	27	14	106
TOTAL (%)		32%	29%	26%	13%	100%

Rt= Radiotherapy (pt no) = patient numbers

All patients with early stage I and II disease received radical radiotherapy without chemotherapy. Most of the patients with stage III disease were treated with radical intent and majority of them received radiotherapy alone (7) only a few received chemotherapy with radiotherapy (4). Reasons for patients with stage III disease not receiving chemotherapy were not clearly documented. In some cases low CD4 count was documented as reason for not giving chemotherapy but this was not always documented in other files. Since an HIV test was not an entry requirement for this study data was collected if documented but was not analysed. Of those with stage III disease treated with palliative intent only one patient was

due to disease progression while awaiting treatment while the other two had poor performance status at initial assessment.

In patients with stage IVa (total 71) majority (40) was treated with radical intent (chemo/Rt and Radical Rt alone) while (31) received palliative treatment. Those with stage IVb (total 15) majority (11) received palliative treatment and only 4 patients were treated with radical intent. Of the total population in the study stage IVa and stage IVb make up for the most of patients treated with palliative intent due to the advanced stage of disease and or poor performance status.

The waiting time was calculated from the date when patient was first seen in our department to the date that treatment was started. Patient delays prior to being seen at our hospital e.g. waiting for histology results from referring hospitals were not included since they are out of our control. The overall mean waiting time for treatment in the study group was 98.5 days. When comparing the waiting time for the different treatment groups, in the group that was treated with palliative intent those patients that had disease progression had a longer waiting time compared to those that had advanced disease at presentation i.e. 187.9 days versus 46.3 days standard deviation of 186.1 ($p=0.014$) which was statistically significant. Patients with advanced disease at presentation have a shorter waiting time because their treatment planning technique is less sophisticated and their treatment time is shorter than radical cases therefore their waiting list is shorter.

The waiting time for patients with disease progression was not statistically significant when compared with patients who were treated with radical intent i.e. Radiation alone and Chemo-Radiotherapy, 187.9 days versus 97.8 days and 109.8 days ($p=0.095$ and $p=0.174$). Since the patients who had disease progression are those who were deemed curable (with good performance status) at initial assessment their waiting time was not statistically different from

the waiting time of other patients treated with curative intent Radiation alone and Chemo-Radiotherapy.

Most of the population (84%) completed treatment (radiation fractions) as prescribed while 16% did not. Of those that were treated with concurrent chemotherapy plus radiotherapy 2.9% completed 3 cycles of chemotherapy, 32.4% received 2 cycles of chemotherapy and 64.7% received only 1 cycle of chemotherapy. Some patients did not receive their 2nd or 3rd cycle of chemotherapy due to low creatinine clearance other patients reasons for not completing chemotherapy was not documentation in their medical records.

A small number of patients (6.6%) had treatment interrupted by the doctor due to toxicity and five patients had a treatment break of less than 15days while the other 2 had a treatment break for more than 15 days. Those patients who had a longer treatment break had a longer overall treatment time and we looked at how that influenced their outcome (table 3.2).

Table 3.2 -**Patients with more than 2 weeks treatment interruption (planned break)**

Patient	Stage	Split duration	Reason for break	Outcome
1)	T4N2 i.e. Group stage IVB	42days	Severe moist desquamation of the skin after 50Gy/25# RTOG grade 3 toxicity	Treatment schedule adjusted to compensate for split and dose completed. Patient had neck fibrosis on follow-up
2)	T3N3 i.e. Group stage IVB	27days	Developed obstructive airway symptoms treatment split for tracheostomy to be done RTOG grade 4 toxicity	Treatment schedule adjusted to compensate for split and dose completed. Patient had disease progression biopsy proven lesion on base of tongue.

Outcome of patient population at last follow-up

- 56 patients (52.8%) reported improvement of symptoms when last seen at the clinic.
- 26 patients (24.5%) reported no improvement or worsening of symptoms. Majority of these patients were treated with palliative course of radiation therapy as they had advanced incurable disease or they were in a poor ECOG status (appendix 2).
- 18 patients (17%) were lost to follow-up i.e. were not seen at our clinic since completion of treatment therefore not known whether symptoms improved or not.
- 6 patients (5.7%) demised during or soon after treatment completion.

