# ACCURACY OF CONTRAST-ENHANCED COMPUTED TOMOGRAPHY SCAN IN ASSESSING DEPTH OF INVASION IN ORAL TONGUE SQUAMOUS CELL CARCINOMA

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Field of Study: **Oral and Maxillofacial Surgery**

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**ACCURACY OF CONTRAST-ENHANCED COMPUTED TOMOGRAPHY SCAN IN ASSESSING DEPTH OF INVASION IN ORAL TONGUE SQUAMOUS CELL CARCINOMA**

## ABSTRACT

**INTRODUCTION:** Depth of invasion (DOI) in oral squamous cell carcinoma is an important predictor of locoregional spread, distant metastasis, disease recurrence and survival. **OBJECTIVES:** To compare DOI measurement between preoperative contrast-enhanced computed tomography (CECT) scan and histopathological examination (HPE) in oral tongue squamous cell carcinoma (OTSCC). To determine the correlation between CECT and HPE measurements. To determine the measurement accuracy of DOI from CECT. **MATERIALS & METHODS:** A retrospective study of 18 OTSCC patients in Faculty of Dentistry, University of Malaya was carried out. Preoperative CECT scans were reviewed by a single observer to measure the DOI on axial and coronal sections, then compared to HPE. Data were analysed for intraobserver reliability and strength of correlation determined using intraclass correlation coefficient (ICC). Mean DOI was compared using repeated measures ANOVA and accuracy was assessed using Bland-Altman plot. **RESULTS:** Intraobserver reliability was excellent, with ICC=0.996 for axial and ICC=0.999 for coronal. Overall, CECT measurement of DOI was 1-2mm smaller than HPE, with mean differences of -0.743mm for axial and -1.106mm for coronal. There was excellent correlation between CECT and histopathological tumour depths in both axial (ICC=0.956) and coronal (ICC=0.965). Bland-Altman analysis showed 95% confidence interval for measurement differences between CECT and histopathological depth were within the limits of agreement, indicating that these two methods can be used interchangeably. **CONCLUSION:** Measurement of DOI from

CECT in OTSCC was comparable to HPE with an average of 1-2mm decrement. There was excellent correlation in both axial and coronal views compared to HPE, with accurate DOI measurement from CECT.

**Keywords**: Computed tomography, depth of invasion, tongue cancer, cancer staging, accuracy

**KETEPATAN IMBASAN TOMOGRAFI BERKOMPUTER BERKONTRAS DALAM MENILAI KEDALAMAN PENCEROBOHAN KARSINOMA SEL SKUAMOUS LIDAH ORAL**

## ABSTRAK

**PENGENALAN:** Kedalaman pencerobohan (DOI) dalam karsinoma sel skuamous oral adalah peramal penting bagi penyebaran locoregional, rebakan ke bahagian lain tubuh, kambuhan penyakit dan kelangsungan hidup. **OBJEKTIF:** Membandingkan ukuran DOI antara imbasan tomografi berkomputer berkontras (CECT) pra-pembedahan dan pemeriksaan histopatologi (HPE) dalam karsinoma sel skuamous lidah oral. Menentukan korelasi antara ukuran CECT dan HPE. Menentukan ketepatan pengukuran DOI daripada imbasan CECT. **BAHAN & KAEDAH:** Kajian retrospektif 18 pesakit OTSCC di Fakulti Pergigian, Universiti Malaya telah dijalankan. Pemeriksaan CECT pra-pembedahan telah dikaji semula oleh pemerhati tunggal untuk mengukur DOI pada hirisan aksial dan koronal, yang kemudiannya dibandingkan dengan HPE. Data dianalisis untuk kebolehpercayaan intrapemerhati dan kekuatan korelasi yang ditentukan menggunakan pekali korelasi intrakelas (ICC). Purata DOI dibandingkan dengan menggunakan pengujian berulang ANOVA dan ketepatan dinilai menggunakan plot Bland-Altman. **KEPUTUSAN:** Kebolehpercayaan intrapemerhati adalah sangat baik, dengan ICC=0.996 untuk aksial dan ICC=0.999 untuk koronal. Secara keseluruhan, ukuran DOI daripada CECT adalah 1-2mm lebih kecil daripada histopatologi, dengan perbezaan purata -0.743mm untuk aksial dan -1.106mm untuk koronal. Korelasi antara kedalaman tumour daripada CECT dan histopatologi adalah sangat baik untuk kedua-dua aksial (ICC=0.956) dan koronal (ICC=0.965). Analisis Bland-Altman menunjukkan selang keyakinan 95% untuk perbezaan pengukuran antara kedalaman CECT dan HPE berada dalam lingkungan had persetujuan, menunjukkan bahawa kedua-dua kaedah ini

boleh digunakan secara bergantian. **KESIMPULAN:** Pengukuran DOI daripada CECT bagi kes OTSCC adalah sebanding dengan HPE dengan purata susutan 1-2mm. Kedua-dua hirisan aksial dan koronal menunjukkan korelasi yang sangat baik berbanding HPE, dan pengukuran DOI daripada CECT adalah tepat.

**Kata kunci:** Tomografi berkomputer, kedalaman pencerobohan, kanser lidah, pemeringkatan kanser, ketepatan

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**TABLE OF CONTENTS**

## LIST OF FIGURES

## LIST OF TABLES

## LIST OF SYMBOLS AND ABBREVIATIONS

| | | |
|---|---|---|
| AJCC | : | American Joint Committee on Cancer |
| CECT | : | Contrast-enhanced computed tomography |
| CI | : | Confidence interval |
| cm | : | centimetre |
| CT | : | Computed tomography |
| DOI | : | Depth of invasion |
| ENE | : | Extranodal extension |
| ETMI | : | Extrinsic tongue muscle invasion |
| FDG-PET | : | Fluorodeoxyglucose – positron emission tomography |
| FOV | : | Field of view |
| HPE | : | Histopathological examination |
| ICC | : | Intraclass correlation coefficient |
| ICD | : | International Classification of Diseases |
| LOA | : | Limits of agreement |
| MRI | : | Magnetic resonance imaging |
| mm | : | millimetre |
| NCCN | : | National Comprehensive Cancer Network |
| OSCC | : | Oral squamous cell carcinoma |
| OTSCC | : | Oral tongue squamous cell carcinoma |
| r | : | Correlation coefficient |
| SCC | : | Squamous cell carcinoma |
| SD | : | Standard deviation |
| TT | : | Tumour thickness |
| USG | : | Ultrasonography |

## LIST OF APPENDICES

# CHAPTER 1: INTRODUCTION

## 1.1 Statement of problem

Oral squamous cell carcinoma (OSCC) comprises of 90% of all oral malignancies, with the most common site on the tongue (Mair et al., 2018). The primary treatment of OSCC is by surgery, especially in early stage tumour (Pfister et al., 2017). The fundamental goal in curative oncological surgery is to completely resect the malignant tumour and to leave no residual viable tumour cells behind. This is achieved by obtaining at least a 5 mm pathologically clear margin. Taking microscopic tumour extension and shrinkage factor during tumour processing into account, surgical margin is taken as 1.0 to 1.5 cm of grossly normal tissue (Schmidt & Cheng, 2016).

Achieving a clear superficial margin is seldom an issue to surgeons as the mucosal extent of tumour is readily palpable. However, clearance of deep margin poses a challenge as clinical examination is often unreliable. Tumours of larger volume and more advanced stage are more likely to have unsatisfactory margin (Girardi, Zanella, & Kroef, 2013). With the aid of radiographic assessment in addition to clinical examination, depth of invasion (DOI) can be determined (Lydiatt et al., 2017). This will be an invaluable information for the surgeon during operation, enabling adequate deep margin to be excised.

Over the past decade, the importance of DOI has rose beyond achieving sound oncological margin. DOI has shown to be an independent predictor of disease specific survival as well as providing a good prognostic indicator for locoregional spread including occult cervical lymph node involvement and distant metastasis (Jerjes et al., 2010; Melchers et al., 2012).

However, the gold standard for DOI is from pathological data, which is obtained from surgical specimen. Therefore, for patients undergoing surgery, depth of surgical excision is purely based on the surgeon's clinical evaluation. In addition, if elective neck dissection was not performed together with primary tumour resection, the risk of occult neck metastasis based on DOI for early staged tumour will be only known after examining the surgical specimen. If the risk is high, surgeon may need to make a tough decision either for close monitoring of the neck or second surgery for neck dissection.

Hence, pre-operative imaging plays a vital role in assessing the tumour size and depth, involvement of adjacent structures and the presence of regional and distant metastasis. Computed tomography (CT) scan, magnetic resonance imaging (MRI) and ultrasonography (USG) imaging have been described in the literature for oral cancer assessments (Blatt, Ziebart, Kruger, & Pabst, 2016; C. Law, R. Chandra, J. Hoang, & P. Phal, 2011).

## 1.2 Aim of the study

This study aims to determine the measurement accuracy of DOI in oral tongue squamous cell carcinoma in contrast-enhanced CT (CECT) scan. The gold standard used for comparison is the DOI reported by oral pathologist in histopathological report of surgical specimen.

## 1.3 Objectives of the study

There are three objectives set for this study:

i. To compare the measurement of the DOI in pre-operative CECT scan with histopathological examination (HPE).
ii. To determine the correlation between the DOI measured from the CECT scan and from HPE.

iii. To determine the accuracy of DOI measured in CECT scan compared to HPE.

## 1.4 Significance of the study

This study will enable the estimation of actual DOI based on CT measurement. With this information, surgeon can determine the depth of tumour excision to achieve clear margin and to preserve healthy tissues. The risk of possible occult neck metastasis in clinically neck negative patients may be weighed with pre-operative radiological DOI, thus aiding in decision for undertaking elective neck dissection in the same setting as primary tumour resection.

## 1.5 Choice of the study topic

For tongue subsite, contrast-enhanced MRI is the recommended choice of imaging due to its superior soft tissue resolution (Arya, Rane, & Deshmukh, 2014). Despite that, majority of tongue cancer patients only have CECT imaging taken as it is relatively cheaper, more readily accessible, faster scanning with high reproducibility and shorter waiting time compared to MRI. This reason also applies to our institution. The CT imaging of head and neck is usually taken as part of staging process (Bartlett, Walters, & Yu, 2013).

As of date, there is no previous study on accuracy of DOI measurement from CT. Due to different planes of measurements for different subsite of oral cavity, only one subsite is investigated in this study to enable standard measurement method. Tongue is selected as it is the most common subsite of oral cavity cancer, therefore allowing the maximum number of sample.

# CHAPTER 2: LITERATURE REVIEW

## 2.1 Oral Squamous Cell Carcinoma (OSCC)

OSCC is a carcinoma with squamous differentiation arising from the mucosal epithelium. More than 90% of all oral malignancies are squamous cell carcinoma (SCC) (Sloan et al., 2017). OSCC is divided into seven subsites, namely lip, buccal mucosa, retromolar trigone, gingiva, hard palate, tongue and floor of mouth.

