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The correlation between tumour volume and survival in oral cavity and oropharyngeal squamous cell carcinoma

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August, 2008

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of M.Sc. in Experimental Surgery

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ISBN: 978-0-494-66890-0

PREFACE

Preliminary results of this research were presented at the:

16th Annual Fraser N Gurd Surgical Research Forum, McGill University Department of Surgery, Montréal, Québec on May 5, 2005.

Canadian Society of Otolaryngology – Head & Neck Surgery 59th Annual Meeting, St. John's, Newfoundland on June 22, 2005.

Further results of this research were presented at the:

McGill University, 14th Annual Department of Otolaryngology Resident Research Day, Montréal, Québec on May 11, 2006.

Canadian Society of Otolaryngology – Head & Neck Surgery 60th Annual Meeting, Kelowna, British Columbia on May 15, 2006.

Association d'oto-rhino-laryngologie et de chirurgie cervico-faciale du Québec Congrès annuel, Québec City, Québec on October 21, 2006.

This research was funded by a bourse de formation de maîtrise Fonds de la Recherche en Santé de Quebéc (FRSQ) M.Sc. training scholarship and the Department of Otolaryngology – Head & Neck Surgery at McGill University.

ACKNOWLEDGEMENTS

I would like to express my appreciation to all those who gave me the opportunity to undertake this thesis.

I want to thank Dr Robert Funnell, Director of Audilab in the Department of BioMedical Engineering, for teaching me the use of *Fie* and *Tr3* software developed in his laboratory. His technical expertise and direction has been invaluable. I would like to thank Dr Mark Levental, Head & Neck Radiologist at the Jewish General Hospital, who reviewed the accuracy of our tumour segmentation. I am bound to Dr Michael Hier and Dr Martin Black, Head & Neck Surgeons at the Jewish General Hospital, who served as my clinical science supervisors throughout this venture. Their stimulating suggestions, feedback and open doors formed the groundwork for our data collection and presentations. I am grateful for their expertise and guidance. I would like to thank Dr Karen Kost and Dr Anthony Zeitouni, Head & Neck Surgeons at the Montreal General and Royal Victoria Hospitals, for their significant assistance and permission to use their patient data. I thank Sebastien Dube at the McGill Research Institute for his support with our statistical analysis.

I would like to express my sincere gratitude to my basic science supervisor, Dr Sam Daniel, Director of the McGill Auditory Sciences Laboratory. He first introduced me to the topic and has shared his knowledge, guidance, and unconditional encouragement throughout this study. His enthusiasm and energy for research has served as a motivation for all of his advisees, including me. This thesis has become a rewarding experience under his direction. He is truly a mentor as I enter the field of Otolaryngology Head & Neck Surgery, a colleague, and a friend.

It has, and continues to be, a pleasure to work alongside many colleagues, including Dr Raymundo Munguia and Dr Yalon Dolev. Our camaraderie and entertainment is truly enjoyable.

This research time was funded by a bourse de formation de maîtrise from le Fonds de la recherche en santé du Québec (FRSQ) for which I am grateful. This thesis project and initiative was funded and supported by the Department of Otolaryngology Head & Neck Surgery at McGill University and the Chairman, Dr Saul Frenkiel. I sincerely thank the whole department for their vital encouragement and support.

I warmly appreciate and wish to thank my parents, brother and twin sister. Their love, encouragement, friendship and support are immeasurable and treasured.

Sumeet M Anand, MD

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ABSTRACT

The Tumour-Node-Metastasis (TNM) classification system of tumour stage does not always reflect the actual tumour mass present at diagnosis. Recent reports propose that volumetric analysis may allow improved stratification of disease recurrence and survival in head and neck squamous cell cancer (SCC). This study aims to assess the prognostic value of tumour volume on the outcome of patients with oral cavity and oropharyngeal SCC.

A retrospective review of 73 patients was completed. Tumours were outlined semi-automatically in digitized computed tomography scans, and volumes computed based on surface triangulations of three-dimensional reconstructions with novel software developed at McGill.

Results illustrate significant interstage variability within the current TNM model. Moreover, in oral cavity and oropharyngeal SCC, tumour volume as well as T-stage are significant and independent predictors of disease free survival and overall survival.

SOMMAIRE

La classification des tumeurs TNM (tumeur-ganglion-métastase) n'indique pas toujours la masse tumorale présente au diagnostic. Selon les rapports récents, l'analyse volumétrique permettrait une meilleure stratification de la récurrence et de la survie du carcinome épidermoide (CE) de la tête et du cou.

Cette étude rétrospective sur 73 patients examine des tumeurs à l'aide de tomodensitogrammes numériques avec un procédé semi-automatique. Les volumes sont calculés par triangulation de surface tridimensionnelle grâce à un logiciel développé à McGill. L'étude vise à démontrer la valeur pronostique du volume tumoral pour les patients ayant le CE de la cavité orale et de l'oropharynx.

Nos résultats démontrent une variabilité inter-stade importante dans le modèle TNM. De plus, les résultats démontrés que le volume tumoral et le stade T sont les indicateurs significatifs et indépendants de survie et de non récurrence de la CE de la cavité orale et de l'oropharynx.

1.0 INTRODUCTION / RATIONALE

1.1 Head and Neck Cancer

Cancers in the head and neck represent a heterogeneous group of tumours as several anatomical subsites comprise possible sources of malignancy. Tumour sites include the oral cavity, nasopharyx, oropharynx, hypopharynx, larynx, salivary glands, paranasal sinuses, thyroid and parathyroid glands. Collectively, 6-8% of all malignancies in the body are found in the head and neck. Canadian cancer statistics conveyed from Health Canada indicate that 4600 new cases of head and neck cancers were reported in Canada in 2003. The reported mortality from head and neck malignancies in 2003 was 1722, giving a death to incidence ratio of 37%[1].

The most common malignancy amongst various tissue types present within the head and neck are epithelial tumours. More than 90% of such epithelial malignancies are squamous cell carcinoma's (SCC's) of the mucosal surfaces of the upper aerodigestive tract[2]. The behaviour of SCC's depends on the anatomic site of tumour origin; each site has its own pattern of disease spread and prognosis. The oral cavity is the most common non-cutaneous subsite of head and neck SCC's, followed by the larynx. More rare tumours of the head and neck are found in bone, muscle or neural tissue.

Head and neck tumours are more common in men than in women at a ratio of 2:1. Average age at diagnosis is 60 with tumours most frequently presenting in the sixth to seventh decades of life. Well accepted risk factors for malignancy are smoking, alcohol

use, reverse smoking, human papilloma virus, betel-nut chewing, tobacco, poor dental hygiene and geographic influences[3].

Common symptoms of head and neck cancers are numerous, including unhealed mouth sores, difficulty or pain when swallowing, lumps on the lips, mouth or in the neck, prolonged hoarseness, change in the voice, earache, pain in the face or jaw, persistent blocked nose, nose bleeds or unusual white or red patches on upper aerodigestive mucosal surfaces. Clinicians use several methods to identify and diagnose head and neck cancer including physical examination, laryngoscopy, direct fiberoptic laryngoscopy, computerized tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET)[3].

Survival from head and neck cancer is related to early diagnosis and successful management of localized disease. Spread of cancer via regional metastases to cervical lymph nodes or systemic metastases to lung, liver or bone are poor prognostic factors associated with a significantly reduced overall survival. In the last 25 years improved surgical techniques and the introduction of concurrent chemotherapy and radiation therapy protocols have lead to vast advances in local and loco-regional tumour control. There has been limited improvement, however, in the overall survival from head and neck SCC.

The severity of head and neck cancers is well known. Recent literature shows the five-year survival in patients with advanced, non-operable cancers is approximately 15-25%[4].

The median survival for patients with recurrent or metastatic disease is approximately 6 months.

1.2 Tumour-Node-Metastasis (TNM) Staging

The principal staging system for head and neck cancer is the Tumour, Node, Metastases system (TNM) devised by the Union Internationale Contre le Cancer (UICC). For more than 50 years, the TNM has served as a benchmark for reporting the anatomic extent of malignant disease[5]. By definition, the principles of the TNM state:

> "the choice of treatment and chance of survival are related to the extent of the tumour at the primary site (T), the presence or absence of tumour in regional lymph nodes (N), and the presence or absence of metastasis beyond regional lymph nodes (M)"[6].

Tumours are graded from T_0, no evidence of a primary tumour, to T_4, tumour which extends into adjacent tissue or bone. To date tumours are graded and classified uni-dimensionally by their largest diameter measurement. T1 tumours are less than 2 cm, T2 tumours are between 2 and 4 cm, and T3 tumours are more than 4 cm in diameter. T4 tumours invade adjacent bone, skin, cartilage, vessels or muscle. T_x designates tumours for which the primary site is unknown or cannot be assessed[3]. Table 1 identifies the most recent TNM classification for head and neck malignancies (Appendix 1).

Staging head and neck cancers serves to classify tumours with a common language, facilitate communication amongst treating physicians, identify prognosis for patients and evaluate therapy. The UICC TNM committee describes the objectives of the TNM classification as five-fold:

a) To aid the clinician in planning treatment

b) To give some indication of prognosis

c) To assist in evaluating the results of treatment

d) To facilitate the exchange of information between treatment centers

e) To contribute to continuing investigations of human malignancies[7]

The TNM staging system has been conventionally used as an indicator of biological progression of malignancy, thus it forms the basis for treatment decisions and is a predictor of overall survival. In grading tumours uni-dimensionally, however, this system does not always reflect the actual tumour mass present at diagnosis. Tumours are three-dimensional structures, developing along different planes and at different rates. Tumours are not spherical, and as such, volume cannot be accurately computed using the largest tumour diameter. Currently, the true three-dimensional tumour size is not often considered in clinical decision-making. Several reports have demonstrated the limitation of the uni-dimensional TNM system to precisely identify true tumour mass and its weakness in differentiating high and low risk patients for local metastasis, recurrence and survival[8,9,10,11].

The clinical and prognostic significance of various tumour dimensions have been studied. Reports have investigated tumour length, diameter, depth, thickness and volume[8,9,10,11, 12, 13, 14,15, 17]. It is suggested that tumour thickness has a significant role in identifying patients susceptible to local lymphatic recurrence[8,11,13,14,17]. It is unclear in these studies, however, the most optimal time to measure tumour thickness, either preoperatively with ultrasonagraphy, MRI or CT or postoperatively by histopathology[8,11,15,16]. Importantly, tumour thickness is still a measure of a single dimension. Further, challenges reported on postoperative histopathology for thickness assessment include the absence of mucosa in some samples, the tangential cutting of some tissue sections, and samples inadequate to allow maximal tumour depth measurement[17].