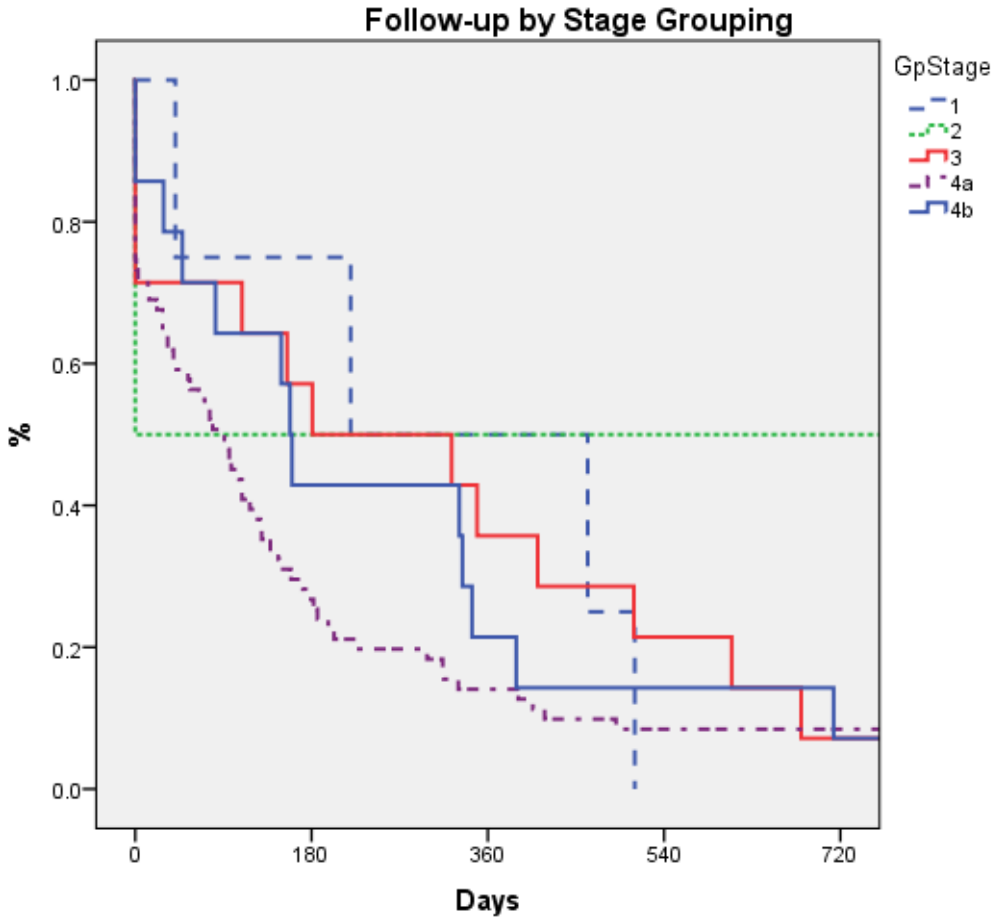

Figure 3.3 Survival in days on last follow-up for different stages of disease (Kaplan Meier)

Survival outcomes were measured from the end of radiotherapy to 1year and 2 years follow up for all the stages of disease. Most of the patients at 2 years follow up were not seen at our clinic either they were lost to follow up or possibly demised. None of the patients with stage I disease which represented 4 % of the population were seen in our clinic at 2 years follow-up and only 50 % of those with stage II were seen at 2 years post treatment. Attempts to call these patients using contact numbers on patient's records were unsuccessful. Patient's identity numbers were not recorded on most patients files to enquire with home affairs whether patients had demised or not.

Patients with advanced stage disease including stage III, IVa and stage IVb who represented the majority of the patients in the study group had survival of less than 20 % at 2 years follow-up. Although stage IVb seems to have done better than stage IVa at 1 year follow-up the graphs come closer together between 1 and 2 years follow-up on the Kaplan Meier and the difference between the two survival outcomes was not statistically significant with the log rank (Mantel-Cox) of 0.628

4. Discussion

Most of the patients seen at our institution during the study period presented with advanced stage of disease stage IVA being the most common followed by stage IVB and stage III. Early stage I & II represented a minority of the total population. Males were more affected than females which correlated with what Perez and Brady 2008 suggested.

Waiting time prior to radiotherapy remains a major problem in most radiation oncology centres. In our study we found that our overall mean waiting time was 98.5 days i.e. from the date when patient was first seen by the oncologist in our department to the date that treatment was started. This is well in excess of that recommended by the standard of care and is reflected in the literature as a worsening prognosis. Fortin A et al, 2002 in their study found that treatment delay of more than 40 days was associated with poorer survival and Jensen AR et al, 2007 also found that 62 % of their patients had increase in tumour volume at 4 weeks waiting time. They concluded that radiotherapy for squamous cell carcinoma of the head and neck should be started preferably within 20-30 days after evaluation by radiation oncologist. We could not evaluate increase in tumour volume in majority of patients during our waiting time as CT scans were not routinely done due to lack of imaging resources.

Disease progression was defined as change in treatment intent from radical to palliative treatment. This was seen in 13% of the study population which is of concern as these are patients who would have received curative treatment if treatment was initiated earlier. We looked at whether patients with disease progression had a longer waiting time for treatment when compared with other patients treated with radical curative intent. Their waiting time was not statistically significant when compared with patients who were treated with radical intent i.e. Radiation alone and Radiotherapy with concurrent chemotherapy, 97.8 days and

109.8 days respectively versus 187.9 days for disease progression group (p=0.095 and p=0.174). The study therefore failed to show that their disease progression was as a result of a longer waiting time. This is probably a result of insufficient numbers to reach statistical significance.