### 2.1.1 Epidemiology

Cancer is the leading cause of mortality worldwide. There were 14.1 million new cancer cases, 8.2 million cancer deaths and 32.6 million people living with cancer in 2012 worldwide (Ferlay et al., 2013). In age-standardised population, oral cavity and lip cancer was listed as the fifteenth most common cancer (Forman & Ferlay, 2014). When combined with other cancers of head and neck region in the nasopharynx and pharynx, they were the seventh most frequent type of cancer by incidence and ninth most common cause of cancer mortality, ranking above cervical cancer (Thompson, 2014).

The risk of developing oral cancer increases between 10- and 100-fold in people who drink and smoke heavily (Thompson, 2014). Habit of tobacco chewing, in combination with paan or betel quid consisting of betel leaf, areca nut, lime, and tobacco which is practised in certain cultures, posed an increased risk for oral cancer development with the highest incidence seen in India (Thompson, 2014).

This is well reflected in the multiracial Malaysian population where mouth cancer was the fourth most common cancer for Indian females and eighth for Indian male, but ranked outside top ten in other ethnic groups (Azizah, Nor Saleha, Noor Hashimah, Asmah, & Mastulu, 2016). However, this may not paint the true picture of oral cancer incidence as

the lip and tongue were coded as separate entities from mouth cancer in the ICD-10 coding used in this National Cancer Registry Report as seen in Table 2.1 below. There were 916 cases were reported under mouth cancer category which comprised of gum, floor of mouth, palate, and other parts of mouth for the year 2007 until 2011. Another 85 cases of lip cancer and 862 cases of tongue cancer were reported in this five-year period.

**Table 2.1: Categorisation of ICD-10 coding in National Cancer Registry Report 2007 – 2011**

| ICD-10 coding | Diagnosis | Categorisation under National Cancer Registry Report 2007 - 2011 |
|---|---|---|
| C00 | Malignant neoplasm of lip | Lip cancer |
| C01 | Malignant neoplasm of base of tongue | Tongue cancer |
| C02 | Malignant neoplasm of other and unspecified parts of tongue | |
| C03 | Malignant neoplasm of gum | Mouth cancer |
| C04 | Malignant neoplasm of floor of mouth | |
| C05 | Malignant neoplasm of palate | |
| C06 | Malignant neoplasm of other and unspecified parts of mouth | |

According to ICD-10 coding (www.icd10data.com), lip cancer (C00.-) comprises of external and inner lip cancer, thus can be classified either as cutaneous or oral cancer respectively. Similarly, tongue base cancer (C01) falls under oropharyngeal cancer while cancer of other parts of tongue (C02.-) is under the purview of oral cancer. Therefore, the number of oral cancer cases in Malaysia was in fact higher if mucosal lip and oral tongue cancers were taken into consideration. In addition, there is also concern of under-

reporting of cases as registration was based primarily on voluntary notification by healthcare workers.

### 2.1.2 **Clinical features**

Early OSCC is usually asymptomatic, therefore often remains unnoticed until it has reached a remarkable size or poses profound symptoms such as pain. In early malignant lesion, it presents as red or red and white areas with a slight roughness and is well demarcated with induration (Bagan, Sarrion, & Jimenez, 2010). The tumour may be ulcerative, exophytic, or endophytic. Ulcerative lesions usually have irregular edge and induration, while exophytic lesions present either as cauliflower-like irregular growth or as flat, pink to pinkish-white proliferative lesions. On the other hand, endophytic lesions appear small superficially, but involve a substantial amount of soft tissue underneath (Shah, Patel, & Singh, 2012).

As the lesion advances further, the pain intensity increases. Other less common presentations are bleeding from abnormal blood vessels supplying to the tumour, delayed socket healing following dental extraction, dysphagia and paraesthesia depending upon location and extent of tumour (Bagan et al., 2010).

The tumour then spreads to involve adjacent anatomical structures and by lymphatic drainage to cervical lymph nodes. Cervical lymphadenopathy may be occasionally present without other symptoms (Bagan et al., 2010) whereas distant metastases occur in late stage of disease.

### 2.1.3 **Oral tongue squamous cell carcinoma (OTSCC)**

Almost half of OSCC (Azizah et al., 2016; Mair et al., 2018) occurs in tongue with majority arising from lateral border of tongue, and a few from ventral surface. Oral tongue, also known as anterior two-third of tongue, is divided from posterior one-third of

tongue by sulcus terminalis. It has a free margin bounded anteriorly and laterally by the alveolar margins.

In oral tongue squamous cell carcinoma (OTSCC), pain can arise at an early stage (Bagan et al., 2010). Specific to tongue subsite, alterations in speech, articulation, and tongue mobility suggest involvement of the extrinsic tongue muscle and hypoglossal nerve (Chinn & Myers, 2015). Due to the lack of anatomic barriers to cancer spread compared to other oral cavity subsites, tongue cancer has a capacity for contralateral spread.

It is imperative to palpate the neck to identify any regional nodal disease which is then followed by radiological imaging. Robust lymphatic drainage of the tongue can lead to difficulty in achieving locoregional control even in early-stage tumours (Chinn & Myers, 2015). Thirty-eight percent of tongue SCC patients have some degree of nodal involvement clinically but only twenty percent is positive on histopathological examination (Yamamoto et al., 2014). On the other hand, the absence of nodal disease on clinical and radiological examinations is not an absolute exclusion as the incidence of occult nodal metastasis is 28.5% (Mair et al., 2018).

### 2.1.4 **Histopathological features**

The gold standard in diagnosis of OSCC is from biopsy, supplemented by radiological imaging for disease staging. Histopathological examination of biopsy specimen reveals the type of carcinoma. Conventional type of OSCC is most commonly seen. Other variants include basaloid, spindle cell, adenosquamous, verrucous, papillary and acantholytic SCC. These subtypes are important in terms of prognostication, with spindle cell and adenoquamous subtypes having worse prognosis than conventional OSCC (Sloan et al., 2017).

Tumours can be graded into well, moderate and poor differentiation (Sloan et al., 2017). Well-differentiated OSCC is characterised by nests, cords, and islands of large cells with pink cytoplasm, prominent intercellular bridges, and round nuclei, which may not be obviously hyperchromatic. Dyskeratotic cells and squamous pearls are prominent. With worsening tumour grade, the presence of cellular and nuclear pleomorphism, nuclear hyperchromasia, and mitotic figures increase (Sloan et al., 2017).

Besides the histological type and grading, there are other aspects of the resected tumour that need to be examined. In accordance with the Royal College of Pathologists, London (Helliwell & Woolgar, 2013), the core pathological data to be included in the histopathological report are:

i. maximum diameter of tumour
ii. maximum depth of invasion
iii. histological type of carcinoma
iv. degree of differentiation
v. pattern of invasion by the carcinoma at its deep margin
vi. distance from invasive carcinoma to both mucosal and deep surgical margins
vii. presence of vascular, nerve or bone invasion
viii. presence of severe dysplasia or carcinoma in-situ adjacent to the primary carcinoma and within 5 mm of the resection margins

These histopathological features are important to be conveyed to the surgeon and oncologist as they will affect the post-operative management and follow up.

### 2.1.5 **Staging of OSCC**

Cancer staging defines the anatomical extent of disease locally, regionally and at a distant site. It is a common language for clinicians to communicate with each other,

providing prognostication and as a guide for patient management. Also known as TNM classification system, cancer staging comprises of three elements: T stands for extent of tumour, N for lymph nodes involvement and M represents distant metastasis. In early stage of OSCC (Stage I and II), tumour is relatively small without nodal involvement whereas in more advanced stage (Stage III and IV), there is presence of cervical nodes infiltration and tumour may be larger in size. Distant metastasis is uncommon at first presentation, but whenever it is present, cancer will be upgraded to Stage IV.

In view of growing evidence of the importance of depth of invasion (DOI) as elaborated in the following subchapter, American Joint Committee on Cancer (AJCC) in 2017 had incorporated this parameter into cancer TNM staging (refer to Appendix A) for better disease stratification of oral cancer (Lydiatt et al., 2017).

In this eighth edition of AJCC staging manual compared to its predecessor (refer to Appendix B), T category is not solely based on greatest tumour dimension but will be upstaged when DOI has exceeded cut-off point of 5 mm and 10 mm respectively (Table 2.2). In the same edition, N category was also revised to include extranodal extension (ENE) in addition to lymph node size. The presence of extranodal extension automatically upstages the N component. This improved classification aids clinician in prognosis and treatment planning.

**Table 2.2: T category for oral cavity cancer, 8th edition AJCC staging manual**

| **T CATEGORY** | **T CRITERIA** |
|---|---|
| Tx | Primary tumour cannot be assessed |
| Tis | Carcinoma in situ |
| T1 | Tumour size not more than 2 cm, DOI not more than 5 mm |
| T2 | Tumour size not more than 2 cm, DOI more than 5 mm but not more than 10 mm; *or*<br>Tumour size more than 2 cm but not more than 4 cm, DOI not more than 10 mm |
| T3 | Tumour size more than 4 cm; *or*<br>Any tumour with DOI more than 10 mm |
| T4 | Moderately advanced or very advanced local disease |
| T4a | Moderately advanced local disease:<br>(lip) tumour invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose);<br>(oral cavity) tumour invades adjacent structures only (eg, through cortical bone of the mandible or maxilla, or involves the maxillary sinus or skin of the face);<br>note that superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumour as T4 |
| T4b | Very advanced local disease; tumour invades masticator space, pterygoid plates, or skull base and/or encases the internal carotid artery |

### 2.1.6 **Treatment**

For stage I and II diseases, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommended resection of primary tumour with or without neck dissection, depending on the tumour thickness and location of tumour. As general rule, for oral cancer in the absence of clinical nodal metastasis, selective neck dissection at least levels I to III is recommended (Pfister et al., 2017).

In tumours with a depth greater than 4 mm, elective neck dissection should be strongly considered following this guidelines. If the depth is less than 2 mm, elective dissection is only indicated for highly selective situations. For those which the DOI falls in between these two figures, the surgeon's clinical judgement must be utilised which includes patient's reliability to follow up, clinical suspicion and other factors (Pfister et al., 2017).

Following surgery, the presence of adverse features in histopathological findings necessitates adjuvant radiotherapy to be considered and the only feature under the surgeon's control is tumour margin. In patients with positive tumour margins, re-resection to achieve negative margin is preferable. If that is not feasible, those patients shall receive radiotherapy. Other adverse features are extracapsular nodal spread, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, and lymphovascular invasion (Pfister et al., 2017; Rogers et al., 2009)

In patients suffering from advanced-staged tumours (stage III and IVa), surgery is still a preferred option with adjuvant radiotherapy indicated post operatively. When adverse features as described above are present, concurrent chemoradiotherapy is recommended (Pfister et al., 2017).

Overall five-year survival rate for oral cancer is 56% and disease-specific survival following primary surgery is 74% (Rogers et al., 2009). However, stage of disease at the

time of presentation significantly affects patient's survival. In early-staged tumour, five-year survival rate is 84% while it drops significantly to 46% in advanced-stage disease (Shah et al., 2012).