Molecular tumour factors including the hypoxic fraction, p53 tumour suppressor function, intrinsic radiosensitivity of tumour cells, and the degree of vascularity have also been studied to identify predictors of tumour response[18,19,20]. To date, however, no consensus has been drawn on the prognostic merit of such molecular factors.

1.3 Tumour Volume

Emerging evidence is showing that tumour volumetry may hold clinical usefulness in the pre-treatment phase in evaluating head and neck SCC. Of specific interest is the predictive role of tumor volume[12,21,22,23-30]. As mentioned above, solid cancers are three-dimensional structures in which cancer cells spread in multiple dimensions and rates, taking a path of least resistance to invade surrounding structures. In classifying tumours

by the largest uni-dimensional diameter as per the current TNM, prognostically favourable superficial tumours may be grouped in the same T-stage as a more adverse irregularly shaped or deeply infiltrative mass. Although differences in tumour volume may be small in early-stage disease, described as T1 and T2 stage tumours by TNM, there may be considerable variation in tumour volume in advanced-stage disease, stage T3 and T4, by factors of up to 80-100X. Overlooking this heterogeneity significantly reduces the power of the TNM as a predictive tool.

Through CT and MRI, cancer physicians are now able to define the extent of a tumour and measure volume more precisely. As such, several reports have recently emerged to evaluate the value of CT- or MRI-determined primary tumour volume, as opposed to uni-dimensional measurements, as a prognostic parameter. Amongst head and neck SCC, studies have been conducted in glottic, supraglottic, hypopharyngeal, and nasopharyngeal SCC's and collectively show that increasing pre-therapeutic primary tumour volume is negatively associated with local control and survival[12,23,24,25,26,27, 28,29]. Particularly in advanced stage tumours, where volume within a stage is highly variable, tumour volumetry is found to allow better stratification of patients in a low or high-risk group for local failure and survival than clinical examination and T-staging alone[12,23-29].

In a review of the literature there has been limited work evaluating the prognostic value of preoperative tumour volume in oropharyngeal and oral cavity SCC. Where studies have been done, moreover, there are inconsistencies amongst the reported results. Nathu and colleagues were the first to study the role of tumour volume on local control for

oropharyngeal SCC and they failed to reveal an important impact of CT-determined primary tumour volume, as a prognostic factor, on the likelihood of tumour control after radiotherapy[30]. A second study on oropharyngeal tonsillar SCC found the relationship between CT-determined primary tumour volume and local control to be marginally significant[31].

In a study evaluating postoperative glossectomy specimens by histopathology, Yuen and colleagues report no correlation between primary tumour volume and recurrence or survival on univariate analysis[11]. A recent report on oral cavity tongue cancers, however, showed a significant relationship between MRI-determined tumour volume and disease-free and overall survival[32]. Notably, this last study reviewed only 17 patients in their report on tumour volume as a prognostic factor for oral cavity tongue SCC.

Methods described in the literature for volumetry analysis involve re-digitizing CT and MRI examinations where necessary, enhancing image size to trace tumour contours manually or using software to extrapolate contours, and subsequently estimating volume by summating the areas of successive two-dimensional image slices. Many of the early volumetry studies in head and neck SCC adopted the method of manually tracing tumour outlines[12,29,30,31,33]. This process has been subjectively described by a select few as either labour intensive[34,35] or open to intra- and inter-observer variance[36]. Others have reported no intra-or inter-observer variance in their volumetric analysis[28,37].

A recent study describes the use of a semi-automated process for volumetric analysis in oral cavity tongue SCC[32]. Chew and colleagues describe using 'Seed Growing (SG)' and 'Region Deformation (RD)'as methods of semi-automated tumour delineation. In SG, a seed is selected manually within the tumour followed by selecting an intensity threshold. Neighbouring pixels within the selected threshold are subsequently included in this region[38]. In RD, an operator draws a rough closed-loop contour outside the lesion and a region-shrinking operation then identifies the object as the area with the same intensity distribution[39]. In an earlier study on 16 patients with tongue SCC, this group believes they validated the use of their semi-automated volume measurements for tongue carcinomas showing minimal interoperator variance[35].

Amongst other cancer sites in the body, volumetry has been studied using a manual tracing method for cervical cancer[40,41] and both manual and semi-automated methods for brain tumours[34,42]. In these reports tumour volume was collectively reported as a significant predictive tool of recurrence and survival. In one study comparing conventional manual tracing versus a semi-automated computer program, there was no significant difference reported between the two methods, though the semi-automated process did require less time[34].

Finite element (FE) modeling is used to create three-dimensional models of complex objects to allow visualization and simulation. FE modeling is able to easily model complex structures and irregular or inhomogeneous shapes. The model can then be applied in additional image reconstruction software or to simulate motion. Original work

at McGill University described a FE model of the cat eardrum[43,44]. Further work has continued in FE models of the human middle ear, in particular the stapes footplate[45,46]. Using microCT images and the FE model, it was shown that the stapes footplate resembled a footprint[46]. In the context of cancerous lesions FE modeling had been used in a preliminary study to evaluate cervical nodal volume in head and neck SCC. It was theorized that determination of CT lymph node volume was more accurate than surface area in estimating the prognosis of patients with advanced N3 nodal head and neck SCC[47].

FE modeling has four stages: image segmentation, reconstruction, model generation and simulation. Volumetric rendering primarily utilizes the first three stages. Segmentation of tumours involves the use of a locally developed software *Fie* (*Fabrication d'imagerie extraordinaire*)[48]. This software is freely available at: http://audilab.bmed.mcgill.ca/~funnell/Audilab/sw/ As seen above, *Fie* has successfully permitted a semi-automated delineation of several anatomical landmarks[43-47]. A second locally developed computer program *Tr3* is used to triangulate three-dimensional surfaces between serial-section contours[48]. Utilizing the surface triangulation technique, *Tr3* reconstructs non-linear curved surfaces between successive two-dimensional slices using small, adjoining triangles and calculates the image volume as the space enclosed by the reconstructed surface. To date, studies of tumour volumetry in head and neck SCC have only measured volume by the summation-of-areas technique[12,23-33,35-37]. This thesis is the first to use surface triangulation to estimate volumetric results. We believe surface triangulation is a better calculation of volume than the conventional method.

In this thesis we look at the predictive role of tumour volume in oral cavity and oropharyngeal SCC. The limited studies in oral cavity and oropharyngeal SCC report conflicting results on the value of primary tumour volume as a predictive tool. Where a semi-automated process was used for tumour delineation only 17 patients were included in their volumetric analysis[32]. In no study of a semi-automated process has multiple primary head and neck SCC tumour sites been evaluated in one report. Predictive assays of the response of tumor and normal tissue offer the possibility of individualized prognosis and treatment decisions. Determining the correlation of primary tumour volume to outcome in oral cavity and oropharyngeal SCC is of great significance and warrants investigation.

2.0 OBJECTIVES

Objectives

The objectives for thesis study are two-fold: (1) to correlate tumour volume with disease stage and classification according to the accepted TNM staging system and (2) to determine the impact of tumour volume on the prognosis of patients with oropharyngeal or oral cavity SCC after surgery, radiotherapy, chemotherapy, or combination therapy.

Our hypothesis is that tumour volumetry analysis will show greater correlation than TNM staging to established patient outcomes, improving the ability to prognosticate disease free and overall survival of oral cavity and oropharyngeal SCC.

In the realm of basic science research, this project aims to enhance the knowledge of how imaging modalities as a science can assist and improve medical care. It is imperative that biomedical technology is able to provide reliable and relatively feasible results before such technologies are translationally applied to patient management decisions. In preliminary reports on tumour volume, inter- and intra-observer variance amongst volume measurements were found in one report[36] and not in others[28,37]. Additional studies have compared semi-automated and manual tracing methods of CT volume measurements[34,35]. Our project contributes to the basic biomedical literature by further evaluating the reliability of tumour volumetry, as well as studying a unique mode of analysis of medical imaging with FE modeling for tumour volumetry measurement.

Clinically this thesis study endeavours to increase the knowledge of head and neck SCC management and prognosis. Our research aims to develop a statistical model to predict the prognosis of head and neck primary cancers from tumor volume for all treatment modalities. Though in its infancy, this type of oncologic research may lead to individualized diagnosis and management based on specific patient characteristics. Volumetry represents a potentially rapid method for initial prediction of prognostic factors in head and neck SCC. Ultimately, our research results may provide empirical evidence for refining current staging systems, and most importantly, refine clinical management of patients with head and neck SCC's.

3.0 PATIENTS & METHODS

3.1 Patients

A retrospective review was performed on 308 patients with oral cavity and oropharyngeal SCC's seen at McGill University Health Center's Royal Victoria Hospital and Montreal General Hospital and the Jewish General Hospital's Otolaryngology Departments between January 1998 and December 2003. 73 patients had a high-quality pretreatment CT scan and were included in the analysis. Patients were excluded from the study if CT scans were not available for reasons including a CT completed prior to 1998 and not kept by provincial rule, only preoperative MRI was available, or a private CT not filed with medical records. All patients had a minimum 2-year follow-up.

Patient features collected included age, gender, date of diagnosis, tumour location, pathology, radiologic TNM stage, type of treatment and treatment interval, date of local or distal recurrence, last cancer status, vital status, disease free survival (DFS) (months) and overall survival (OS) (months).

3.2 CT Imaging

CT scans from the Jewish General Hospital were redigitized with a large bed scanner (Microtek Scanmaker 9800XL; Cerritos, California). Patient CT scans from the Royal Victoria and Montreal General Hospital's were available in a digital format. Contrast enhanced axial CT images were used with slices at 5mm intervals with a 25cm field of view. No important differences were noticed by the author between images from the

different institutions. All digital images were transformed into JPEG files for further software manipulations.

3.3 Volumetric Rendering

Volumetric rendering utilizes the first three stages of FE modeling: image segmentation, reconstruction, and model generation.