The disease progression group however had a statistically significant longer waiting time when compared with other patients treated with palliative intent due to advanced disease at presentation i.e. 187.9 days versus 46.3 days standard deviation of 186.1 (p=0.014). This is expected as in our department palliative patients are treated sooner because their treatment technique is not sophisticated and does not require specialised treatment planning.

A significant number of our patients (29%) were considered unsuitable for curative treatment at initial assessment. This is a concern in that many patients that could be potentially cured or have a better prognosis if they were seen with earlier stage disease and with better performance status. This reflects a lack of resources to detect and diagnose oncology problems in the communities where the patients are living and a lack of resources and delays with imaging, pathology, referral and transport in the public health environment that the CMJAH functions.

Treatment completion rates and overall treatment time for patients in the study group were assessed. We looked at patients who had their treatment interrupted by the doctor due to toxicity using the RTOG toxicity grading as one of the aims was to assess how patients tolerated treatment. Patients who had treatment interruption on their own were not assessed as some missed treatment because of social reasons not toxicity e.g. lack of money to come for treatment. Although these reasons were not well documented in some files they are common causes for patients to default during treatment and at follow-up.

Seven patients (6.6% of the population) had planned treatment interruption and most of them had a break of less than 15 days while two patients had a treatment break longer than 15 days. Reasons for a longer break were assessed for those patients and shown in table 3.2. The results of longer overall treatment time for our patients were in keeping with results from (Hliniak A et al, 1983 and Overgaard J et al, 1998) as one patient had disease progression while the other patient had severe neck fibrosis. Longer overall treatment time had poor local tumour control and did not reduce the severity of late complications.

Assessment of treatment completion rates for the total population showed that sixteen percent of the patients did not complete treatment as prescribed. Of the radical cases only one third of them received the recommended approach of concurrent chemotherapy plus radiotherapy. Most of the patients in the chemotherapy plus radiotherapy group only received 1 cycle of chemotherapy instead of the recommended 3 cycles. Reasons for not completing chemotherapy were not clearly documented in most patient records, in some patients low creatinine clearance after the first cycle was noted while in some patients low CD4 count was documented. HIV test was not recorded for most patients and since it was not one of the entry requirements for this study, data was collected if documented but was not analysed.

In the RTOG 91-11 study which established the use of concurrent cisplatin and radiotherapy as the superior non surgical larynx preserving strategy patients received 3 cycles of chemotherapy with radiotherapy (Forastiere AA et al 2003). Since most of our patients did not receive treatment according to the recommended schedule our results could not be compared with those in other studies for local control or survival.

Due to lack of resources response to treatment could only be judged by change in symptoms and clinical examination e.g. (IDL) indirect laryngoscope for patients who were followed up. If patients had persistent symptoms or had suspicious IDL examination at follow- up they

were then reviewed with ENT surgeons to do direct laryngoscope and a follow up CT scan. Post treatment CT scans were not routinely done for all patients. Majority of the patients (52.8%) reported improvement of symptoms.

Survival outcomes were measured at 1 year and 2 years follow up. At 1year patients with stage I disease and stage II had 50% follow up, those with stage III had 45% follow up while IVb had 20% and stage IVa had less than 20% follow up. At 2 years none of the patients with stage I disease came for follow up and 50% of patients with stage II disease were followed up. Only 10% of patients with stage III, IVa and IVb disease were followed up at 2 years. The difference in survival at last follow-up was not statistically significant for advanced stage disease i.e. stage III, IVa and IVb with the log rank (Mantel-Cox) of p=0.628.

5. Study Limitations

This is a retrospective study therefore the information recorded in patient's files was not consistent as patients were seen by different doctors who recorded events during treatment differently. In most cases functional outcome and quality of voice post treatment was not recorded therefore we were unable to assess percentage of functional larynx preservation in our study.

Disease progression was defined as change in treatment intent from radical to palliative treatment. Those patients who could have progressed in the T-N-M stage but were still fit for radical treatment could not be assessed as restaging is not routinely done at the start of treatment after waiting time. Our results for patients with disease progression are incomplete.

A significant number of patients (81patients) seen at our institution during the study period had to be excluded because they were not treated and the reasons for not treating were unclear. There was quite a high percentage (17%) of patients with no follow up post

treatment. Response to treatment could only be judged by change in symptoms and (IDL) Indirect Laryngoscope examination findings for those patients who were followed up, post treatment CT scans were not routinely done to assess response. As patients were examined by different doctors at follow up, there was lack of consistency in documenting IDL findings in patient's records.

We could not compare our results of patients treated with the recommended radical concurrent chemotherapy plus radiotherapy with results from other studies as majority of our patient (64.7%) in that treatment arm received suboptimal chemotherapy. Survival outcomes could only be measured for patients who came for follow up post treatment.