## 2.2 Depth of invasion and its significance

In recent years, DOI has gained increasing importance in management of OSCC. The terms "depth of invasion" and "tumour thickness" were often used interchangeably in the literature (Park et al., 2011). In several papers, authors did not make clear distinction between DOI and tumour thickness (TT) (Lwin et al., 2012; Madana et al., 2015). It is crucial to understand that these two terms are not synonyms.

DOI is defined as the tumour invasion from the original surface, which reflects the invasion potency of a tumour. It is measured by drawing a horizontal reference line connecting the surface of adjacent normal mucosa and DOI is represented by the perpendicular length from the reference line to deepest reaching front of tumour infiltration (Almangush et al., 2013; Fukano, Matsuura, Hasegawa, & Nakamura, 1997; Jung et al., 2009; Kane, Gupta, Kakade, & Cruz, 2006; Kurokawa et al., 2002; Yamamoto et al., 2014). Ulcerated lesion is measured in the same way whereas exophytic part of a tumour is not included (Figure 2.1). Hence, DOI is unaffected by the tumour growth pattern.

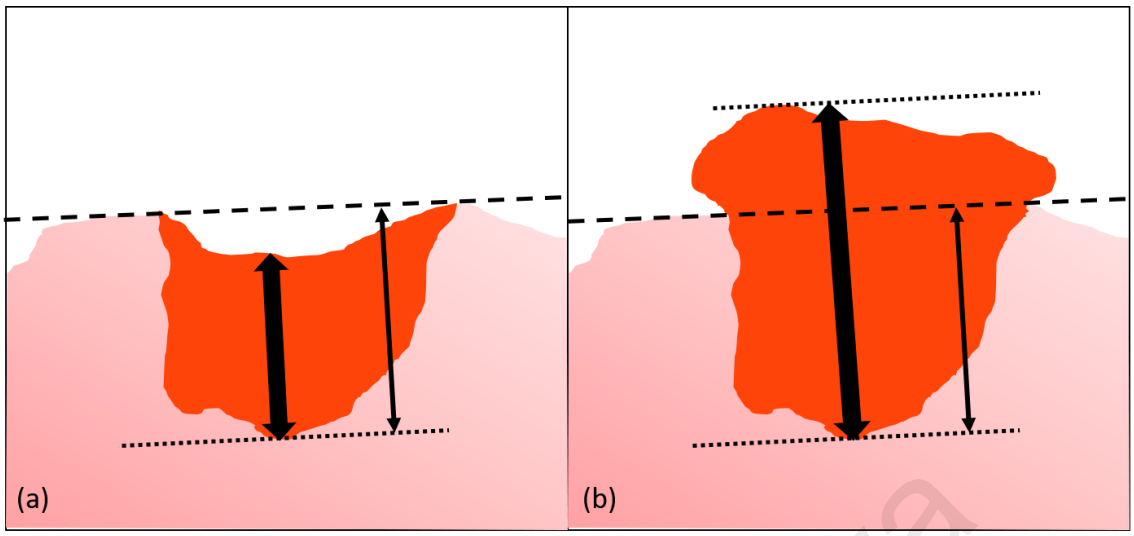



**Figure 2.1: Depth of invasion vs tumour thickness.**
(a)Endophytic tumour. (b)Exophytic tumour. Dashed line is a reference line drawn connecting the surface of adjacent normal mucosa. Thin arrow represents depth of invasion and thick arrow represents tumour thickness. Both depth of invasion and tumour thickness are measured perpendicular to the reference line to the deepest reaching front of tumour.

On the other hand, TT is the maximal tumour dimension from the surface of tumour to the point of deepest invasion as seen in Figure 2.1. Tumour surface refers to either the most projected surface of an exophytic tumour or the base of ulcer of an endophytic tumour. The measurement is made perpendicular to the reference line, which joins tumour-mucosa junctions on each side. (Kane et al., 2006; Lam et al., 2004). Therefore, TT can vary depending on the tumour growth pattern although the DOI are the same.

The precise definition of DOI has also been clarified in the 8$^{th}$ edition of AJCC tumour staging manual. Pathologically, DOI is measured from the basement membrane of the closest adjacent mucosa, then dropping a "plumb line" from this plane to deepest point of tumour invasion. Clinically, DOI is assessed by careful palpation supplemented by radiographic assessment (Lydiatt et al., 2017). However, the manual did not explain on how radiographic assessment should be performed.

Over the years, numerous research were conducted to investigate the factors that affect prognosis and survival of OSCC patients. Many of them found that the presence of locoregional spread, distant metastasis, disease recurrence and survival are associated with DOI.

### 2.2.1 **DOI in locoregional spread**

Melchers et al. in 2012 explored the infiltration depth as predictor for the occult cervical lymph nodes metastasis. They found that in clinically negative neck nodes, cut-off point of 4.59 mm resulted in the best predictive value for nodal status in Stage I and II OSCC. The authors recommended neck dissection to be performed when DOI is at least 4 mm and watchful waiting when it is less than 4 mm (Melchers et al., 2012).

This finding was similar to Kurokawa et al. (2002) in their paper that tumour depth of 4 mm or more in moderately differentiated squamous cell carcinoma of the tongue has a high potential for postoperative cervical lymph nodes metastasis. These patients may benefit from elective neck dissection.

An earlier Japanese study (Fukano et al., 1997) on tongue carcinoma found that cervical lymph node metastasis started at a depth exceeding 3 mm and increased markedly when it was over 5 mm. Subclinical lymph node metastasis of 5.9% was found with DOI less than 5 mm and 64.7% when it exceeded 5 mm. These results were in agreement with Mair et al. (2018) who found that tumour invasion depth of more than 5 mm was the only factor predicting occult nodal metastasis. Based on this, Fukano et al. (1997) suggested that elective regional neck dissection should be considered for tongue tumours exceeding 5 mm invasion.

However, Jung et al. (2009) proposed a cut-off point value that was twice larger than other studies. They demonstrated that the rate of occult node metastasis had decreased

from 26% to only 7% when they incorporated DOI into revised clinical nodal staging (Jung et al., 2009). The clinical DOI was based on gadolinium-enhanced T1 weighted MRI depths, which were then grouped by cut-off value of 11 mm, the depth that could determine the existence of nodal metastasis. Those with DOI less than 11 mm were considered as clinically low risk group while DOI of 11 mm or more were high risk for nodal metastasis. For histopathological DOI, the cut-off value is 9 mm which is lesser than on MRI probably explainable by shrinkage and distortion of the surgical specimen. Nodal metastasis rate is only 10% when histopathological DOI is less than 9 mm, and drastically increased to 53% when DOI is at least 9 mm.

In the study of tongue SCC, Yamamoto et al. (2014) classified tumour depth according to anatomical layers into (1) in situ cancer; (2) submucosal invasion; (3) shallow invasion of the muscularis propria; (4) deep invasion of the muscularis propria. The authors concluded that an increase in primary tumour depth showed a close correlation with other clinicopathological prognosis factors, especially mode of invasion, degree of differentiation, and cervical lymph node metastasis with significant differences in survival rate. This suggests that primary tumour depth may be used as a prognostic factor in tongue SCC.

### 2.2.2 **DOI in disease recurrence and survival**

With the increase in DOI, patient is more likely to have poorer prognosis. DOI of more than 5 mm is a significant predictor of extracapsular spread and significantly associated with poorer disease-free survival and overall survival (Mair et al., 2018).

In a study of early stage OSCC patients, mean DOI in disease recurrence was 7.6 mm whereby death within 3 years of diagnosis was related to tumour depth. Alive patients registered a tumour DOI of 4.8 mm, compared to 8.6 mm for patients who died from locoregional spread and 9.6 mm for those who died from distant disease. Interestingly,

out of those who died of distant metastasis, 45.5% had their primary disease in tongue (Jerjes et al., 2010).

Almangush et al. in 2013 found that in addition to depth of invasion, tumour budding and worst pattern of invasion were independent predictors of patient's prognosis in early stage OTSCC. They concluded that DOI of 4 mm or more is associated with poor prognosis and significantly higher mortality rate.

In the same year, Ling et al. retrospectively analysed SCC of the tongue for prognostic factors that may influence survival of patients with this disease. Tumour invasion depth, perineural invasion, resection margin, treatment, and clinical stages were identified to be independent prognostic factors for five-year survival. Tumours with an invasion depth of less than 4 mm had a 5-year disease-specific survival rate of 74.9%, which is significantly better than those that were 4 mm to 9 mm (56.2%) or more than 9 mm (17.4%). Those with DOI of more than 9 mm is 7.7 times more likely to die earlier than their counterparts who had a DOI of less than 4 mm (Ling, Mijiti, & Moming, 2013).

Majority of the reviewed literature agreed that DOI of 4 mm to 5 mm has increased incidence of locoregional spread, and poorer disease outcome in terms of distant metastasis, disease recurrence and poor survival rate.

## 2.3 Imaging in oral cancer

Imaging is performed in clinically detected oral cancers to determine depth of extension, invasion of adjacent structures as well as nodal and metastatic spread (Olliff et al., 2014). According to NCCN guidelines version 2.2017, it was recommended to perform CT with contrast and/or MRI with contrast of primary and neck, and chest CT (with or without contrast) as clinically indicated. In addition, fluorodeoxyglucose -

positron emission tomography/computed tomography (FDG-PET/CT) should be considered for stage III and IV disease in the workup of oral cancer (Pfister et al., 2017).

In head and neck cancer, assessment using CT and MRI complement each other and are currently the gold standard for accurately evaluating the extension of the primary tumour site (Blatt et al., 2016). CT gives better evaluation of bone invasion in terms of bone erosion, marrow infiltration and involvement of inferior alveolar canal. It also has the advantage of including the chest in one examination. On the other side, MRI provides superior soft tissue resolution (Arya et al., 2014).

The presence of bone or extrinsic tongue muscle invasion (ETMI) upstages a tumour to T4a, which necessitate adjuvant radiotherapy. Despite that, the presence ETMI was not routinely reported by surgeons and pathologists. A 2017 study by Junn and colleagues on 33 oral cavity cancer patients using CECT found radiologic detection of ETMI has 100% sensitivity with 76% specificity against surgical - gross pathologic evaluation as the criterion standard, with mass-like enhancement being the most predictive feature. It was difficult to be examined from formalin-fixed specimen due to loss of orientation and tissue distortion, therefore radiologic identification is important to prompt surgeon and pathologist for more detailed evaluation (Junn et al., 2017). In equivocal cases, MRI may play a role.

By principle, the preferred choice of imaging for tongue carcinoma is contrast-enhanced MRI which displays detailed anatomical structures including intrinsic and extrinsic muscles, the floor of mouth and the lingual vascular bundle. On axial imaging, a line joining the anterior aspect of the mandibular rami may be used as the dividing line between anterior two-third and posterior one-third of tongue (Ong & Chong, 2006).

Despite that, majority of tongue cancer patients in our institution only have CT of head and neck taken since it can be combined with chest CT for disease staging. CT scan is better tolerated in patients with head and neck cancer, inexpensive, relatively accessible within most communities, and quick (Bartlett et al., 2013) as compared to MRI. The major disadvantage of CT for tongue imaging is inadequate soft tissue characterisation.