3.3A Image Segmentation

Each digitized slice was imported into *Fie*, an interactive image-segmentation software developed in the Biomedical Engineering department at McGill University[48]. Tumours were outlined semi-automatically with a mouse-controlled cursor. Parameters in *Fie* slither ahead to define items by density based on thresholding of the CT grey-level values. Additional parameters permitted enlargement of the images. Where tumours invade adjacent muscle or soft tissue with similar grey-levels individual segmentation was undertaken, making the process semi-automatic. Tumours were delineated on each image slice containing the lesion by one individual (S.M.A.) to avoid measurement bias. This process is referred to as image segmentation. Accuracy was optimized with the guidance of a head & neck radiologist (M.L.). Both individuals were blinded to patient outcome. Primary oral cavity and oropharyngeal SCC's were segmented. Additional structures, including lymph nodes, were included in a separate model for visualization and model generation. Individual structures were colour coded consistently from slide to slide. During data entry in *Fie*, each tumour slice is appropriately scaled in pixels/mm as

per the distance reference line (scale bar) found on the right margin of the CT image. Figure 1 shows an example of *Fie* volumetric analysis (Appendix 2).

3.3B Reconstruction / Triangulation

Segmented contours are preserved in text files and imported for surface triangulation using *Tr3*[48]. *Tr3* is also an interactive software developed locally in the Biomedical Engineering department; it allows triangulating three-dimensional surfaces between serial-section contours. The software creates a mesh overlying each segmented structure by optimally linking contours in successive two-dimensional slices with triangles. Using this surface triangulation technique Tr3 constructs non-linear curved surfaces between image slices, computing the image volume as the space enclosed by the reconstructed surface. Each microscopic triangle can be assigned mechanical properties if the operator elects to evaluate a FE model[45]. Collectively the triangles between adjacent two-dimensional slices combine to accurately represent the three-dimensional anatomy of the tumour. The number of triangular elements that can represent the model is variable; a larger number of triangles representing the tumour, for instance, will generate a finer overlying mesh and more accurately represent the cancerous lesion. A very fine mesh, however, is computationally demanding as the greater the number of segments the greater the time necessary to solve all of the equations in the system. At a certain point the higher number of segments becomes more power- and time-consuming with limited corresponding improvements in accuracy.

Tr3 produces a volume output converted from pixels to mm^3. Analysis of images per pixels intrinsically eliminates any variability in volume measurements between images in the same CT scan and between individual CT scans. Figure 2 shows an example of surface triangulation with *TR3* software (Appendix 3).

3.3C Model Generation

Three-dimensional images are represented with VRML (virtual reality mark-up language) as the screen descriptive language. *Tr3* is able to create triangulated models in VRML format for interactive visualization[48]. In this stage the model achieves a representative three-dimensional shape. Readily accessible VRML viewers can allow interaction, rotation, flipping, enlargement, and observation of the tumour from a variety of angles. Figure 3 illustrates the simulation of a three-dimensional tumour model of an oral cavity tongue SCC with bilateral cervical lymphadenopathy created with Cosmo Player interactive VRML software (Appendix 4).

3.4 Volumetric Analysis

To dichotomize patients according to tumour volume two methods were used. Firstly, to create comparable models of volumetric stage versus TNM stage four volumetric categories were selected, analogous to the four T-stages. Prior to significance calculations, collectively evaluating all 73 patients over an approximately five year

follow-up period revealed that four categories of 0-4 cm^3, 4-14 cm^3, 14-36 cm^3, and > 36 cm^3 showed similar patient results with data clustering together. This division also showed the greatest correlation with outcome and importantly permitted nearly equal distribution of patients among the categories, a trait recognized as an ideal criteria for a staging system[49].

The second mode of comparison divided tumour volume and TNM stage into early and advanced disease. The mean tumour volume among 73 cases was 13.6 cm^3, as such tumour volume of 13.6 cm^3 or less was considered as early disease and higher than or equal to 13.6 cm^3 as advanced disease. T1-T2 staged tumours are commonly classified as early disease and T3-T4 as advanced disease, allowing for comparison of early and advanced volume with TNM stage.

3.5 Statistical Methods

DFS was calculated from the date of pathological tumour diagnosis to the documented date of clinical recurrence (in months). OS was calculated from the date of pathological tumour diagnosis to the date of last follow-up or death from oropharyngeal or oral cavity SCC (in months). Patients lost to follow-up beyond the minimum inclusion criteria of two years were included in all analyses, and were censored on the date of last follow-up.

Survival curves were plotted using the Kaplan-Meier product limit method[50], providing cumulative DFS and OS rates. The log-rank test evaluated differences between DFS and

OS of groups according to primary tumour volume and T-stage. Univariate analysis was completed to establish prognostic factors. Multivariate cox forward linear regression analysis was used to evaluate interrelationships among other predictors of outcome. A *p*-value of ≤ 0.05 was considered to be statistically significant; all *p*-values were two-tailed. Analysis was completed with Statistical Program for Social Sciences (SPSS) computer software.

4.0 RESULTS

4.1 Patient Characteristics

Of the 73 patients in the study 46 were male and 27 were female. The age at diagnosis ranged from 35 to 88 years (median 64 years). The number of patients with oropharyngeal and oral cavity SCC's were 37 and 36 respectively. The mean follow-up was 32.6 months with a median follow-up of 30 months. The distribution of patients classified according to TNM staging by radiologic presentation showed of the 37 oropharyngeal SCC's 11 as T1 lesions, 12 as T2, 10 as T3 and 4 as T4. Of the 36 oral cavity SCC's, 6 were staged as T1, 14 as T2, 6 as T3 and 10 as T4. Patient characteristics as per tumour site and TNM stage are summarized in Table 2 (Appendix 5).

All patients underwent primary treatment with curative intent. Of oral cavity SCC's 3 underwent surgery alone, 15 underwent surgery with immediate post-operative external beam radiation (EBXRT), 10 received concomitant chemotherapy and EBXRT, 7 received EBXRT alone and 1 underwent surgery with immediate post-operative concomitant chemotherapy and EBXRT. Among oropharyngeal SCC's 4 underwent surgery alone, 4 underwent surgery with immediate post-operative EBXRT, 19 received concomitant chemotherapy and EBXRT and 10 received EBXRT alone.

4.2 Volume Distribution vs. T-stage

Tumour volume ranged from 0.69 cm^3 to 94.96 cm^3. The mean tumour volume for all patients was 13.6 cm^3, the median tumour volume was 9.06 cm^3.

Within oral cavity SCC's the mean primary tumour volume was 4.69 ± 5.30 cm^3 in patients with T1 tumours, 7.47 ± 5.17 cm^3 in patients with T2 tumours, 11.64 ± 6.06 cm^3 in patients with T3 tumours, and 27.23 ± 20.60 cm^3 in patients with T4 tumours. The range of tumour volumes was from 1.74-15.39 cm^3 in T1 tumours, 1.69-19.04 cm^3 in T2 tumours, 5.41-21.83 cm^3 in T3 tumours and 6.70-67.59 cm^3 in T4 tumours.

Within oropharyngeal SCC's the mean primary tumour volume was 2.37 ± 1.30 cm^3 in patients with T1 tumours, 8.44 ± 5.18 cm^3 in patients with T2 tumours, 28.45 ± 25.37 cm^3 in patients with T3 tumours, and 28.40 ± 13.08 cm^3 in patients with T4 tumours. The range of tumour volumes was from 0.69-4.28 cm^3 in T1 tumours, 1.17-16.20 cm^3 in T2 tumours, 5.43-94.96 cm^3 in T3 tumours and 9.06-37.90 cm^3 in T4 tumours.

As T-stage increases from T1 to T4 disease the tumour volume intuitively increased for both oral cavity and oropharyngeal SCC's. Oropharyngeal SCC's graded as T3 tumours, however, had a slightly higher volume than those graded as T4. Notably, the primary tumour volume was heterogeneous for both cancer subsites within every T-stage. Figure 4 describes the graphical distribution of tumour volumes within each T-stage for oral cavity and oropharyngeal SCC patients (Appendix 6). Within the same T-stage there are

tumours that are both very high and very low in volume, resulting in substantial volume ranges and standard deviations. Volume heterogeneity was particularly prominent in patients with advanced-stage disease.

4.3 Volumetric Results – V1-V4 Volume Stages and Disease Free Survival

As described, four volumetric stages were selected and direct comparison was made with the four T-stages. The five-year cumulative DFS of tumours between 0 – 4 cm^3 were 76.36%, of tumours between 4 – 14 cm^3 were 50.60%, of tumours between 14 – 36 cm^3 were 38.10% and of tumours > 36 cm^3 were 0%. Figure 5 illustrates the Kaplan Meier survival curves of each volumetric stage versus DFS (Appendix 7).

The five-year cumulative DFS of T1 tumours were 81.25%, of T2 tumours 51.11%, of T3 tumours 55% and of T4 tumours 10.71%. Survival analysis of T-stage versus DFS is shown in Figure 6 (Appendix 8).

Both the volumetric and T-staging classification systems were statistically significant and independent predictors of DFS, with $p = 0.0076$ and $p = 0.006$ respectively. Significance in log rank values establishes that the four volumetric and T-stage groups are statistically different in their prediction of DFS. Moreover, both models were consistent with current predictions of DFS[3], except for a clustering among T2 and T3 staged tumours. In actuality, within our patients those with T3 tumours had a higher DFS at five-years follow-up than T2 tumours. Table 3 reports the prediction of DFS by the literature,

volumetric stage and T-stage (Appendix 9). Power was significant (>0.80) in both prognostic models.

4.4 Volumetric Results - Early / Advanced Volume Stages and Disease Free Survival

The five-year cumulative DFS of early volume tumours (< 13.6 cm^3) was 61.96% and of advanced volume tumours (> 13.6 cm^3) was 35.80%. The five-year cumulative DFS of early T-stage tumours (T1-T2) was 63.18% and of advanced T-stage tumours (T3-T4) was 33.52%. Kaplan-Meier survival curves are illustrated in Figure 7 (Appendix 10) and Figure 8 (Appendix 11) for early and advanced volume and T-stage versus DFS.

Both early and advanced volumetric and T-stage models are independently significant predictors of cumulative DFS, with $p = 0.031$ and $p = 0.012$ respectively, and as well are in line with expected predictions[3]. Using two categories of tumour volume and T-stage, cumulative DFS curves were separated clearly.

4.5 Volumetric Results and Overall Survival

The five-year cumulative OS of tumours between 0 – 4 cm^3 were 76.77%, of tumours between 4 – 14 cm^3 were 47.37%, of tumours between 14 – 36 cm^3 were 44.32% and of tumours > 36 cm^3 were 0%. Figure 9 illustrates the Kaplan Meier survival curves of each volumetric stage versus OS (Appendix 12).