6. Conclusion

Cancer of the larynx is a significant disease burden in patients referred to CMJAH. Most patients (81%) presented with advanced stage IV disease (IVa + IVb combined). A significant number of these have disease that is potentially salvageable but delays in treatment delivery are impairing the treatment efficiency. The overriding conclusion in this study was that patients with Head and Neck cancer referred to CMJAH are being inadequately treated with regards to the standards of care as published in evidence based literature. The causes are multi-factorial and relate to the overall functioning of the health services in Gauteng province.

Our institution Charlotte Maxeke Johannesburg Academic hospital as the one centre rendering service to many hospitals for treatment of cancer is under resourced for patient volumes. Waiting time prior to radiotherapy is a major problem in our institution as our overall mean waiting time was 98.5 days which is more that the preferred 20-30 days waiting

time for head and neck cancers (Jensen AR et al). Although the study could not shown that the patients who had their treatment intent changed from radical to palliative i.e. disease progression had a statistically significant longer waiting time compared to patients treated with radical intent, the disease progression group had a mean waiting time of 187.9 days which is almost double our overall mean waiting time of 98.5 days. This is a call for concern for the department to try and reduce treatment waiting times. The causes for delays are multi-factorial and include referring patients for dental assessment and clearance after the initial assessment in the oncology centre, imaging for staging and booking patients for immobilisation and in some instances there is lack of material used for immobilisation which further increase the waiting before treatment planning can be done.

Lack of diagnostic and radiological capacity resulted in us not having measurable tumour volume changes to properly evaluate disease progression during waiting time and to evaluate response to treatment at follow-up. Lack of resources again may partly be responsible for our poor patient follow up as they have to travel long distances after treatment to be followed up. With the increase in the unemployed rates in South Africa of 25.2% shown in recent (Statistics South Africa survey, 2013), patients cannot afford travelling expenses.

Although induction chemotherapy followed by radiotherapy versus concurrent chemotherapy plus radiotherapy has been extensively studied and the latter was found to be superior for larynx preservation, this study has shown that most of our patients do not receive the concurrent chemo-radiotherapy as recommended. A prospective study to evaluate whether, induction chemotherapy given during the waiting time in our institution especially to patients with advanced stage of disease but still in good (ECOG status) would not reduce the number of patients who have disease progression and allow more patients to be treated with radical instead of palliative intent would be useful for our setting.

In view of the available evidence that suggest that increasing the dose per fraction from 2Gy to 2.25Gy for patients with early glottis carcinoma showed superior local control and further shortened overall treatment time (Yamazaki H et al, 2006), protocols in our department need to be reviewed. Patients with early disease should be treated with a shorter regimen and a higher dose fractionation schedule of 2.25Gy as this will also reduce our overall treatment time and waiting time for treatment while improving local control.

It is important that treatment protocols are guided by literature from results of large randomised studies but they should also be adjusted according to circumstances of individual institution. For our institution it would be important to increase the number of patients that are treated with radical intent.

To win the battle and improve our results South Africa's oncology services need to improve so that more centres that can treat cancer are accessible to patients promptly. Dedicated oncology hospitals would be of benefit where cancer patients would not have to wait for investigations with other medical or surgical patients. Multiple oncology centres with adequate and well maintained equipment such as radiology and radiation treatment machines to cope with patient loads are needed.

Improving the unemployment rate, therefore improving patient's socioeconomic status and nutritional status would also have a big impact in on our cancer patients. Education is also a key to success and will help patients with understanding their disease and the need for treatment which will yield better treatment compliance and better follow-up after treatment completion.

Appendix 1:

AJCC (TNM) Staging for Laryngeal Cancer

Supraglottis	
T1	tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the the supraglottis (e.g. mucosa of base of tongue , vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic tissues, paraglottic space and/or minor thyroid erosion.
T4a	tumor invades through the thyroid cartilage and/or invades beyond the larynx (e.g. trachea,soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles,thyroid or esophagus
T4b	tumor invades prevertebral space, encases carotid artery or invades mediastinal structures
Glottis	
T1	tumor limited to vocal cord(s) may involve anterior or posterior commissure with normal mobility
T1a	tumor invades one vocal cord
T1b	tumor invade both cord cords
T2	tumor extends to supraglottis, and/or subglottis and/or with impaired vocal cord mobility
T3	tumor limited to the larynx with vocal cord fixation and/or invades paraglottic space and/or minor thyroid cartilage erosion (e.g. inner cortex)
T4a	tumor invades through the thyroid cartilage and/or tissues beyond the larynx (trachea, soft tissues of the neck including deep extrinsic muscles of the tongue, strap muscles, thyroid or esophagus
T4b	tumor invades prevertebral space , encases carotid artery, or invades mediatinal structures
Subglottis	
T1	tumor limited to the subglottis
T2	tumor extends to vocal cord(s) with normal or impaired mobility
T3	tumor limited to larynx with vocal cord fixation
T4a	moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and or invades beyond the larynx (e.g. trachea , soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles thyroid, or esophagus.
T4b	very advanced local disease. Tumor invades prevertebral space , encases carotid artery, or invades mediastinal structures
Regional Lymph Nodes	