Administration of contrast material is necessary to improve visualisation of soft tissue lesion in CT. A study by Groell et al.(2001) showed tumours of the head and neck were better delineated on CECT, resulting in better determination of tumour size and tumour discrimination against adjacent soft-tissue structures such as musculature, pharyngeal and laryngeal wall, and cutis. Harris et al.(1996) found greater conspicuity of neck neoplasms on delayed images rather than early scans, with maximum contrast material uptake by SCC on scans taken at 180-seconds delay (Groell et al., 2001).

A point worth noting is that both CT and MRI suffer from artefacts in the presence of dental amalgam (Tibrewala, Roplekar, & Varma, 2013). If initial routine CT scan reveals significant dental-related artefacts, an angled gantry is taken to minimise the effects (Harris et al., 1996).

For neck staging purpose in OSCC, Mazzawi et al. (2018) investigated the effectiveness of commonly used imaging modalities. PET/CT was the most sensitive modality (sensitivity 80%) in detecting metastatic neck lymph nodes compared to CT (48%), and MRI (43.8%). Despite better soft tissue resolution, MRI performed less well compared to CT in identification of nodal involvement. In Saafan et al. (2013), CT was found to be inferior to ultrasound scanning in this matter. In another study, MRI provides only moderate agreement in N staging (kappa statistics 0.458) when histopathology staging was used as benchmark (Singh et al., 2017).

Routine screening of distant metastases for head and neck cancers has been carried out by using PET, CT, PET/CT or whole body MRI (Peters et al., 2015). Unfortunately, there was no comparison of these different imaging modalities in terms of accuracy. Senft et al. (2008) stated that chest examination is the most important in screening of distant metastases due to the high incidence of lung metastases and the frequent combination of distant metastases at other sites. Addition of FDG-PET to chest CT increases the sensitivity of detection (Senft et al., 2008). Patients at increased risk for distant metastases are: (1) 3 or more lymph node metastases, (2) bilateral lymph node metastases, (3) lymph node metastases of 6 cm or more, (4) low jugular lymph node metastases, (5) locoregional tumour recurrence, and (6) second primary tumours (Peters et al., 2015).

Besides neck staging, ultrasound has also been used for assessment of oral cavity tumour. With the use of intraoral probe, ultrasonography is conveniently used intraoperatively to assess tongue TT and margin clearance (C. P. Law, R. V. Chandra, J. K. Hoang, & P. M. Phal, 2011). As the probe design is small to enable intraoral use, technical shortfall may occur when TT exceeds the ultrasound transducer depth assessment limit, leading to inaccurate measure (Taylor et al., 2010) especially in late stage disease. Although the use of intraoral ultrasound is inexpensive, quick and well tolerated by patients, it requires operator skill and expertise to be maintained with suitable case load and practice (Yesuratnam et al., 2014). Hence, it is difficult to recommend all institutions to apply ultrasound imaging for OTSCC. Furthermore, comprehensive imaging assessment of the neck and thorax is still required in order to obtain accurate disease staging (Yesuratnam et al., 2014).

In 2014, Yesuratnam et al. and Olliff et al. had suggested that clinicians should consider performing imaging prior to biopsy in cases with high confidence of clinical diagnosis (Olliff et al., 2014; Yesuratnam et al., 2014). This is to avoid overestimation

secondary to post-operative oedema which is a major factor that reduced accuracy of pre-operative imaging. Both intraoral ultrasound and MRI were unable to differentiate post-excisional biopsy haematoma and squamous dysplasia from invasive SCC.

In a retrospective review of clinical records and histopathological databases of 58 patients with SCC of the tongue (Howe, Khurram, Hunter, Martin, & Fry, 2017), the authors found that the accuracy of clinical staging is not significantly affected whether patients had MRI done before or after biopsy. However, it was not stated which staging system the authors had used. Instead, they found that the time between initial biopsy or MRI and excision was significantly longer if patient were to go for MRI first prior to biopsy. This may unnecessarily delay treatment for the patient.

## 2.4 Accuracy of DOI in radiological imaging

Accuracy is defined as the closeness or agreement between a measured quantity value and a true quantity value of a measurand (JGCM, 2012). A measurement is said to be more accurate when it offers a smaller measurement error.

In the case of DOI as the measurand, 'true quantity value' is the histopathological DOI. This value determines the final T-staging of OSCC as described earlier. Unfortunately, this can only be obtained following an oncological curative surgery. By measuring DOI pre-operatively from an imaging record, 'measured quantity value' is obtained and compared with the 'true quantity value'. If the measurement error is acceptable, radiological DOI can be deemed as accurate and this may permit pre-operative clinical T-staging of OSCC.

Consequently, oncological surgeon will be able to accurately stage the tumour and to explain to the patient of the disease prognosis. The need for elective neck dissection in N0 patients can be decided early, as evidence in the literature has shown the correlation

between DOI and occult neck metastasis. This will prevent a two-step surgery of removing the tumour first and neck dissection later upon finding the DOI from histopathological examination. More importantly, the extent of tumour resection can be clearly defined to achieve clear deep margin while preserving healthy tissues.

There has been limited literature on the use of imaging assessment to measure DOI in OTSCC with no standardised measurement method as well. Most of the previous studies were done on TT, until recently when more data on importance of DOI are available.

For tongue, the most commonly applied method for measurement of DOI on imaging is same as histopathological measurement. It is measured perpendicularly from adjacent normal mucosal junction of the tumour to the deepest point of tumour infiltration (Alsaffar et al., 2016; Jung et al., 2009). Similarly, TT is determined by measuring from surface of tumour to the deepest extent of the carcinoma (Iwai, Kyomoto, Ha-Kawa, Lee, & Yamashita, 2002).

Iwai et al. in 2002 evaluated MRI to determine preoperative TT in oral tongue carcinoma. They divided TT into two types: actual TT (measured from surface of the tumour to the point of maximum invasion) and reconstructed TT (measured from reconstructed mucosal line to the point of maximum invasion). On imaging, it was expressed as the difference between the distance from the surface to the septum of tongue on the unaffected side and the distance from the septum to the deepest extent of the tongue carcinoma. This is in assumption that the distance between the septum and normal mucosal lines on both sides should be symmetrical (Iwai et al., 2002). Using the definition given in this paper, reconstructed TT used by Iwai et al. is equivalent to DOI. The authors found that the correlation between histopathological and MRI examinations was more significant in terms of reconstructed TT (Correlation coefficient = 0.839) than actual TT (0.609).

The reliability of pre-operative MRI to measure DOI in oral tongue cancer was investigated retrospectively, comparing with pathological measurements (Murakami et al., 2018). They had MRI of 29 patients with T2N0 stage and used three different methods to measure the DOI: Axial reconstructed thickness, axial invasive portion and coronal invasive portion (Figure 2.2). In terms of inter-rater reliability, axial invasive portion was superior (ICC = 0.829, $p<0.001$) than coronal invasive portion (ICC = 0.647, $p<0.001$). When MRI and pathological measurements were compared, coronal invasive portion demonstrated a fair correlation (ICC = 0.583, $p<0.001$) compared to axial invasive portion which is poor (ICC = 0.265, $p<0.001$). In general, all the DOI measurements were 2 to 3 mm larger on MRI than pathology.

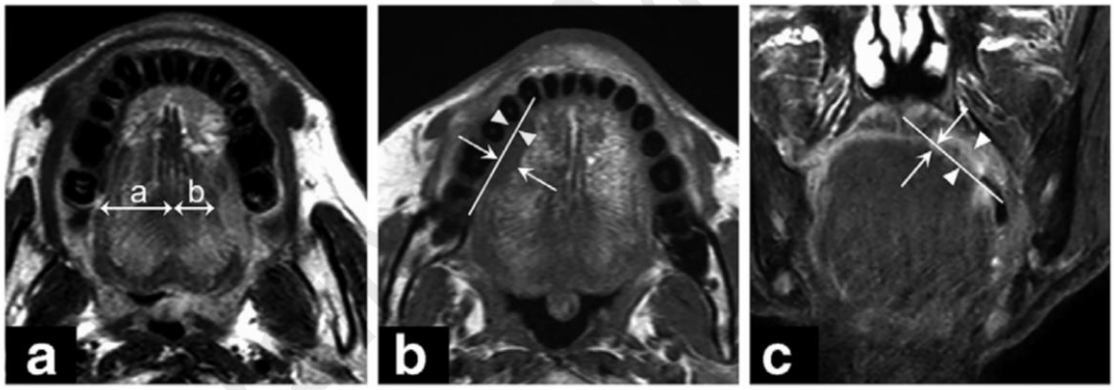



**Figure 2.2: Different methods of DOI measurement on MRI.**
(a) Axial reconstructed thickness: the difference between a and b on a horizontal line, where a is the distance between the surface and the lingual septum on the unaffected side and b is the distance between the septum and the point of deepest invasion. (b) Axial invasive portion: measured on axial MRI, perpendicularly form reference line connecting tumour-normal mucosa junction on both sides to the deepest point of invasion. (c) Coronal invasive portion: measured on coronal MRI. (Murakami et al., 2018)

Alsaffar et al. (2016) compared preoperative clinical and radiological depth evaluation in OTSCC using the standard pathological depth. In this study, the mean DOI by MRI is larger than by histology. They then further subdivided the tumours into 2 groups based on 5 mm cut off point on pathological measurement. For tumours measuring 5 mm or

more in both clinical and radiographic depth measurement, they correlated well with pathological DOI. However, for those measured lesser than 5 mm on pathological measurement, neither clinical nor radiographic examination correlated well with pathologic depth. In this study, MRI was shown to correlate well with pathological depth and is more sensitive and specific for depth measurements than clinical assessment (Alsaffar et al., 2016).

Retrospective study by Park et al. (2011) assessed the accuracy of tumour DOI based on pre-operative MRI. A total of 114 patients were studied and they found that the Pearson's correlation coefficients for histologic and MRI invasion depths in oral tongue was r = 0.949, which was highest compared to tongue base (r = 0.941) and tonsil (r = 0.578). The 49 oral tongue tumour sample in this study were made up of larger-sized tumours, mostly more than 5 mm depth.

CT scanning was used by Madana et al. (2015) to measure pre-operative TT. However, it was not described in their paper regarding the method of measurement. They found that the correlation between TT obtained from CT and postoperative final pathological tumour thickness was highly significant (r = 0.755) and suggested that CT may provide an accurate estimation of true TT. A more recent study to determine the radiologic-pathologic TT correlation demonstrated good correlations for CT and MRI of 0.76 and 0.80 respectively. (Weimar et al., 2018). Although there was slightly higher correlation for MRI-based TT compared to CT, the difference was not significant.