The five-year cumulative OS of T1 tumours were 76.02%, of T2 tumours 53.77%, of T3 tumours 42.86% and of T4 tumours 28.57%. Survival analysis of T-stage versus OS is shown in Figure 10 (Appendix 13).

Volumetric and T-stage models are both independently highly significant predictors of cumulative OS, with $p = 0.0001$ and $p = 0.0154$ respectively. As with DFS, both classification systems are in line with expected predictions of OS at five-years[3].

4.6 Multivariate Analysis

Multivariate analysis was completed to look at age, gender, and sex to identify parameters with influence on volumetric results. Age was the only factor that proved to be an additional predictor influencing DFS and OS outcomes. Table 4 shows the results of the multivariate analysis for DFS using the cox regression model (Appendix 14). With tumour volumes greater than 14 cm^3 the relative risk of tumour recurrence was significantly higher ($p = 0.014$ for age and tumour volume between 14-36 cm^3 and $p = 0.017$ for age and tumour volume ≥ 36 cm^3). Comparatively, significance was only seen among age and T4 tumours ($p = 0.010$). The greater likelihood of recurrence in advanced tumour stages (T3-T4) was not significant with age as a co-variate ($p = 0.070$), although there was significance among large volume tumours > 13.6 cm^3 ($p = 0.022$). Ultimately with age as a co-variate, tumour volume showed greater value in the prediction of recurrence than T-stage.

Multivariate analysis of age and tumour volume and T-stage for OS was significant amongst all advanced volumes, 14-36 cm^3 and > 36 cm^3, and T-stages, T3 and T4, when evaluated individually and as grouped advanced disease (volume > 13.6cm^3 and T3-T4 stage) with $p \leq 0.02$ in each instance.

5.0 DISCUSSION

5.1 Tumour Volumetry

Since its introduction in 1944, the TNM staging system has been the most readily used classification tool to identify head and neck malignancies and their regional and distant spread[51]. The principal purposes of the TNM are to assist in planning treatment, evaluate treatment results, facilitate communication, and to provide an indication of expected patient outcomes[7]. Preferably, the TNM should identify patients with a similar prognosis. Unfortunately, the current method of defining head and neck SCC's is quantitatively imprecise as the largest diameter of a malignancy does not often reflect total tumour bulk. Superficial spreading carcinomas devoid of deep infiltration, for instance, carry a differing tumour burden than similar diameter deeply penetrating malignancies, though they are classified the same. Despite its simplicity, tumour diameter alone may not represent the most ideal factor to suggest prognosis.

Advancements in imaging technology have permitted physicians to precisely define the extent of a tumour and measure the actual tumour burden. High-resolution CT and MRI have overcome areas not clinically accessible, such as the oro- and nasopharynx, which have previously limited the precise staging of head and neck malignancies[52]. Additional sensitivity with newer imaging tools offers useful information to quantitate tumours more realistically in a three-dimensional model[33].

Recently imaging based on three-dimensional volumetric measurement has been reported to represent the most accurate means for assessment of tumours in the head and neck[12, 23-

[29]. Much recent research, inclusive of this thesis, has gone into evaluating the utility of tumour volumetry [12, 21-33, 35-37]. Volumetric analysis holds strengths in identifying malignancies that tend to be infiltrative, are not easily accessible clinically, and which often have highly irregular contours[29]. Despite these advantages, tumour volumetry has yet to gain acceptance as common practice [29].

On a cellular level the correlation of tumour volume to predict the probability for local control has been understood for several years. Tumour volume has been defined as an indirect measure of clonogen number[53]. Increasing tumour volume means that increasing number of tumour clonogen cells warrant sterilization[37]. As such, an inverse relationship of increasing tumour volume to worsening local disease control has been seen.

Among head and neck cancers it is suggested that tumour volumetry can enable the division between favourable and unfavourable prognostic subgroups that could not previously be done[33]. Dubben and colleagues report that tumour volume is the most precise and relevant predictor of radiotherapy outcome and can be measured with sufficient accuracy in most oncologic centers[21]. They believe that individual tumour volume should be routinely reported and considered in treatment decisions. Other studies, however, have shown that tumour volumetry is not a significant predictor of prognosis[11,30]. A consensus on the utility of tumour volumetry for head and neck SCC is still outstanding. It is well understood though that precise tumour classification is imperative in the management of head and neck malignancies. Superior prognostic guides than the TNM require investigation.

5.2 Volumetric Rendering

Initial methods to measure preoperative tumour volume in the head and neck as a prognostic tool lacked complexity. Van den Bogaert and colleagues described in a study of advanced head and neck cancers that volume was estimated clinically with 'crude methods'[54]. No further details were provided in their report on the method of measurement. For volumetric calculations another report estimated the size of T1 glottic and supraglottic carcinomas using laryngoscopy[55], classifying tumours according to the clinically estimated average diameter. In these two studies, tumour volume was described to have a significant impact on DFS and OS rates even though the means of volumetric analysis were relatively unsophisticated.

Conventionally, the measurement of tumour volume has involved tracing tumour outlines manually from two-dimensional image slices [12, 28-31, 33, 37, 56]. Volume was subsequently calculated by the summation-of-areas technique or by multiplying the sum of all areas by the image reconstruction interval [11, 28, 30-33, 35, 37, 56, 57].

Ideally, volumetric analysis should be efficient and accurate for it to be readily accepted. Manually tracing outlines has been described in some reports as tedious and labour intensive[32, 34, 35, 56]. Measuring tumour volume by the summation of areas technique, moreover, can be inaccurate. With tumour slices commonly taken at 3 to 5 mm intervals, a significant amount of the true tumour bulk is lost with a step-like summation between serial image slices. In a comparison to volumes determined by water displacement it was

shown that the average percent error of volume calculations using the summation-of-areas techniques was approximately 10%[58,59]. Recently, tumour volumetry has been made progressively more accurate and efficient with recently described semi-automated methods[32].

FE modeling has been used extensively at McGill University to create three-dimensional models of complex structures to allow visualization and simulation[43-47]. This technology has significant advantages in that it can readily handle complex boundary shapes, nonlinearities, and irregular geometries[45] – attractive features for delineating oral cavity and oropharyngeal SCC's. Among oncologic applications, the FE model was used previously to study cervical nodal volume in head and neck SCC[47].

Volumetric rendering utilizes the first three stages of FE modeling: image segmentation, reconstruction and model generation. We used volume rendering to delineate oral cavity and oropharyngeal SCC's semi-automatically. A recent study described the use of a semi-automated process for volumetric analysis in oral cavity tongue SCC[32]. They reported using SG and RD as methods of semi-automated tumour delineation. Fie acts similar to RD in that the operator creates a closed loop contour outside the lesion and a region-shrinking operation subsequently identifies the object as the area with the same CT grey-level intensity. Whereas Chew and colleagues reviewed 17 oral cavity SCC patients, this thesis reports on 36 patients with oral cavity SCC and a total of 73 patients with oral cavity and oropharyngeal SCC.

Utilizing a surface triangulation technique, *Tr3* reconstructs non-linear curved surfaces between successive two-dimensional slices using small, adjoining triangles and calculates the image volume as the space enclosed by the reconstructed surface. A sophisticated estimation and inclusion of tumour shape and bulk at the periphery between image slices, via the computed mesh in *Tr3*, presents a more realistic representation of true tumour size. Volume information is not lost at the periphery as in the summation-of-areas technique. We feel surface triangulation can therefore better estimate volume than the older method.

5.3 Volumetric Groups

Evaluating the patient data over the follow-up period showed similar DFS and OS outcomes and clustering of data within the four selected strata of 0-4 cm^3, 4-14 cm^3, 14-36 cm^3 and > 36 cm^3. Previous authors had divided volumetric groups by the median volume into low and high volume groups[32, 60]. This is something we completed as well. Other authors selected volumetric groups as per the most significant correlation with patient outcome [57, 61]. Allowing statistical significance to dichotomize patients presents a subjective bias in data analysis. This thesis rather chose to allow volumetric groups to differentiate themselves. We further aimed to establish a nearly equal distribution of patients among the categories, as other reports[29].

5.4 Variability in Volume

The results of our study showed as T stage increases tumour volume similarly increased for both oral cavity and oropharyngeal SCC. Notably, there was a substantial heterogeneity of primary tumour volume in all T stages, particularly in advanced stage disease. Significant interstage variability in volume is reported in other reports of the oropharynx and oral cavity[30-32, 56, 60] as well as other head and neck malignancy sites[22-23, 28-29, 33, 37, 51, 52, 54, 55]. A study to reflect tumour volume variability in similarly staged T3 tumours of the head and neck showed a striking heterogeneity in the larynx, oropharynx and hypopharynx with variations exceeding 100%[56].

Considerable overlap of volume results also occurred between oral cavity and oropharyngeal SCC T-stages. This observation has been reported in other studies[28, 29, 37]. The interstage variability and overlap illustrates the limitations of the current TNM to accurately classify patients into distinct categories. For our dataset the TNM system failed to set apart small and large tumour burden, a finding that served as a premise for our volumetric analysis.

5.5 Utility of Volumetric and TNM systems

A select number of studies have evaluated tumour volumetry to establish if it holds utility as a prognosticator in oral cavity and oropharyngeal SCC.

In a histopathological study of 85 patients with oral tongue scc, treated with glossectomy, post-operative primary tumour volume was not found to be a significant predictor of DFS or OS[11]. The authors report their results did not meet their original expectations. Among 114 oropharyngeal SCC's treated with radiotherapy and/or chemotherapy T-stage was found to significantly influence local control ($p = 0.02$), whereas tumour volume displayed a marginal and non-significant role ($p = 0.10$)[30]. The impact of CT tumour volume was herein less pronounced than other studies in nasopharyngeal, glottic, supraglottic and pyriform sinus SCC[12,23-29].

Herman and colleagues studied 112 oropharyngeal tonsillar SCC's and found a significant correlation between primary tumour volume and local disease control ($p = 0.047$)[31]. They report that overall patients with larger volume tumours had a worse DFS rate than smaller volume tumours, however, this relationship was not linear. Those patients with a tumour volume of 6 – 14.5 mL had a better local control rate than patients with tumour volumes < 6 mL. This non-linearity was a finding we saw amongst intermediate T-stage groups, T2 and T3 staged tumours. On multivariate analysis, however, T-stage was found to be an independent predictor for local control and not tumour volume.