N0	no regional lymph node metastasis
N1	metastasis in a single ipsilateral lymph node < 3cm in greatest dimension
N2a	metastasis in a single ipsilateral lymph node > 3cm but < 6cm in greatest dimension
N2b	metastasis in multiple ipsilateral lymph nodes, none > 6cm in greatest dimension
N2c	metastasis in bilateral or contralateral lymph nodes, none > 6cm in greatest dimension
N3	metastasis in a lymph node > 6cm in greatest dimension
Distant Metastases	
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

American Joint Committee on Cancer manual 7th edition 2010 (Leibel and Phillips, 2010)

Appendix 2

: ECOG (Eastern Cooperative Oncology Group) Performance Status

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 self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

Oken M et al (1982)

Appendix 3:

: RTOG/EORTC Acute Radiation Toxicity Grading for Larynx Treatment

Tissue	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Follicular, faint or dull erythema/ epilation/ dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist dequamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, haemorrhage, necrosis
Mucous membrane	Injection/ may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge/ may experience moderate pain requiring analgesia	Confluent fibrinous mucositis/ may include severe pain requiring narcotic	Ulceration, haemorrhage, necrosis
Salivary glands	Mild mouth dryness/ slightly thickened saliva may have slightly altered taste such as metallic taste/ these not reflected in alteration in baseline feeding behaviour, such as increased use of liquid with meals	Moderate to complete dryness/ thick, sticky saliva/ markedly altered taste	None	Acute salivary gland necrosis
Pharynx and esophagus	Mild dysphagia or odynophagia/ may require topical anesthetic or non-narcotic analgesisics/ may require soft diet	Moderate dysphagia or odynophagia/ may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss >15% from pretreatment baseline requiring NG feeding tube,	Complete obstruction, ulceration, perforation, fistula

			IV fluids or hyperalimentation	
Larynx	Mild or intermittent hoarseness/ cough not requiring antitissive/ erythema of mucosa	Persistent hoarseness but able to vocalize/ referred ear pain, sore throat, patchy fibrinous exudates or mild arytenoids edema not requiring narcotic/ cough not requiring antitussive	Whispered speech, throat pain or referred ear pain requiring narcotic/ confluent fribrinous exudates, marked arytenoids edema	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary
Ear	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication/ serous otitis media/ hypoacusis on testing only	Severe external otitis with discharge or moist desquamation/ symptomatic hypoacusis/ tinnitus, not drug related	Deafness
HAEMATOLOGICAL				
WBC	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
Platelets	75 - <100	50 - <75	25 - <50	<25orspontaneous bleeding
Hgb	11 - 9.5	<9.5 – 7.5	<7.5 – 5.0(packed cell transfusion required)	None
Neutrophils	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis

Cox JD et al (1995)

Appendix 4:

: Summary of studies showing local control and larynx preservation with Radiation Therapy and Surgical salvage for T1 & T2 Ca glottis

Reference	Patients n	Local control	Larynx Preservation	Surgical Salvage n/n
Mendenhall et al (2001)	291	98	95	18/18
Mittal et al (1983)	177	96	90	23/30
Wang et al (1990)	723	97	90	46/59
Le et al (1997)	315	97	89	41/52
Johansen et al (1990)	358	94	91	40/55
Amornmarn et al (1985)	86	99	92	6/7
Spector et al (1999)	104	96	89	7/11
Cellai (2005)	831	94	87	70/121
Yamazaki (2006)	180	98	94	23/25

n/n = number of patients salvaged/ number of patients who underwent salvage treatment

Studies showing local control and larynx preservation for T2 ca of glottis with Radiation therapy and Surgical salvage

Reference	Patients n	Local control	Larynx Preservation	Surgical Salvage n/n
Mendenhall et al (2001)	146	96	82	40/49
Wang et al (1990)	173	86	71	28/43
Le et al (1997)	83	92	72	20/27
Howell-Burke et al (1990)	114	94	74	25/34
Amornmarn et al (1985)	34	94	88	2/4

n/n = number of patients salvaged /number of patients who underwent salvage treatment

Appendix 5:

: Summary of trials that demonstrated the feasibility of larynx preservation over surgery for locally advanced cancer of the larynx.