So far, published literature had focused on the use of MRI to establish the accuracy of pre-operative determination of tumour depth, which was then linked to locoregional spread, disease-free and overall survival rates, hence guiding patient management. For CT imaging, there was only pre-operative determination of TT but not DOI in the literature. This is probably due to the known poor soft tissue resolution as compared to

MRI. However, if TT can be determined from CT, obtaining DOI is not impossible. In addition, determination of DOI does not need detailed visualisation of extrinsic tongue muscles or lingual vascular bundle as seen on MRI scan. As long as the tumour can be visualised in CT especially following contrast enhancement, measurement can be performed. Since CT is the most basic imaging that most oral cancer patients will have for disease staging, it is therefore important to explore the potential of measuring DOI from this modality.

# CHAPTER 3: MATERIALS AND METHOD

## 3.1 Research ethics

This study was approved by the Medical Ethics Committee, Faculty of Dentistry, University of Malaya [Reference number: DF OS1722/0050(P)] and Medical Research Ethics Committee, University Malaya Medical Centre [MREC ID NO: 2017106-5659]. Data collection was carried out from 1st November 2017 until 31st December 2018.

## 3.2 Study population

A retrospective search of the Malaysian Oral Cancer Database and Tissue Bank System (MOCDTBS) at Oral Cancer Research & Coordinating Centre (OCRCC), Faculty of Dentistry, University of Malaya was conducted to identify suitable cases for this study. There were 68 patients with squamous cell carcinoma (SCC) of the tongue diagnosed from 1st January 2009 to 31st December 2018. Out of this, 59 patients underwent surgery, and the remaining nine underwent non-surgical management.

Prior to surgery, 36 patients had pre-operative CECT scan of the neck but only 27 were available in soft copies. These copies were obtained with permission from the Department of Biomedical Imaging, University Malaya Medical Centre and stored in compact discs (CDs). The CT scanners involved in this study were Siemens Somatom Definition AS+, Siemens Sensation 16 and Toshiba Aquilion One. The scanning protocol was not standardised prior to this study. Histopathological reports of these 27 patients were traced from Oral Pathology Diagnostic and Research Laboratory, Faculty of Dentistry, University of Malaya. Only 25 reports were available. To fulfil the objectives, specific data being extracted from the histopathology reports were tumour DOI and margin

clearance. Other information being collected were the demographic data, tumour stage and treatment rendered.

Patients that received non-curative surgery or appeared as recurrence cases were excluded. Those with histopathology report of positive margins (1 patient), no recorded DOI measurement (5 patients), and CT slice thickness of more than 3.0 mm (1 patient) were also eliminated. To ensure the accuracy of the image taken by CT scan, there should not be more than one month gap between the image taken and the surgery date, as in Murakami et al. (2018). Therefore, only 18 patients fulfilled the inclusion and exclusion criteria for this study.

### 3.3 Sample size calculation

Sample size was calculated based on correlation coefficient using the formula (*http://www.sample-size.net/correlation-sample-size/*):

$$N = [(Z_\alpha + Z_\beta)/C]^2 + 3$$

where $\alpha$, two-tailed (type I error rate) = 0.05

$Z_\alpha$ (normal standard distribution for $\alpha$) = 1.960

$\beta$ (type II error rate) = 0.20

$Z_\beta$ (normal standard distribution for $\beta$) = 0.842

$C = 0.5 * \ln[(1+r)/(1-r)] = 1.822$; where $r = 0.949$ (Park et al. 2011)

Hence, the calculated sample size is 5.

### 3.4 Sampling method

Due to the relatively low number of cases in the ten-year study period that fulfil the inclusion and exclusion criteria, all 18 cases available were included in this study by convenient sampling.

### 3.5 Image interpretation

CT scans were interpreted by a single clinician who had undergone calibration sessions with a radiologist specialised in the head and neck region prior to the commencement of this study. The images were read on two separate occasions, at least one month apart to minimise potential learning effects. To avoid bias, the histopathological DOI was not known to the clinician until both CT readings for each sample were completed.

Images were viewed on contrasted soft tissue window where the tumour tissue on the tongue appeared denser compared to surrounding normal soft tissue. An imaginary line joining the anterior border of the mandibular rami on both sides was taken as the distinction between oral tongue (anterior two-third) and base of tongue (posterior one-third).

For exophytic or endophytic tumour, DOI was measured from a reconstructed mucosal line perpendicularly to the deepest point of invasion as shown in Figure 3.1. The reconstructed mucosal line was drawn connecting intact mucosal surface on either side of the lesion. Measurement was done on axial section of CT scan using measurement tool provided in the imaging software and, where available, on coronal section as well. To improve visualisation and measurement of the lesion, the clinician was allowed to manipulate the zoom factor, grey-scale centre level and the window width setting. Each CT slice of the oral tongue was carefully examined to obtain the maximum dimension of DOI in millimetres (mm), rounding to the nearest one decimal point.

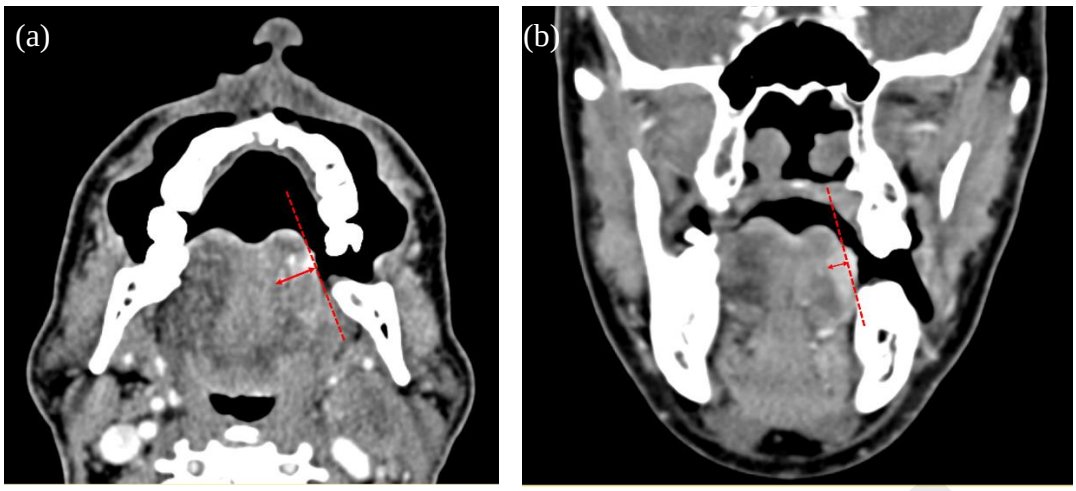



**Figure 3.1: Measurement of DOI from CECT of a patient with oral tongue SCC (exophytic tumour) at left lateral border of tongue.**
Dotted line represents the reconstructed mucosal line joining the normal mucosal surface on adjacent sides of the lesion. Double-ended arrow is the tumour depth, measured perpendicularly from reconstructed mucosal line. (a) Axial CT. (b) Coronal CT.

Data analysis was performed using Statistical Package for the Social Sciences (SPSS) software version 25.0. The intraclass correlation coefficient (ICC) was used to assess the intraobserver reliability in measurement of DOI from CT. ICC estimates and their 95% confidence intervals were calculated based on single measures, absolute-agreement, two-way mixed effects model. Measurement reliability was interpreted as poor (ICC < 0.50), moderate (0.50 – 0.75), good (0.75 – 0.90) and excellent (> 0.90) (Koo & Li, 2016). The mean of the two CT measurements was used for further analysis. To compare the CT measurement of DOI to that of histopathological report, repeated measures ANOVA was used to calculate the mean difference and 95% confidence interval. ICC was again utilised to measure the strength of correlation and agreement between CT and histopathology. The statistical significance was set as p-value less than 0.05. Finally, accuracy of CT measurement of DOI was visually assessed by plotting the difference between the measurements from CT reading and histopathological report against the latter (as gold standard) using Bland - Altmann plot (Bland & Altman, 1986). Limits of agreement (LOA) was calculated as 'Mean difference ± 1.96SD'. If the 95% confidence interval of

the measurement difference falls within their respective limits of agreement, CT and histopathological methods were considered to be in agreement with each other, therefore may be used interchangeably.

The null hypothesis for this study was that there was no agreement in measurement of DOI between CECT and histopathological examination, therefore the method of measuring DOI from CT is inaccurate.

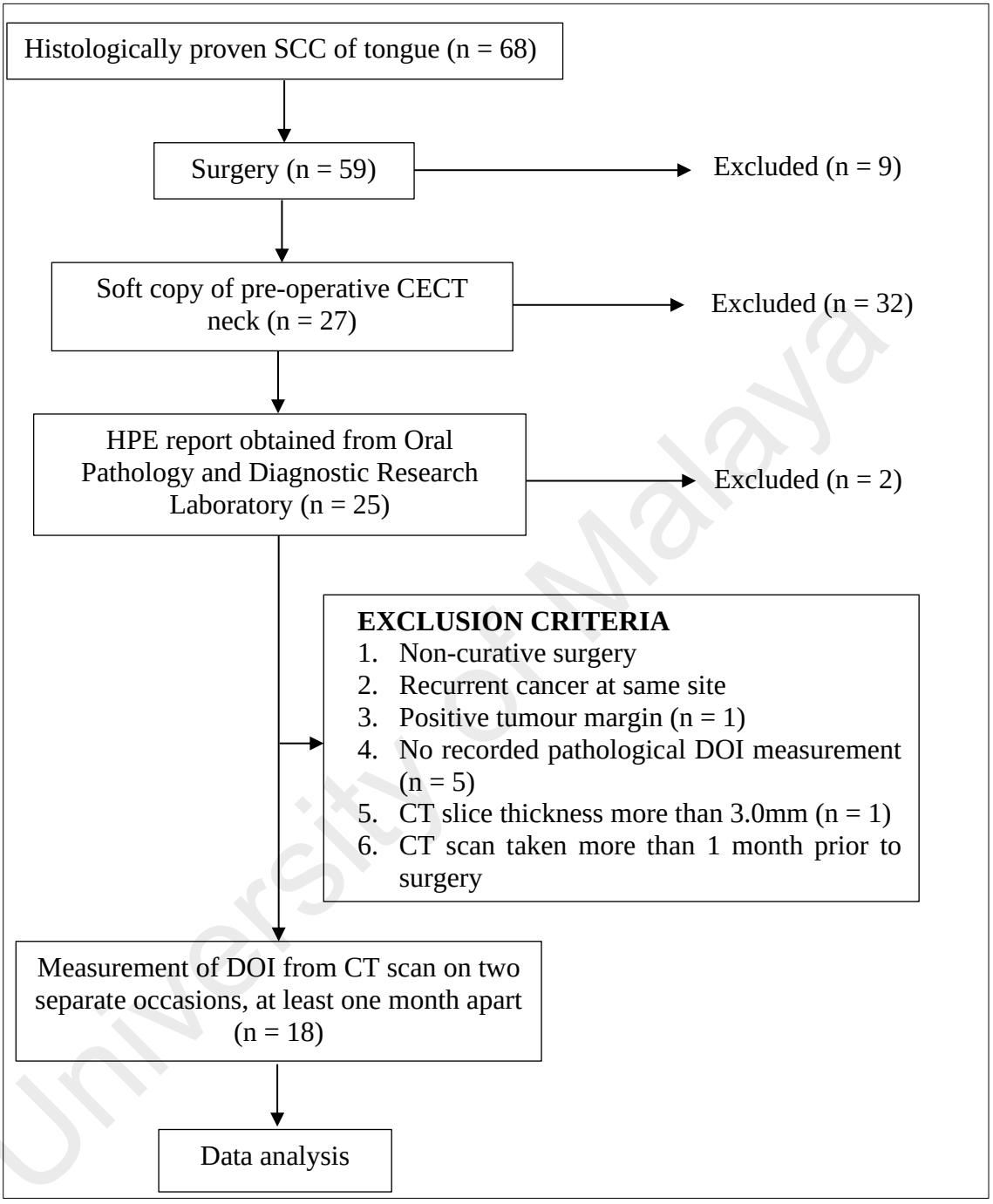



**Figure 3.2: Research procedures algorithm**

# CHAPTER 4: RESULTS

## 4.1 Study population

In the total 18 patients included in our study, mean age at diagnosis was 60.9 years old with median of 61. There were equal numbers of male and female patients. Majority of them were Chinese, followed by Indian and Malay (Table 4.1). Left lateral border of tongue was the most commonly involved site of tumour (Figure 4.1) and majority of patients were diagnosed in early stage of disease. All five patients (27.8%) with clinically positive neck nodes underwent neck dissection, in addition to another 6 patients (33.3%) with clinically negative neck.