Chew and colleagues report that primary oral cavity tongue SCC's with a tumour volume greater than 13 cc have a poorer DFS and OS[32]. They did not report on DFS and OS as predicted by T-stage. Kuriakose and colleagues found that both T-stage and tumour volume predicted DFS for oral cavity SCC[60]. In their report, tumour volume, however,

was the lone significant indicator of OS ($p < 0.003$). They suggest tumour volume is an important adjunct in the clinical staging of oral cavity SCC.

Our data shows that both tumour volume and T-stage are statistically significant and independent predictors of survival for oral cavity and oropharyngeal SCC. This was revealed by log rank analysis upon division into four volumetric stages and as well with segregation into early and advanced disease. Both classification systems are approximately in line with expected DFS[3], except for T2 and T3 staged tumours. T3 staged tumours had a greater chance for disease control at 5-year follow-up, a reversal of expectations. Furthermore, there is a close proximity of DFS predictions among the intermediate T2 and T3 staged tumours. In these regards, tumour volume may permit superior disease stratification in examining results among four stage groups.

In predicting OS both tumour volume and T-stage were both independently highly significant prognostic tools. Tumour volume was statistically a greater indicator though the results of OS at 5-year follow-up were quite close among intermediate volume groups of 4-14 cm^3 and 14-36 cm^3.

In the multivariate analysis age proved to be an additional predictor of DFS and OS. In the same cox regression model, primary tumour volume was seen to be significant amongst advanced volume groups individually (14-36 cm^3 and > 36 cm^3) and as a whole (> 13.6 cm^3), whereas T-stage was insignificant in all but T4 tumours. For DFS, primary tumour volume was the most important outcome as in other reports of oral cavity and

oropharyngeal SCC's[60] and other head and neck SCC's[12, 21, 22, 24, 28, 33, 37, 54]. To predict OS, both models were significant on multivariate analysis among advanced stages. Advanced age may have adversely affected DFS and OS as a result of additional patient co-morbidities. Elder patients may have been selected for less invasive treatment regimens of radiotherapy, chemotherapy or surgery. Undertreatment secondary to co-morbid conditions could explain our finding of age as a significant co-factor.

5.6 Additional Co-Factors

Additional variables contributing to a tumours response to management require consideration. Tumour and patient factors, in addition to anatomic characteristics of a malignancy are important. The hypoxic fraction of tumours and intrinsic radiosensitivity of tumour cells have been proposed as possible indicators of tumour response[21]. A patient's immune, nutritional, performance and psychological status, as well as past medical history, can influence treatment outcomes. It is important to account for each of these described factors when deciding on treatment and considering survival outcomes.

Head and neck primary tumours in the glottic and supraglottic area are known to display different radiosensitivities than oropharyngeal and oral cavity SCC[23, 25, 27, 30]. It is reported that exophytically growing tumours are generally more radiosensitive than infiltrating tumours due to a smaller anoxic component than deep growing cancers[62]. Oropharyngeal and oral cavity SCC's tend to be more exophytic than deeper infiltrating nasopharyngeal and glottic SCC's. The impact of tumour volume on DFS and OS we

report for oropharyngeal and oral cavity SCC as such may not apply to nasopharyngeal or glottic SCC's.

For the purpose of this thesis we focused only on T stage of oral cavity and oropharyngeal SCC being fully aware that nodal (N) stage is a cofounding variable that can affect treatment decisions as well as DFS and OS. Despite tumours being in the same volumetric or T-stage group they may have different amounts of nodal disease and hence total tumour burden. Our objective was to compare the utility of primary tumour volume and T-stage alone. In this thesis, as well as other reports, each classification system has an equal opportunity to influence from nodal stage. Currently we are undertaking a further study to evaluate the prognostic significance of nodal volume on oral cavity and oropharyngeal SCC patients.

As a whole, the inclusion of tumour and host factors, in addition to volumetric staging, may afford individualized patient management decisions and more precise prognosis.

5.7 Limitations

Limitations in our study include the time commitment for volumetric analysis and inter- and intra-observer variability. The semi-automated segmentation system of RD that is very similar to *Fie*, however, has shown a reduction in time required as well as inter-observer variance over manual tracing[34,35]. Although we did not formally evaluate these limiting characteristics in our study, we believe that FE modeling benefits our analysis in

much the same manner as RD. Evaluating volume and T-stage as groups as opposed to size as a continuous variable may have also aided in partly decreasing interobserver variances. Reports looking at nasopharyngeal SCC have further shown that if a single trained observer estimates the tumour volume the information bias can be minimalized [28, 37]. One trained observer completed our analysis.

Our observations result from a retrospective trial. This was advantageous for volumetric analysis of older CT images as we could correlate volumetric data with long-term outcomes. To extrapolate on our findings, however, a prospective trial could further establish the utility of primary tumour volume for outcome prediction in oral cavity and oropharyngeal SCC.

As mentioned above additional patient and tumour factors can influence the outcome of DFS and OS. Different treatment paradigms were also given to our patient group. For oropharyngeal and oral cavity SCC the literature shows that either surgery or radiotherapy and chemotherapy can be selected as a primary treatment option with similar expected outcomes[2,3]. For this reason we did not segregate data by primary treatment modality. Differing extents of surgery or doses of radiation and chemotherapy were not accounted for. A future study with a larger patient population evaluating the influence of primary treatment choice may aid our understanding of tumour volume utility.

5.8 Clinical Applications

Oncology centers are currently taking primary tumour volume into consideration in treatment planning[63, 64]. Particularly with large and advanced nasopharyngeal SCC, it is reported that information from primary tumour volume rather than conventional staging is being used to plan radiation and chemotherapy protocols[37].

Tumour volumetry may help to individualize the treatment of patients according to their anatomy. Patients can also be given a greater amount of information to predict tumour recurrence and OS. Our data shows that tumours above a critical volume of 36 cm^3 showed a significantly poorer outcome with recurrence in each patient within the first two years. Such a subgroup of oral cavity and oropharyngeal SCC patients may benefit from targeted treatment protocols and more frequent post-treatment follow-up. This may also represent a subgroup of patients who could be offered newer, experimental modalities such as epidermal growth factor receptor inhibitors or immunotherapy despite not yet understanding the potential benefit or harm of these anticancer therapies[65,66].

To realize widespread clinical implementation of tumour volumetry refinements to allow even more accurate and easily accessible volumetric measurements, however, should continue to be sought after.

6.0 CONCLUSIONS / SUMMARY

Conclusions / Summary

This thesis has established that *Fie* and *Tr3* software are effective tools for tumour volumetry. It is the first report to utilize surface triangulation to estimate volumetric results.

We have illustrated significant interstage variability as well as an overlap among different stage groups present within the current TNM classification system for oral cavity and oropharyngeal SCC. Both tumour volume and T-stage proved to be independently effective and comparative models for anatomical classification, showing significance in their predictions of DFS and OS. In the future the incorporation of tumour volume may assist in the better selection of treatment protocols and offer more precise prognosis, particularly in advanced T-stages where tumour volume is highly variable. We believe, primary tumour volume determined by CT should be considered a relevant prognostic factor in oral cavity and oropharyngeal SCC.

7.0 APPENDIX (TABLES / FIGURES)

Appendix 1.

Table 1. Tumour Node Metastasis (TNM) staging of oral cavity and oropharyngeal SCC [67]

Primary Tumour (T)
(from Tx – T3 T-stage for oral cavity and oropharynx SCC is the same)

Tx	Unassessable
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour 2 cm or less
T2	Tumour > 2 cm but not > 4 cm
T3	Tumour > 4cm
T4a (oral cavity)	Tumour invades adjacent structures (through cortical bone, into deep/extrinsic muscle of the tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), maxillary sinus, or skin)
T4b (oral cavity)	Tumour invades masticator space, pterygoid plates, or skull base, and/or encases internal carotid artery
T4a (oropharynx)	Tumour invades adjacent structures (larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus and styloglossus), medial pterygoid, hard palate or mandible)
T4b (oropharynx)	Tumour invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base, or encases the carotid artery

Regional Lymph Nodes (N)

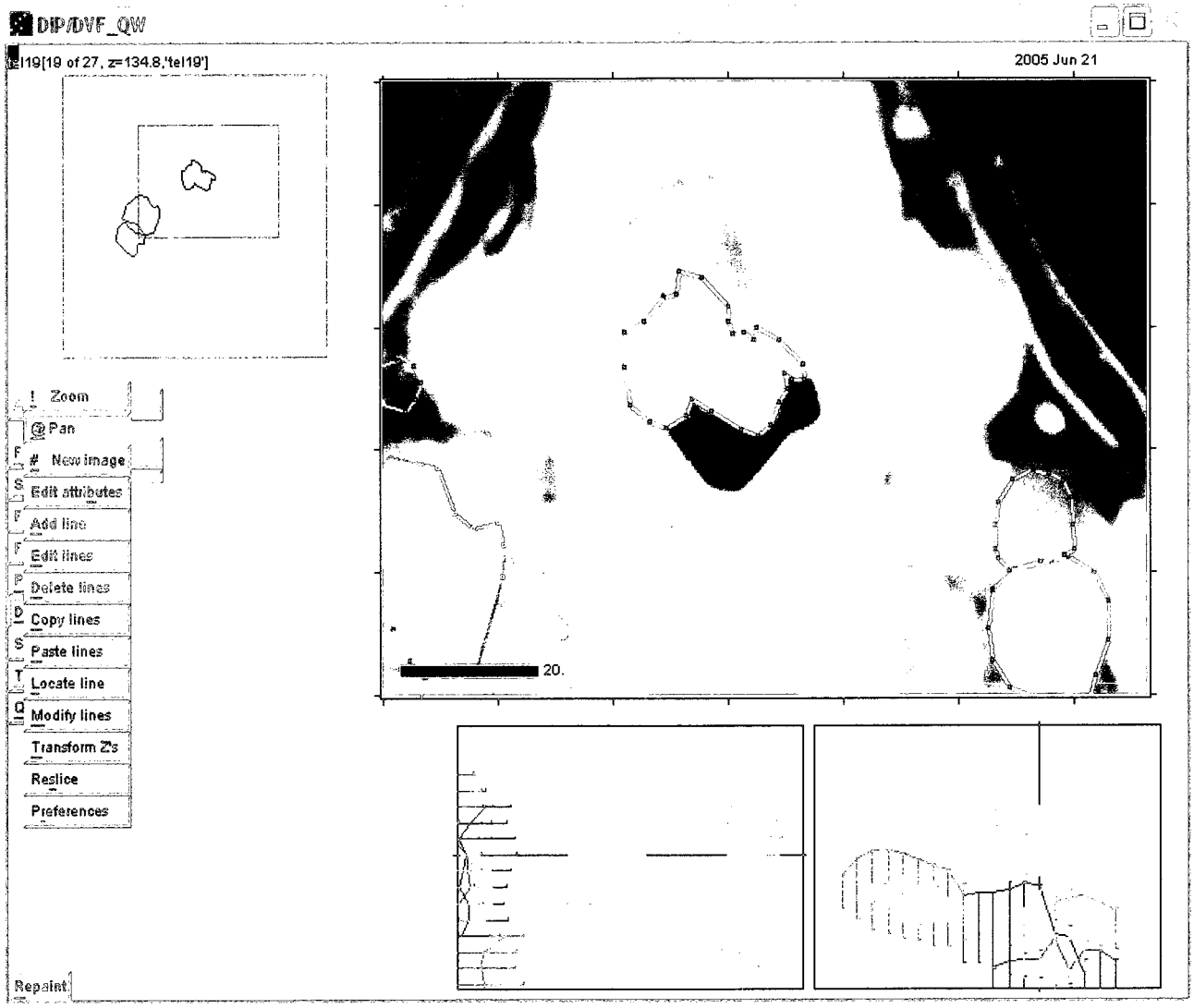
Nx	Unassessable
N0	No regional lymph node metastasis
N1	Single ipsilateral lymph node, 3 cm or less
N2a	Single ipsilateral lymph node > 3 cm but not > 6 cm
N2b	Multiple ipsilateral lymph nodes, none > 6 cm
N3	Any lymph node > 6 cm