Trial	Patients n	Stage	Study Arms	Larynx Preservation
VA Trial (1991) (Veterans Affairs)	332	III/IV	1) Surgery + RT Vs 2) Induction chemo + RT if CR/PR	nil 64%
EORTC (24891) Lefebvre et al 1996	202		1) Surgery + RT Vs 2) Induction chemo + RT if CR/PR	nil 42% at 3yrs 35% at 5 yrs
RTOG 91-11 Forastier et al 2003	547	III/IV	1) RT alone Vs 2) Induction chemo + RT if CR/PR Vs 3) Cocurrent Chemo-RT	66% 71% 84%
RT= Radiation Therapy CR/PR= Complete Response/ Partial Response				

Trial	Patients n	Stage	Study Arms	Larynx Preservation	Overall Survival
GORTEC Pointreau et al. 2000-01	220		1) 3cycles Induction chemo (TPF) Vs 2) 3cycles PF > if CR/PR pts had RT	70% at 3yrs 58% at 3yrs	80% 59%
TAX 324 Posner et al (2007)	501	III/IV	1) 3cycles Induction chemo (TPF) Vs 2) 3cycles PF > if CR/PR pts had CRT with carboplat		62% at 3yrs 48% at 3yrs
EORTC (24954) Lefebvre et al 2009	450	T3/T4 Disease	1) 2cycles Induction chemo (PF) if CR/PR pt had CRT with PF Vs 2) 4cycles chemo(PF) alternating with RT wks 1,4,7,10. 20GY/10# to 60Gy	No difference	
TPF= Doxetaxel, cisplatin, 5FU CR/PR= Complete Response /Partial Response CRT= Chemo-Radiation Therapy					

Appendix 6

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr TD Mutsoane

CLEARANCE CERTIFICATE **M10927**

PROJECT Patients treated with radical course of radiation therapy for carcinoma of the larynx at Charlotte Maxeke Johannesburg Academic Hospital.

INVESTIGATORS	Dr TD Mutsoane.
DEPARTMENT	Department of Radiotion Oncology
DATE CONSIDERED	01/10/2010
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 29/11/2010 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof Roy Lakier

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix 7

Data Sheet

Age	
Gender	
Stage	
Date of 1st visit	
Date treatment started	
Waiting time	
Treatment group	
Treatment break	
Duration of break	
Treatment completed (Yes/No) and date	
Radiation dose	
Chemo cycles	
Date at last follow-up	
Improvement of symptoms	

Treatment group = (1) Radical radiotherapy only

(2) Radical chemotherapy plus radiotherapy

(3) Disease progression (palliative)

(4) Advanced disease at presentation (palliative)

References

Amornmarn, R., Prempree, T., Viravathana, T., Donavanik, V. & Wizenberg, M.J. A therapeutic approach to early vocal cord carcinoma *Acta radiologica Oncology* 1985; 24(4): 321-325.

Cahlon O., Lee N., Le QT., Kaplan M.J., Colevas A.D., Cancer of the Laynx, Leibel and Phillips Textbook of Radiation Oncology Third Edition, Hoppe R.T., Phillips T.L., Roach III M., Elsevier Saunders, Philadelphia, 2010 (31): 642-665

Cellai, E., Frata, P., Magrini, S.M., Paiar, F., Barca, R., Fondelli, S., Polli, C., Livi, L., Bonetti, B., Vitali, E., De Stefani, A., Buglione, M. & Biti, G. Radical radiotherapy for early glottic cancer: Results in a series of 1087 patients from two Italian radiation oncology centers. I.The case of T1N0 disease *International journal of radiation oncology, biology, physics* 2005; 63(5): 1378-1386.

Christiaan M. S, Shao Hui H, Sharon Fung. Retrospective study of palliative radiotherapy in newly diagnosed head and neck carcinoma *International journal of radiation oncology, biology, physics* 2011; 8(4): 958-963.

Cox J.D., Stetz J., Pajak T.F. Toxicity criteria of Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) *International journal of radiation oncology, biology, physics* 1995; 31(5); 1341-1346.

Faluyi, O.O., Masinghe, S.P., Hayward, R.L. & Clive, S. Accuracy of GFR estimation by the Cockroft and Gault, MDRD, and Wright equations in Oncology patients with renal impairment *Medical oncology (Northwood, London, England)* 2012; 29 (2): 755-760.

Miles K., Miles Kelley Art Library: Anatomy of the larynx, available from: http://www.dwp.gov.uk/img/laryngeal-cancer1.jpg 2012. , 28 0ctober

Forastiere, A.A., Goepfert, H., Maor, M., Pajak, T.F., Weber, R., Morrison, W., Glisson, B., Trotti, A., Ridge, J.A., Chao, C., Peters, G., Lee, D.J., Leaf, A., Ensley, J. & Cooper, J. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer *The New England journal of medicine* 2003; 349(22): 2091-2098.

Fortin, A., Bairati, I., Albert, M., Moore, L., Allard, J. & Couture, C. Effect of treatment delay on outcome of patients with early-stage head-and-neck carcinoma receiving radical radiotherapy *International journal of radiation oncology, biology, physics* 2002; 52(4): 929-936.