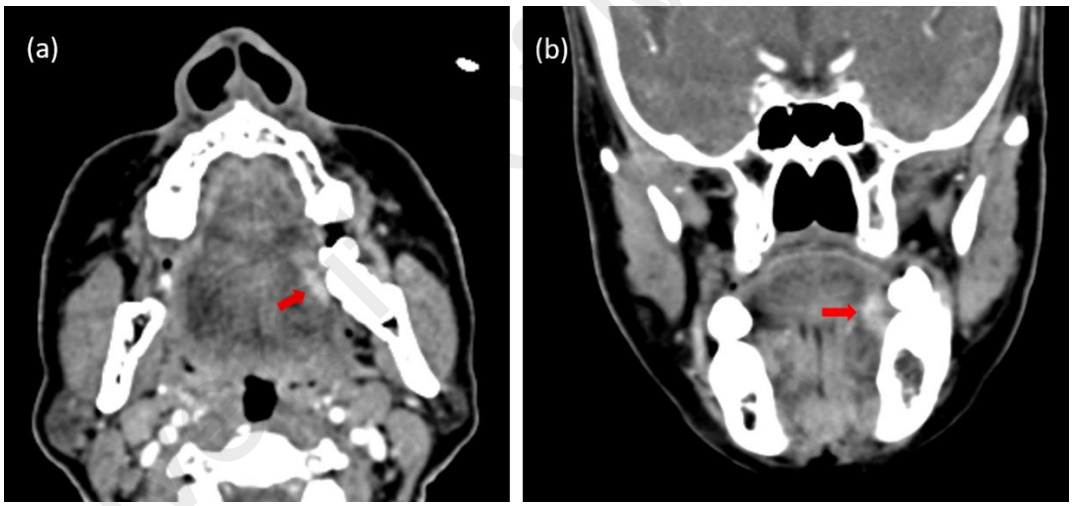



**Figure 4.1: Endophytic tumour on CECT**
Endophytic tumour at left lateral border of tongue indicated by arrow. (a) Axial CT. (b) Coronal CT

**Table 4.1: Demographic data of oral tongue SCC patients (N=18)**

| | Frequency (%) |
|---|---|
| **Gender** | |
| Male | 9 (50.0) |
| Female | 9 (50.0) |
| **Ethnicity** | |
| Malay | 2 (11.1) |
| Chinese | 12 (66.7) |
| Indian | 4 (22.2) |
| **Age at diagnosis** [years, median(range)] | 61 (34 – 81) |
| **Site of tongue cancer** | |
| Right lateral border | 6 (33.3) |
| Left lateral border | 11 (61.1) |
| Ventral surface | 1 (5.6) |
| **Clinical tumour stage*** | |
| T1 | 6 (33.3) |
| T2 | 10 (55.6) |
| T3 | 1 (5.6) |
| T4 | 1 (5.6) |
| **Clinical nodal stage**** | |
| N0 | 13 (72.2) |
| N1 | 3 (16.7) |
| N2 | 2 (11.1) |
| N3 | 0 |

**Table 4.1, continued**

| | Frequency (%) |
|---|---|
| **Treatment** | |
| Resection of primary tumour only | 7 (38.9) |
| Resection of primary tumour and ipsilateral neck dissection | 10 (55.6) |
| Resection of primary tumour and bilateral neck dissection | 1 (5.6) |

* maximum tumour dimension, T1 = 2 cm or less; T2 = more than 2 cm but no greater than 4 cm; T3 = more than 4 cm; T4 = more than 4 cm with involvement of adjacent structures.

** nodal size and location, N1 = single ipsilateral lymph node measuring 3 cm or less; N2 = single ipsilateral lymph node more than 3 cm but no greater than 6 cm, or multiple ipsilateral, bilateral or contralateral lymph nodes less than 6 cm; N3 = lymph node measuring more than 6 cm

In this study, there were four patients in which the CT data was not reconstructed into coronal plane. Therefore, 18 axial and only 14 coronal CT data were eligible for further analysis, with varying slice thickness. Axial scans were mostly of 0.8 mm thickness whereas 3.0 mm for coronal scan (Table 4.2).

**Table 4.2: Slice thickness of axial and coronal CT**

| CT sections | CT slice thickness | | | Total |
|---|---|---|---|---|
| | 0.8 mm | 1.0 mm | 3.0 mm | |
| Axial | 12 (66.7%) | 1 (5.6%) | 5 (27.8%) | 18 (100%) |
| Coronal * | 1 (7.1%) | 0 | 13 (92.9%) | 14 (100%) |

*four CT data did not have coronal section

## 4.2 Intraobserver reliability of CT measurement of DOI

**Table 4.3: Intraobsever reliability of DOI measurement from CT**

| | **n** | **ICC** | **95% CI** | ***p*-value** |
|---|---|---|---|---|
| **Axial CT** | 18 | 0.996 | 0.990, 0.999 | <0.001 |
| **Coronal CT** | 14 | 0.999 | 0.996, 1.000 | <0.001 |

There was excellent intraobserver reliability between two separate measurements of DOI for each sample in CT, both axial and coronal as shown in Table 4.3. Thus, subsequent analyses utilised the mean of axial and coronal CT measurements to represent the data.

## 4.3 Comparison of means between CT and histopathological DOI using repeated measures ANOVA

**Table 4.4: Comparison of means between CT and histopathological DOI**

| | Mean DOI (mm) | Mean difference[a] (mm) | Std. Error | 95% confidence interval | p-value[b] |
|---|---|---|---|---|---|
| Axial CT | 9.257 | -0.743 | 0.505 | -2.129, 0.643 | 0.495 |
| Coronal CT | 8.894 | -1.106 | 0.523 | -2.542, 0.330 | 0.163 |

[a] paired difference [(CT) – (histopathology)]

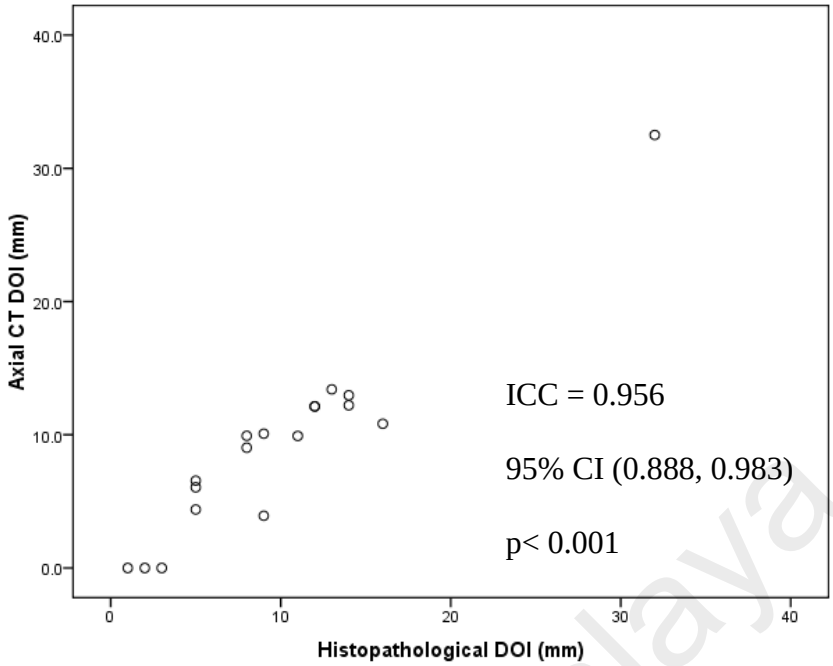
[b] Adjustments for multiple comparisons: Bonferroni

Mean of histopathological DOI was 10 mm. Axial and coronal CT generally yielded smaller mean tumour depth (9.257 mm and 8.894 mm, respectively), but none had statistically significant difference.

## 4.4 Correlation of CT to histopathological DOI

Axial and coronal CT both exhibited good to excellent correlation to histopathological DOI, with ICC = 0.956 and ICC = 0.965 respectively (Figure 4.2). The correlations were statistically significant with $p < 0.001$. From the scatterplots in Figure 4.2, there were three cases of undetectable tumour tissue in axial and coronal CT, recorded as 0mm. Figure 4.3 shows a CT example of such case.