Distant Metastasis (M)

Mx	Unassessable
M0	No distant metastasis
M1	Distant metastasis

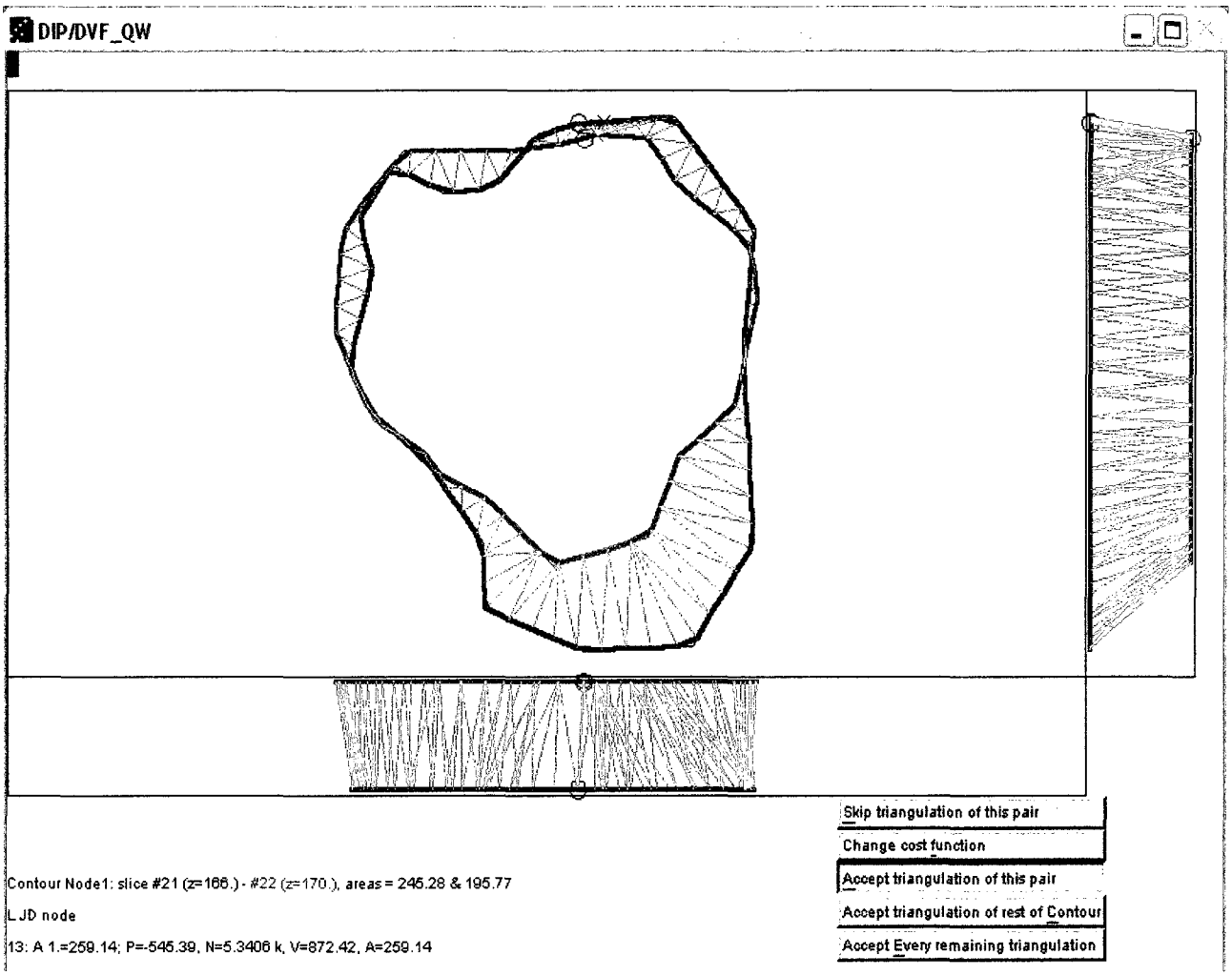
Appendix 2.

Figure 1. Volumetric analysis with Fie imaging software.



Appendix 3

Figure 2. TR3 software illustrating surface triangulation in volumetry calculations.



Appendix 4

Figure 3. Cosmo player illustrating reconstruction of the 3D tumour model of a tongue oral cavity SCC with bilateral cervical lymphadenopathy.

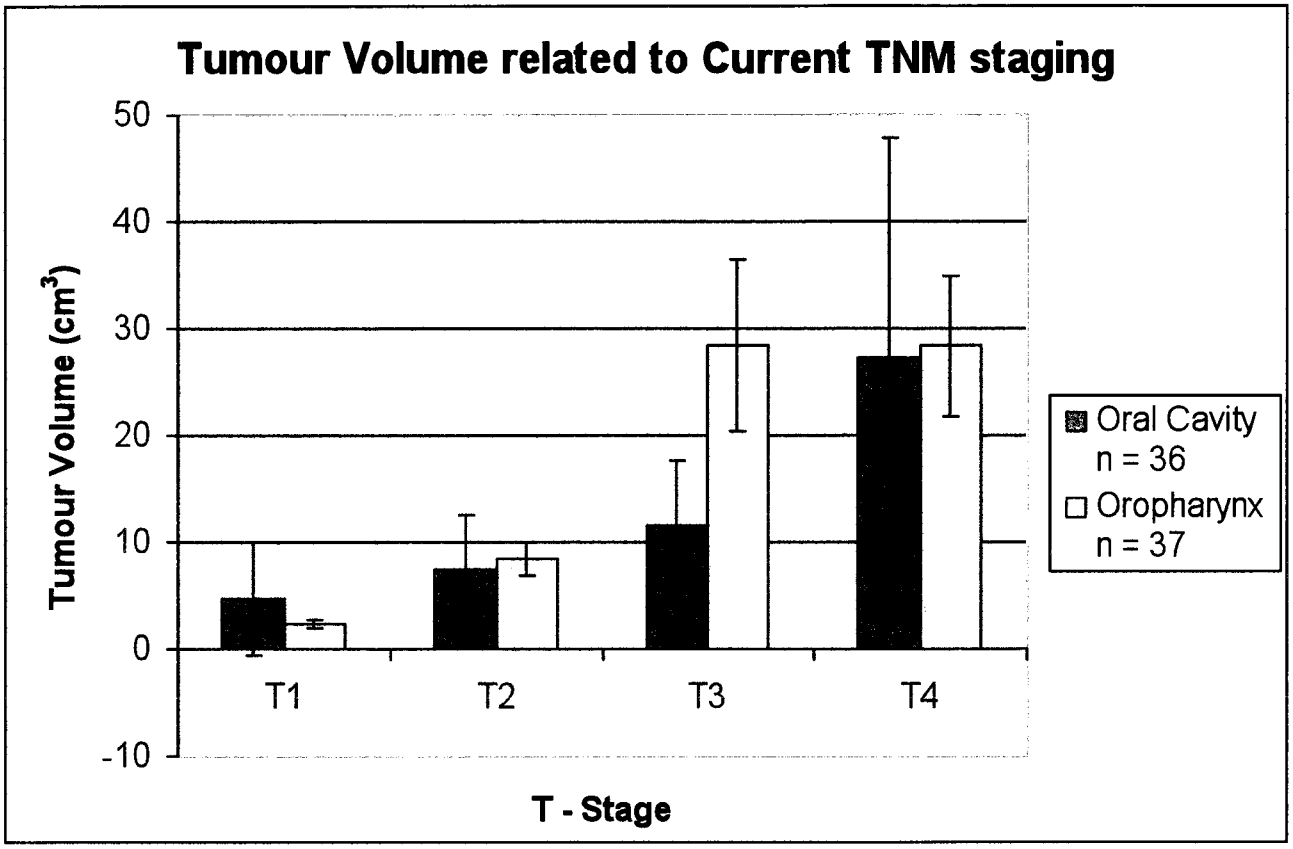
Appendix 5.

Table 2. Distribution of patients according to TNM stage for oral cavity and oropharyngeal SCC.