Frata, P., Cellai, E., Magrini, S.M., Bonetti, B., Vitali, E., Tonoli, S., Buglione, M., Paiar, F., Barca, R., Fondelli, S., Polli, C., Livi, L. & Biti, G. Radical radiotherapy for early glottic cancer: Results in a series of 1087 patients from two Italian radiation oncology centers. II. The case of T2N0 disease *International journal of radiation oncology, biology, physics* 2005; 63(5): 1387-1394.

Gaillard F.: Anatomy of lymph node levels for head and neck, available from: http://radiopaedia.org/images/26383, 28 October 2012.

Hall E.J., Time, Dose and Fractionation in Radiotherapy, Radiobiology for the radiologist Fifth Edition, John J.R, Sutton P, Marino D, Lippincott Williams & Wilkins, Philadelphia USA, 2000;(22): 397-417.

Hanna, E., Alexiou, M., Morgan, J., Badley, J., Maddox, A.M., Penagaricano, J., Fan, C.Y., Breau, R. & Suen, J. Intensive chemoradiotherapy as a primary treatment for organ preservation in patients with advanced cancer of the head and neck: efficacy, toxic effects, and limitations *Archives of Otolaryngology--Head & Neck Surgery* 2004*;* 130 (7): 861-867.

Hansen, O., Larsen, S., Bastholt, L., Godballe, C. & Jorgensen, K.E. Duration of symptoms: impact on outcome of radiotherapy in glottic cancer patients *International journal of radiation oncology, biology, physics* 2005; 61(3): 789-794.

Hliniak, A., Maciejewski, B. & Trott, K.R. The influence of the number of fractions, overall treatment time and field size on the local control of cancer of the skin *The British journal of radiology* 1983; 56(668): 596-598.

Howell-Burke, D., Peters, L.J., Goepfert, H. & Oswald, M.J. T2 glottic cancer. Recurrence, salvage, and survival after definitive radiotherapy *Archives of Otolaryngology--Head & Neck Surgery* 1990; 116(7): 830-835.

Jensen, A.R., Nellemann, H.M & Overgaard, J. Tumor progression in waiting time for radiotherapy in head and neck cancer *Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology* 2007; 84(1): 5-10.

Johansen, L.V., Overgaard, J., Hjelm-Hansen, M. & Gadeberg, C.C. Primary radiotherapy of T1 squamous cell carcinoma of the larynx: analysis of 478 patients treated from 1963 to

1985 *International journal of radiation oncology, biology, physics* 1990; 18(6): 1307-1313.

Le, Q.T., Fu, K.K., Kroll, S., Rvu, J.K., Quivey, J.M., Meyler, T.S., Krieg, R.M. & Phillips, T.L. Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma *International journal of radiation oncology, biology, physics* 1997; 39(1): 115-126.

Lefebvre, J.L., Chevalier, D., Luboinski, B., Kirkpatrick, A., Collette, L. & Sahmoud, T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group *Journal of the National Cancer Institute* 1996; 88(13): 890-899.

Map data ©2013 AfriGIS (Pty) Ltd, Google, Distance from Mafikeng to Johannesburg available from: https://maps.google.com/

Mendenhall, W.M., Amdur, R.J., Morris, C.G. & Hinerman, R.W. T1-T2N0 squamous cell carcinoma of the glottic larynx treated with radiation therapy *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2001; 19(20): 4029-4036.

Mendenhall W.M., Werning J.W., Pfister D.G., Cancer of the head and neck, DeVita, Hellman & Rosenberg's Cancer: Principles & Practice of Oncology Eighth Edition, Devita V.T., Lawrence T.S., Rosenberg S.A., Lippincott Wilkins, 2008,(36): 844-851.

Mendenhall W.M., Hinerman R.W., Amdur R.J., Mancuso A.A., Villaret D.B., Werning J.W., Head and Neck Tumors: Larynx, Perez and Brady's Principles and Practice of

Radiation Oncology Fifth Edition, Halperin E.C., Perez C.A., Brady L.W., Lippincott Williams & Wilkins, 2008,(44): 975-993.

Miles K., Miles Kelley Art Library: Anatomy of the larynx, available from: http://www.dwp.gov.uk/img/laryngeal-cancer1.jpg 2012. , 28 0ctober

Mittal, B., Rao, D.V., Marks, J.E. & Perez, C.A. Role of radiation in the management of early vocal cord carcinoma *International journal of radiation oncology, biology, physics* 1983; 9(7): 997-1002.

Moore K.L., The Neck, Clinically Oriented Anatomy Third Edition, Satterfield T.S., Napora L., Lumpkin K., Williams & Wilkins, Baltimore, 1992; (8): 838-849.

Netter F.H., Craig J., Machado C.: Right Lateral View of the larynx, available from: http://www.netterimages.com/images/vpv/000/000/004/4607-0550x0475.jpg, 10 November 2012.

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T. & Carbone, P.P. Toxicity and response criteria of the Eastern Cooperative Oncology Group *American journal of clinical oncology* 1982; 5(6): 649-655.