(a)




(b)

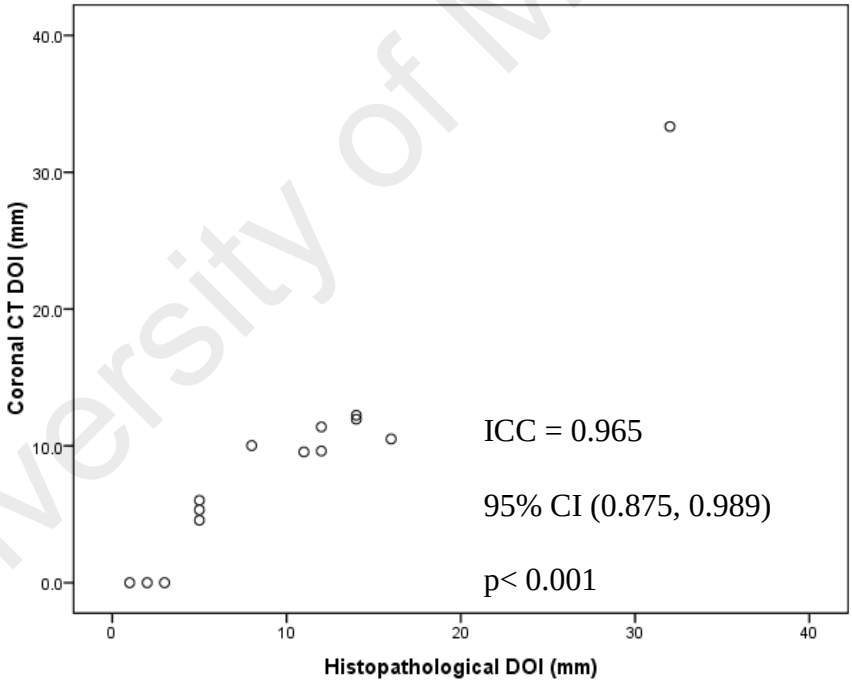



**Figure 4.2: Correlation of CT to histopathological DOI**
(a) Axial CT. (b) Coronal CT.

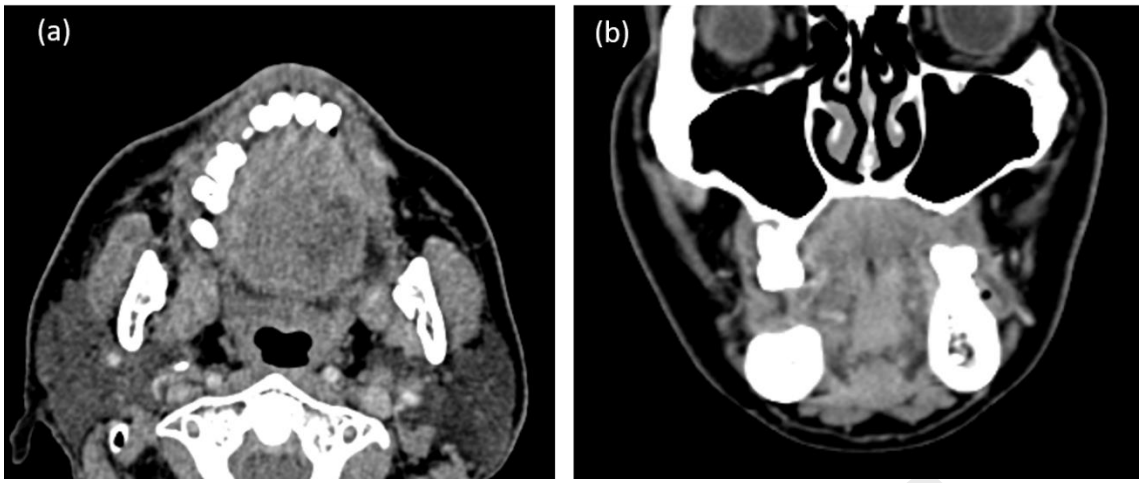
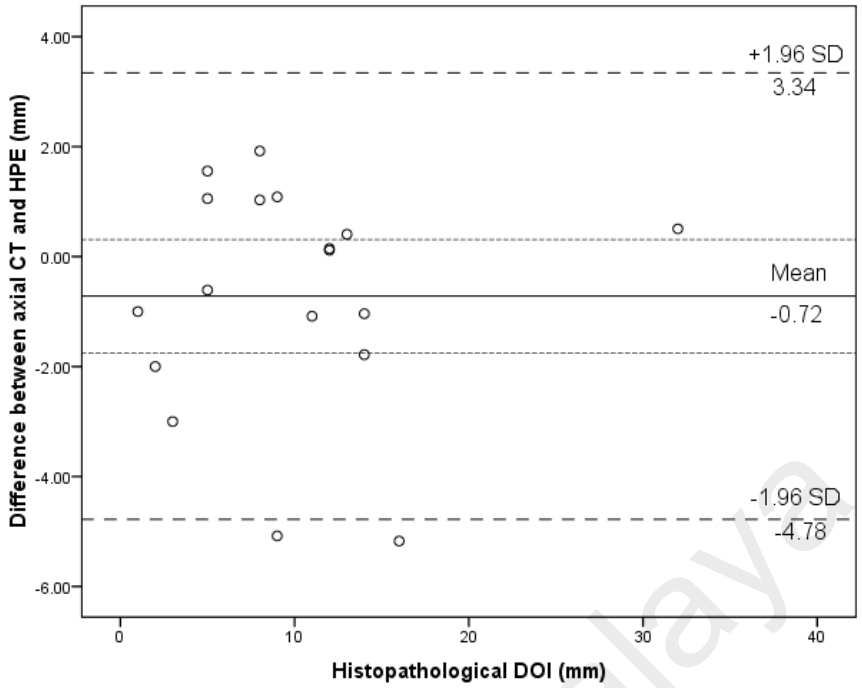



**Figure 4.3: Normal tongue appearance on CECT of a patient with SCC at left lateral border of tongue with histopathological DOI of 2mm.**
(a) Axial CT. (b) Coronal CT.

## 4.5 Accuracy of CT measurement of DOI

The accuracy of axial and coronal CT in measuring DOI was evaluated using Bland-Altman analysis (Figure 4.4). The differences in DOI measurement from axial and coronal CT were plotted against histopathological DOI. Negative value plotted indicates that CT tumour depth was smaller than HPE whereas positive value means CT tumour depth was larger than HPE. The mean difference for axial CT was -0.72 mm (SD 2.072) with 95% CI (-1.750, 0.310). Coronal CT displayed mean difference of -1.11 mm (SD 1.96) and 95% CI (-2.236, 0.023). The 95% CI for both measurement differences were within their respective limits of agreement.

(a)




(b)

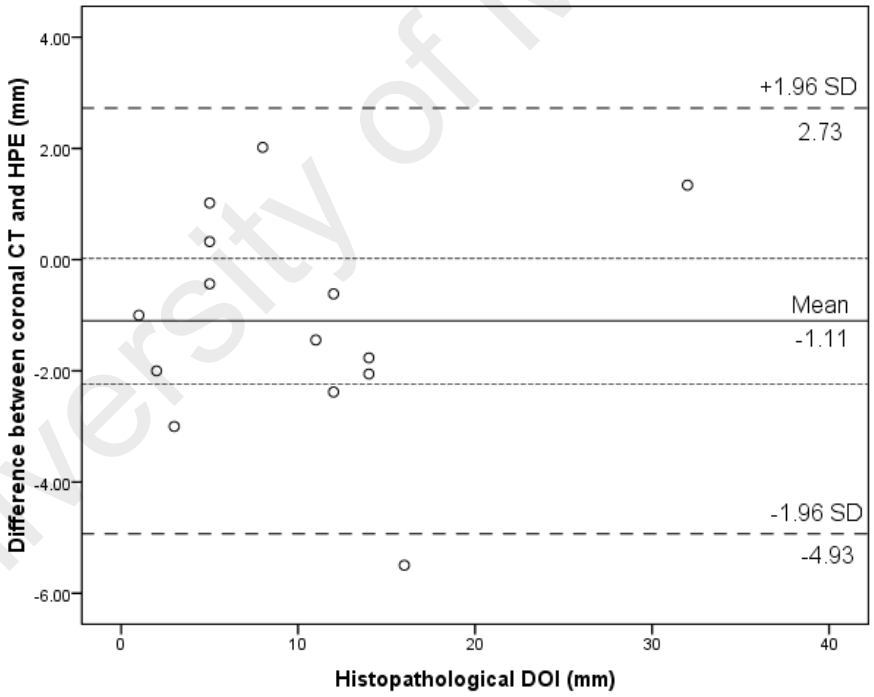



**Figure 4.4: Bland-Altman plots comparing the agreement between CT and histopathological measurements for the DOI.**

Solid line represents the mean difference, dotted lines indicate the 95% confidence interval, and dashed lines are limits of agreement (Mean difference ± 1.96 SD). (a) Axial CT. (b) Coronal CT

# CHAPTER 5: DISCUSSION

## 5.1 Study findings

In this study, there was an equal distribution of gender diagnosed with OTSCC, with majority of them were Chinese, followed by Indian and Malay. However, this cannot be considered the true representation of OTSCC in the country as there were fifty out of 68 patients who were excluded as they did not fulfil the inclusion and exclusion criteria. The major reason of exclusion being the missing CT data of 22 patients while nine were not available in soft copies. According to Malaysian statistics (Azizah et al., 2016), mouth cancer was more common in Indian females. The finding of almost all oral tongue SCC occurred at lateral border of the tongue was consistent with published literature (Ling et al., 2013).

As of date, there is no standardised radiological method established for measuring DOI as developed for pathological method. However, this study adopted the most commonly used method in the literature which was similar as pathological measurement method. By measuring perpendicularly from a reference line joining both tumour-mucosal junctions, radiological DOI is reproducible. In a study of 29 patients, this was reported as the most optimal method to measure DOI using MRI images in most OTSCC cases (Murakami et al., 2018).

Comparing axial and coronal CT in this study, both showed excellent reliability with repeated DOI measurements. The single-observer ICC recorded for axial CT was 0.996 ($p<0.001$) while for coronal CT was 0.999 ($p<0.001$), suggesting that the observer was highly reliable in performing this measurement method. There was more varied reliability when a study was carried out using more than one observer, possibly due to subjectivity

and variability in experience. The use of similar method in MRI by two different observers in a study by Murakami et al. (2018) found that the interobserver reliability was excellent for axial (ICC = 0.829, $p<0.001$) and good for coronal (ICC = 0.647, $p<0.001$), both which were lower than current study. In Alsaffar et al. (2016), correlation of MRI depth measurement in OTSCC between two head and neck radiologists was reported as 0.64 ($p<0.001$). It was however not mentioned in which plane the measurement was made.

The current study also found that the CT tumour depth was on average 1-2 mm smaller than histopathological depth, with lesser deviation in axial CT than coronal CT. This was in accordance to a prospective study on 53 consecutive patients carried out in Toronto (Alsaffar et al., 2016), where the authors found the mean MRI tumour depth in OTSCC was 10.9 mm in comparison to mean pathological depth of 11.1 mm. However, an MRI study by Murakami et al. (2018) discovered radiological DOI was generally 2 to 3 mm larger than that of pathological. Their mean difference of radiological DOI to pathological DOI was 2.3 mm (SD 3.2) for axial MRI and 1.9 mm (SD 2.1) coronal MRI. There are two possible reasonings for the disparity; first, the study design, and second, CT resolution versus specimen shrinkage. In Murakami et al., they excluded 43 out of 72 patients due to poor MRI sequences, those with no detectable tumours on MRI and ill-defined tumours due to dental artefacts or patient motion. Therefore, their samples were likely made up of larger-sized tumours whereas Alsaffar had included all patients with MRI. When all patients were included regardless of the quality of the imaging or whether tumour was visualised, obtaining lower mean value is possible. Less distinct soft tissue delineation in CT resulting in smaller radiological DOI may instead played an advantage in this study. When combined with specimen processing shrinkage, reported as shrinkage factor of 0.87 – 0.91 (Lwin et al., 2012; Weimar et al., 2018), CT invasion depths corresponded better to HPE than previous MRI studies.