Oral Cavity n = 36	**T1 – 6**
	T2 – 14
	T3 – 6
	T4 – 10
Oropharyngeal n = 37	**T1 – 11**
	T2 – 12
	T3 – 10
	T4 – 4

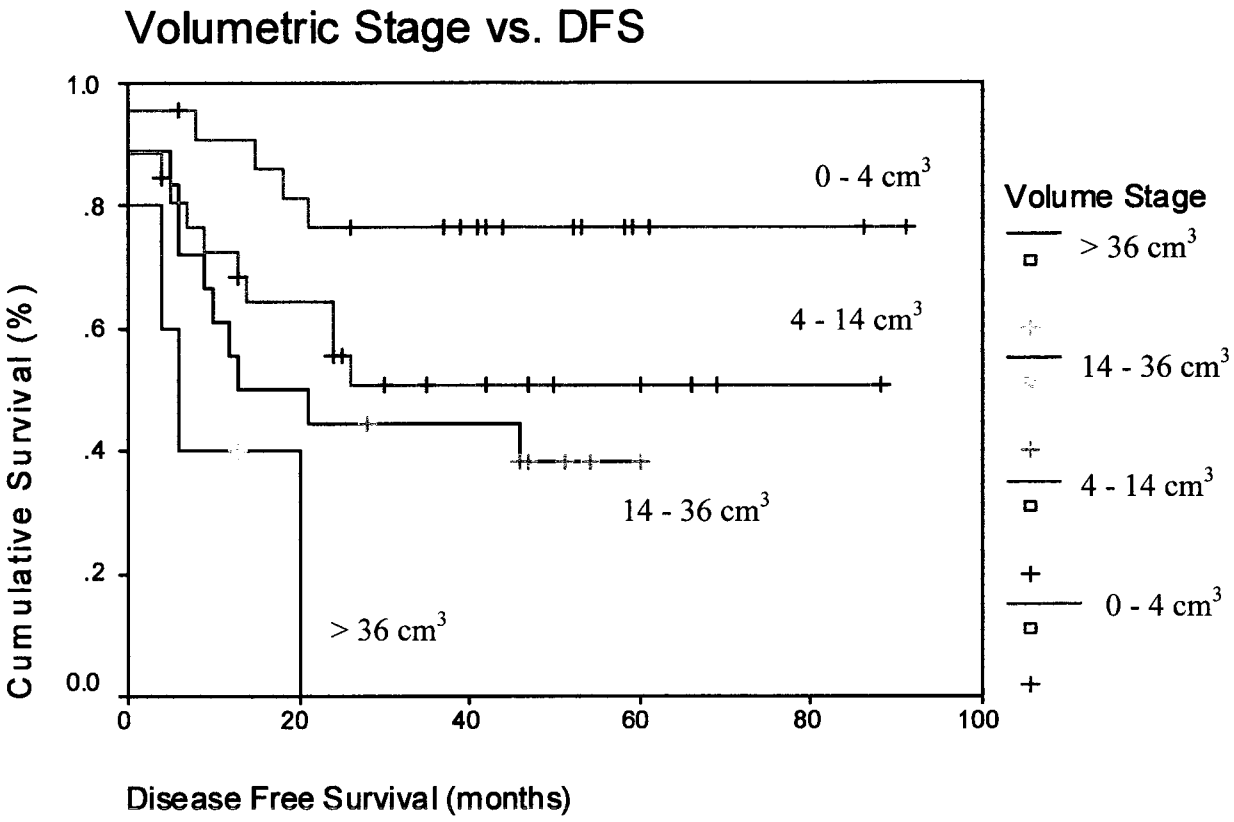
Appendix 6

Figure 4. Tumour volume related to T-Stage per oral cavity and oropharyngeal SCC patients.



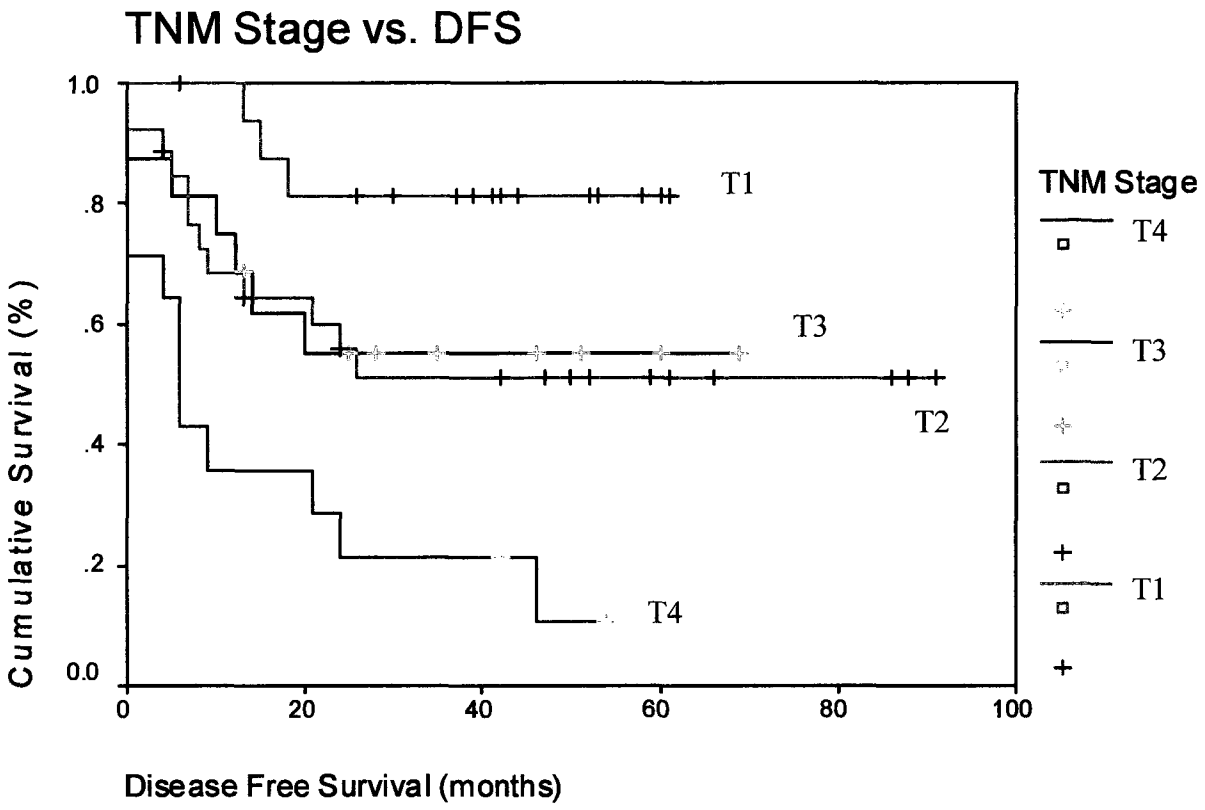
Appendix 7

Figure 5. Volumetric Stage vs DFS.



Appendix 8

Figure 6. TNM Stage vs DFS.



Appendix 9

Table 3. Prediction of DFS by the literature, volumetric stage, TNM stage.

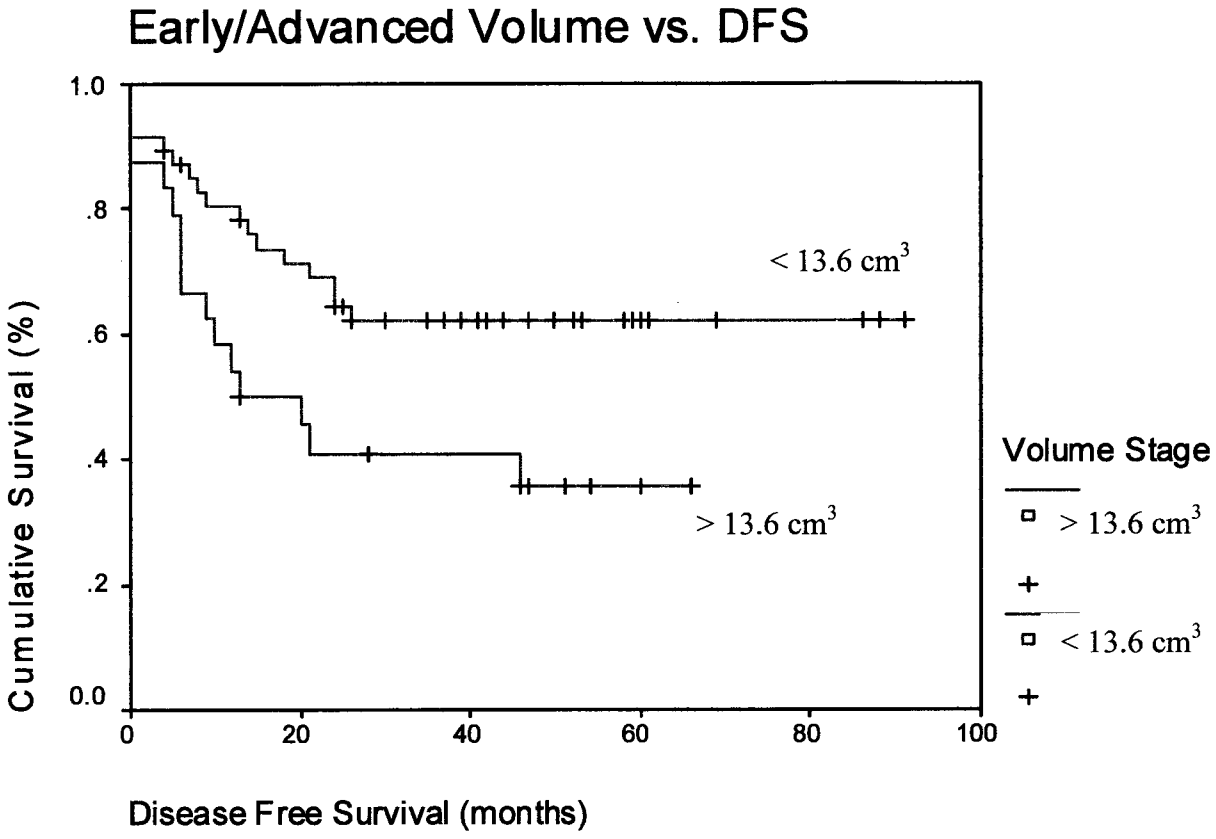
Literature	Volumetric Results	TNM staging
T1 (0-2 cm) 84%	0 – 4 cm^3 76.36%	T1 (0-2 cm) 81.25%
T2 (2-4 cm) 71%	4 - 14 cm^3 50.60%	T2 (2-4 cm) 51.11%
T3 (>4 cm) 40%	14 - 36 cm^3 38.10%	T3 (>4 cm) 55.0%
T4 (adjac invasion) 20%	> 36 cm^3 0%	T4 (adjac invasion) 10.71%