Overgaard, J., Hjelm-Hansen, M., Johansen, L.V. & Andersen, A.P. Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx *Acta Oncologica (Stockholm, Sweden)* 1988; 27(2): 147-152.

Pejavar S., Hansen E.K., Yom S.S., Schechter N.R., Laynx and Hypopharynx Cancer, Hand book of Evidence-Based Radiation Oncology, Second Edition, Hansen E.K., Roach III M., Springer Science and Business Media, United States of America, 2010,(9): 145-163.

Pfister, D.G. & Ridge, J.A. Induction chemotherapy for larynx preservation: patient selection or therapeutic effect? *Journal of clinical oncology: official journal of the American Society of Clinical Oncology* 2006; 24(4): 540-543.

Pfister, D.G., Laurie, S.A., Weinstein, G.S., Mendenhall, W.M., Adelstein, D.J., Ang, K.K., Clayman, G.L., Fisher, S.G., Forastiere, A.A., Harrison, L.B., Lefebvre, J.L., Leupold, N., List, M.A., O'Malley, B.O., Patel, S., Posner, M.R., Schwartz, M.A. & Wolf, G.T. American Society of Clinical Oncology clinical practice guideline for the use of larynx-preservation strategies in the treatment of laryngeal cancer *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2006;24(22): 3693-3704.

Pignon, J.P., le Maitre, A., Bourhis, J. & MACH-NC Collaborative Group Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC): an update *International journal of radiation oncology, biology, physics* 2007; 69(2) Suppl: S112-4.

Pointreau, Y., Garaud, P., Chapet, S., Sire, C., Tuchais, C., Tortochaux, J., Faivre, S., Guerrif, S., Alfonsi, M. & Calais, G. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation *Journal of the National Cancer Institute* 2009; 101(7): 498-506.

Quarterly labour force survey, Statistics South Africa, available from: http://www.statssa.gov.za/news_archive/Docs/QLFS_Press_statement_Q1_2013.pdf, 06 May 2013.

Steel, G.G. & Peckham, M.J. Exploitable mechanisms in combined radiotherapy-chemotherapy: the concept of additivity *International journal of radiation oncology, biology, physics* 1979; 5(1): 85-91.

Spector J.G., Stage I (T1N0M0) squamous cell carcinoma of the laryngeal glottis therapeutic results and voice preservation. Head Neck 1999; 21(8):707-717.

Sykes, A.J., Slevin, N.J., Gupta, N.K. & Brewster, A.E. 331 Cases of Clinically Node-Negative Supraglottic Carcinoma of the Larynx: a Study of a Modest Size Fixed Field Radiotherapy Approach *International journal of radiation oncology, biology, physics* 2000; 46(5): 1109-1115.

Tupchong, L., Scott, C.B., Blitzer, P.H., Marcial, V.A., Lowry, L.D., Jacobs, J.R., Stetz, J., Davis, L.W., Snow, J.B. & Chandler, R. Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03 *International journal of radiation oncology, biology, physics* 1991; 20(1): 21-28.

Underwood J.C.E., Respiratory tract, General and Systematic Pathology, Second Edition, Underwood J.C.E., Hunter J.,199,Churchill Livingstone, London, 1996,(14): 370-371.

Vokes, E.E., Haraf, D.J. & Kies, M.S. The use of concurrent chemotherapy and radiotherapy for locoregionally advanced head and neck cancer *Seminars in oncology* 2000; 27(4) Suppl 8: 34-38.

Vokes, E.E., Kies, M.S., Haraf, D.J., Stenson, K., List, M., Humerickhouse, R., Dolan, M.E., Pelzer, H., Sulzen, L., Witt, M.E., Hsieh, Y.C., Mittal, B.B. & Weichselbaum, R.R. Concomitant chemoradiotherapy as primary therapy for locoregionally advanced head and neck cancer *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2000; 18(8): 1652-1661.

Wang C.C, Carcinoma of the larynx, Radiation therapy for head and neck neoplasm: indications, techniques and results, Year book medical publishers; Chicago, 1990; 223.

Weber, R.S., Berkey, B.A., Forastiere, A., Cooper, J., Maor, M., Goepfert, H., Morrison, W., Glisson, B., Trotti, A., Ridge, J.A., Chao, K.S., Peters, G., Lee, D.J., Leaf, A. & Ensley, J. Outcome of salvage total laryngectomy following organ preservation therapy: the Radiation Therapy Oncology Group trial 91-11 *Archives of Otolaryngology--Head & Neck Surgery* 2003;129(1): 44-49.

Wolf Et Al, 1991 Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer, available from: http:// www.nejm.org/doi/pdf/10.1056/NEJM199106133242402, 23 November 2012.

Yamazaki, H., Nishiyama, K., Tanaka, E., Koizumi, M. & Chatani, M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time *International journal of radiation oncology, biology, physics* 2006; 64(1): 77-82.