A good to excellent correlation was demonstrated for DOI measurement between CT and histopathological DOI. ICC from coronal CT was only slightly higher ICC = 0.965, p<0.001) compared to axial CT (ICC = 0.956, p<0.001). Our results contrasted with Murakami et al. (2018) study of 29 patients with clinical T2N0 oral tongue cancer which gave a much lower correlation value. The correlation for DOI measurement from axial MRI was poor (ICC = 0.265, p = 0.030) whereas coronal MRI exhibited only fair correlation (ICC = 0.583, p<0.001). On the other hand, a study of 61 patients (Goel et al., 2016) reported a correlation of r = 0.988 (p<0.001) between MRI and pathological depth of invasion, whereas Alsaffar et al. (2016) reported correlation of r = 0.91 (p<0.001). The better correlation of radiological to histopathological tumour depth in the present study may be attributed to the thinner slice of CT ranging from 0.8 mm to 3 mm, compared to 4 mm slice thickness of MRI in published literature (Goel et al., 2016; Murakami et al., 2018). The thickness of the CT slices included in this study was according to the standard of CT imaging for head and neck cancer recommended by South East Scotland Cancer Network (Dept of Clinical Neurosciences).

In a retrospective review of 114 patients by Park et al. (2011), an overall Pearson correlation coefficient of 0.825 was reported for histologic and T1-weighted MRI invasion depths, which varied for different sites of oral cavity. Their study found that oral tongue had the best correlation coefficient of 0.949 for histologic and MRI invasion depths, compared to 0.941 for tongue base, and 0.578 for tonsil cancers (Park et al., 2011). However, the invasion depth was measured by adding the exophytic and endophytic parts of the tumour, which actually represented TT as defined earlier in this study. In other studies comparing radiological TT to pathological TT, both MRI and CT had shown thicker tumour than pathological specimen. Mean TT measured on MRI was 0.8 mm larger in contrast-enhanced T1-weighted images (r = 0.938, p< 0.0005) and 2 mm larger

in T2-weighted images ($r = 0.941$, $p<0.0005$) than the histologically determined thickness (Lam et al., 2004).

From Bland-Altman plots in the current study, 95% confidence intervals of the mean differences between CT and histopathological DOI were within the limits of agreement, implying that these two methods were in good agreement. In other words, measurements of DOI from CECT, both axial and coronal, are accurate compared to histopathological measurement. Therefore, the null hypothesis in this study is rejected. The results of invasion depth from CT imaging hence may be judiciously used to guide decision on elective neck dissection.

The changes in the direction of DOI measurement in CT and in histopathology may had contributed in discrepancies of reading. It was impossible to ensure that grossing of pathological specimen was done exactly parallel to the CT slices. In addition, the specimen would have had underwent distortion and shrinkage following tumour resection. These may lead to both underestimation or overestimation of tumour depth when there is no parallelism. To overcome this, a surgeon may mark the specimen according to CT slicing prior to excision to serve as a guide for the pathologist's specimen grossing later. Another possible solution is to ensure axial and coronal CT slices were taken parallel and perpendicular to the tongue axis respectively as in pathological specimen grossing.

In previous studies of measurement of DOI and TT, reading of CT and MRI data were done by either experienced head and neck radiologists (Alsaffar et al., 2016; Park et al., 2011) or oral and maxillofacial radiologists (OMFRs) (Figueiredo et al., 2010). There was concordance between medical radiologists and OMFRs in determination of tumour size from pre-operative CT (Figueiredo et al., 2010). For the current study, CT measurement was done by the author trained in Oral and Maxillofacial Surgery after a short training

with a clinical radiologist. It was noted that CT scan reading of DOI is simple and straightforward, however, has been frequently missed out on CT report as the importance might not been highlighted to our radiologists. In the event of absence of DOI value in CT report, the operating surgeon can perform the DOI measurement from the CT scan image prior to surgery provided the concept is well understood. Another advantage that was observed in this study was that the surgeon has information of exact clinical location of tumour on CT, which eased the identification of tumour mass especially when the contrasted image was less clear.

In recent years, there were increasing numbers of patients diagnosed at early stage of disease due to increasing awareness of oral cancer and better access to healthcare facilities. Some of the tumours were still at early superficial lesions, which were not visualised on imaging. In three out of 18 CT data analysed, DOI was recorded as 0 mm because there was no tumour tissue visualised in the scans. Those cases recorded histopathological DOI of 3 mm, 2 mm and 1 mm respectively. This suggests that early superficial lesions cannot be examined in CECT, despite of the slice thickness was less than pathological tumour depth, i.e. 0.8 mm. This finding was supported by Alsaffar et al. (2016) where MRI examination did not correlate well with pathological depth ($r = -0.211$, $p = 0.56$) for superficial tumour cohort, defined as pathological DOI less than 5 mm. Some cases of early lesions that were excised completely during excisional biopsy procedure as evidenced by absence of tumour cells in subsequent wide excision specimen were already excluded from this study.

Although Yesuratnam et al. (2014) and Oliff et al. (2014) had recommended that imaging should be performed prior to any biopsy to prevent inaccurate staging due to post-operative oedema, it was in the surgeon's opinion to not delay diagnosis and treatment for patients. If the patient were to go for MRI first prior to biopsy, time to

excision was significantly longer compared to biopsy-first patients, which may unnecessarily delay treatment for the patient (Howe et al., 2017). This is known as professional delay, defined as the time elapsed since the first consultation by a professional until the start of definitive treatment (Jafari, Najafi, Moradi, Kharazifard, & Khami, 2013). Other factors that contributed to professional delay were failure of health workers to recognise malignancy, waiting time for biopsy results, radiological appointment or radiotherapy, and lack of operating theatre time (Howe et al., 2017; Lee et al., 2011). Another cause of treatment delay was known as patient delay, defined as time elapsed between symptom discovery and the first medical contact with a medical doctor or dentist concerning that symptom (Warnakulasuriya, Lanfranchi, & Rapidis, 2016). The reasons cited for patient delay were lack of patient awareness, seeking traditional treatment, lack of accessibility to health care facility and poor financial support (Lee et al., 2011). Minimising professional delay is crucial considering the additive effect of patient delay. The increasing time to treatment initiation may raise the probability of lymph node dissemination in Stage I-II cancer and significantly decrease the 5-year overall survival of oral cavity cancer patients (Polesel et al., 2017).

## 5.2 Challenges in this study

The main challenge in conducting this study was handling of different CT image quality which are described in terms of contrast, spatial resolution, image noise, and artefacts (Goldman, 2007). These are contributed by multiple factors, including field of view (FOV), pixel matrix, scanning kilovoltage (kV) and patient's motion to name a few. The current study included three different types of CT scanners. Though all scanners used a standard 120kV scanning and 512x512 matrix, variable FOV was applied at head and neck region resulting in different pixel and voxel sizes, hence inconsistent image resolution.

The injection of contrast material in CT enables better delineation of tumour, resulting in better tumour discrimination against adjacent soft tissue structures (Groell et al. 2001). Despite being contrast-enhanced, not all samples in this study exhibited excellent visualisation of the tongue tumour. This led to difficulty in precise determination of tumour – normal soft tissue border.

The presence of amalgam streak artefact may be overcome by repeating the scan in an angled gantry, which typically introduces a scan delay of 10 to 20 minutes (Harris et al. 1996). A limited repeat scan with imaging along the line of the mandible, parallel to the plane containing the metal, provides another imaging plane to visualise oral cavity (C. Law et al., 2011). On the other hand, flow rate of contrast material and scan delay time can affect the contrast enhancement of lesion. A study by Groell et al. (1999) stated that timing of CT studies of the head and neck should balance between two factors: it should be early enough to benefit from sufficient intravascular contrast material and it should be delayed enough to allow for adequate soft-tissue enhancement. However, both flow rate of contrast material and scan delay time were not specified in the present study due to its retrospective nature.

## 5.3 Limitations of study

Due to the retrospective nature of this study, imaging protocol varied according to the centre that performed the CT. As University of Malaya's Dental Faculty is one of the referral centres for oral cancer management located in Kuala Lumpur, patients came from various places in and around Klang Valley, and occasionally from another state. Hence, CT scans were sometimes done at the respective hospital prior to referral to this centre or at other radiological centre upon diagnosis due to logistics reason. There was no standardisation of imaging protocol and CT slice thickness from one centre to another. For head and neck cancer patients, the University Malaya Medical Centre practises a slice

thickness of 0.8 mm for neck CT, then reconstructed in the thickness of 3.0 mm for axial and coronal planes. From the findings of this study, the outcome in terms of reliability and accuracy was comparable if not superior compared to other studies using MRI. Therefore, this CT protocol is recommended if MRI cannot be done for oral cancer patients for any reasons.

Secondly, the study sample was relatively small in comparison to total number of OTSCC patients in the 10-year period. The main reason of exclusion was the loss of CT data from the database due to storage system failure and the lack of backup storage. There is a need to improve the electronic medical records to ensure proper documentation and lost data can be automatically retrieved. This requires an excellent information technology (IT) support that readily responds and resolve problems concerning the storage, retrieval and protection of patients' data. There should be more prudent record keeping especially for oral cancer patients who require long term follow up. Medical records of cancer patients should be retained for 30 years upon the diagnosis of cancer or, until eight years after death (Beaumont et al., 2016). Following the end of the retention period, the records may be reviewed and considered for transfer to a Place of Deposit. Due to the small sample and not normally distributed data, regression analysis cannot be performed. For the same reason, analysis by T-stage and tongue site was not performed.

The next limitation in this study was the CT data evaluation performed only by a single observer. The results showed high reproducibility of the data however no second observer to ensure that the results can be reliably produced by different individuals. Hence, there may be some elements of bias, although effort was taken to minimise that with at least one-month period between the two measurements. The initial idea was to explore the reliability of CT in assessing tumour depth. Thus, single observer measurement was

applied in the current study. Since the results were promising, future study should be conducted with improvised design to validate the current results.

## 5.4 Recommendations for future study

For future study, a prospective study should be planned with larger sample size, involving different subsites of oral cavity tumour. This would allow the application of pre-operative determination of DOI from CECT if the results were favourable. By the virtue of prospective study, imaging protocol should be standardised following the standard for head and neck cancer. The type of CT machine, matrix size, FOV, type of contrast material and timing delay should be standardised to reduce factors that may influence poor visualisation of tumour tissue and to improve CT resolution.

It is recommended to have at least two observers in head and neck specialty, preferably from radiology and surgical background respectively, to perform the measurement of DOI from CT images in order to determine the reliability between differently experienced individuals. Further data analysis can be done to predict nodal metastasis, recurrence and survival using pre-operatively determined DOI from CECT.

# CHAPTER 6: CONCLUSION

This study concludes that the measurement of DOI in pre-operative CECT scan was comparable to HPE in OTSCC cases. CECT measurement underestimated DOI by an average of 1-2 mm against the gold standard of histopathological measurement. There was excellent correlation between CT-based tumour invasion depth and histopathological depth in both axial and coronal sections. The two methods were in good agreement and therefore DOI measurement from CECT was accurate. Hence, our results suggest that CECT may be utilised for pre-operative determination of invasion depth in OTSCC cases with consideration that early superficial lesions up to 3 mm cannot be visualised on CT. This is clinically advantageous as CT scanning is faster, less expensive and more widely available than MRI. Further research is recommended to validate and explore the application of CT for this purpose.

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