p = 0.0076 p = 0.006

Power > 0.80

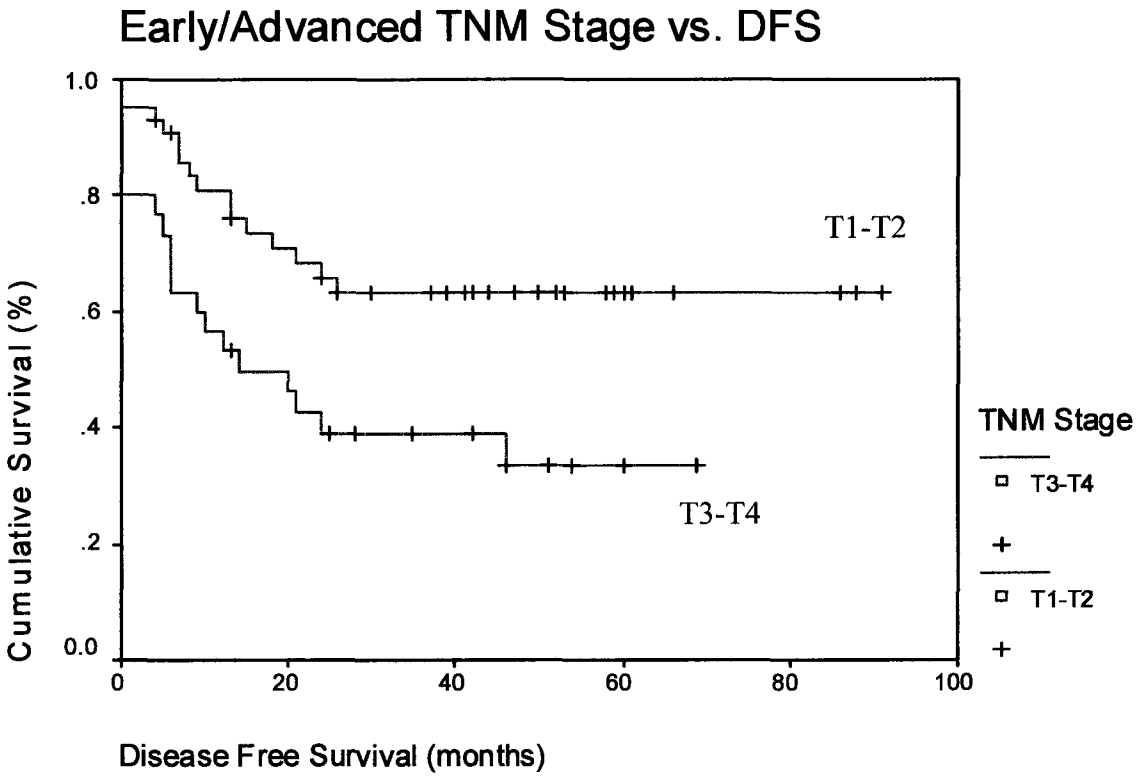
Appendix 10

Figure 7. Early/Advanced Volume vs DFS.



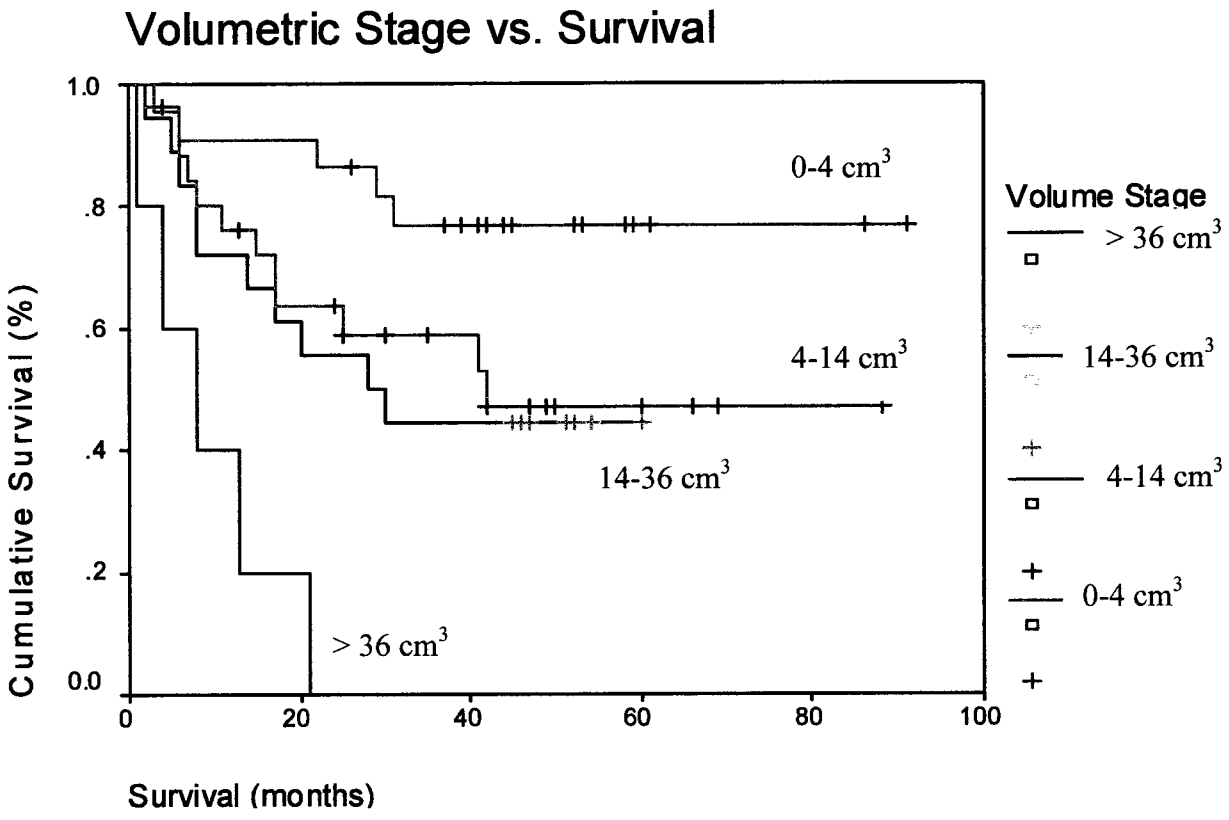
Appendix 11

Figure 8. Early / Advanced TNM stage vs DFS.



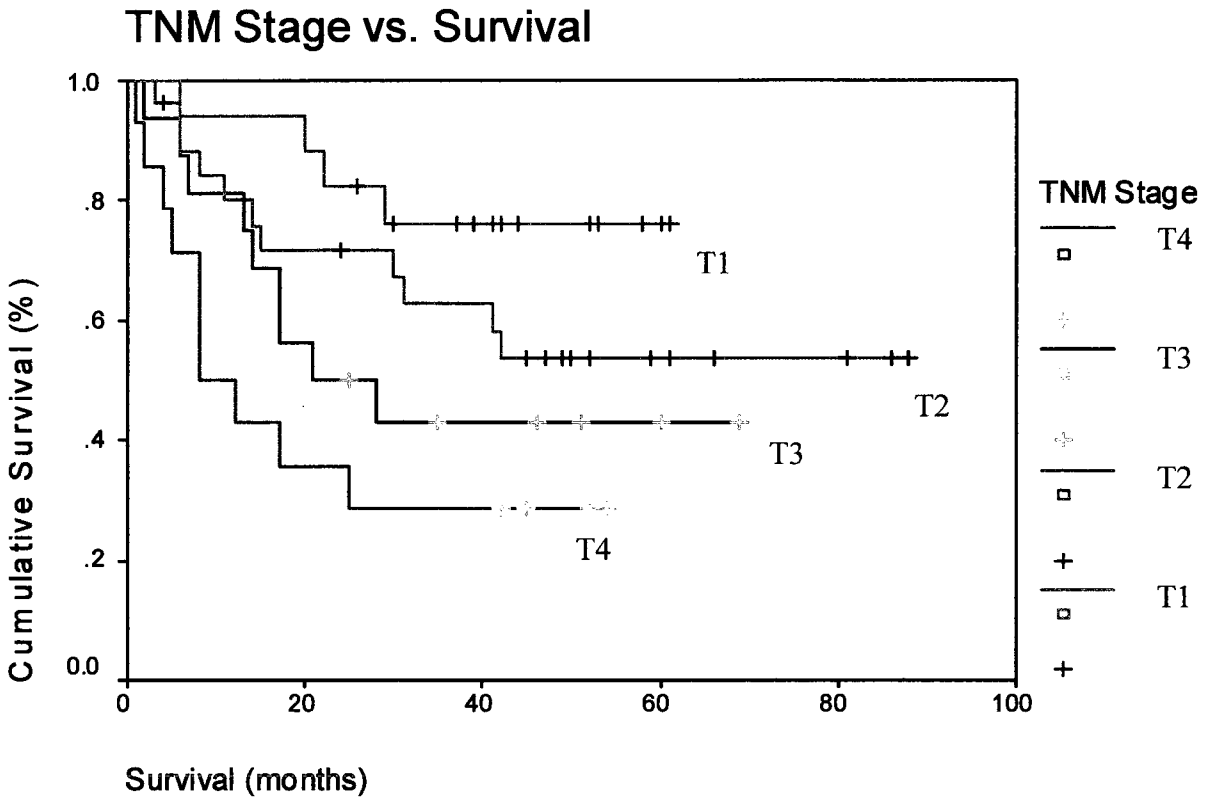
Appendix 12

Figure 9. Volumetric stage vs. overall survival.



Appendix 13

Figure 10. TNM stage vs overall survival.



Appendix 14

Table 4. Multivariate Analysis for DFS. Cox Regression Model

	Relative Risk (e^b)	*p*
Age + 0-4 cm3		
Age + 4-14 cm3	**2.497**	***0.128***
Age + 14-36 cm3	**4.388**	***0.014***
Age + >36 cm3	**6.914**	***0.017***

	Relative Risk (e^b)	*p*
Age + T1		
Age + T2	**3.450**	***0.065***
Age + T3	**3.336**	***0.111***
Age + T4	**5.763**	***0.010***

	Relative Risk (e^b)	*p*
Age + < 13.6 cm3		
Age + > 13.6 cm3	**2.510**	***0.022***

	Relative Risk (e^b)	*p*
Age + T1/T2		
Age + T3/T4	**2.040**	***0.070***

8.0 REFERENCE LIST

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