OPTIMISING INVERSE PLANNING SIMULATED ANNEALING (IPSA) PARAMETERS FOR BRACHYTHERAPY PLANNING DOSE CALCULATION IN ORAL TONGUE CANCER PATIENTS

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by

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CERTIFICATE

This is to certify that the dissertation entitled **"OPTIMISING INVERSE PLANNING SIMULATED ANNEALING (IPSA) PARAMETERS FOR BRACHYTHERAPY PLANNING DOSE CALCULATION IN ORAL TONGUE CANCER PATIENTS"** is the bona fide record of the research work done by **SITI NORALIZA BINTI OSMAN** during the period from October 2024 to July 2025 under my supervision. I have read this dissertation and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation to be submitted in partial fulfilment for the degree of Bachelor of Health Sciences (Honours) (Medical Radiation).

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DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated and duly acknowledged. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at Universiti Sains Malaysia or other institutions. I grant Universiti Sains Malaysia the right to use the dissertation for teaching, research and promotional purposes.

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SITI NORALIZA BINTI OSMAN

Date: July 2025

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LIST OF ABBREVIATIONS AND ACRONYMS

CI	Conformity Index
CTV	Clinical Target Volume

D_{2cc}	The most exposed dose to 2 cm^3
DVH	Dose-Volume Histogram
EBRT	External Beam Radiation Therapy
GrO	Graphical Optimisation
GTV	Gross Tumour Volume
HDR	High Dose Rate
HyBIRT	Hybrid Brachytherapy-Intensity Modulated Radiotherapy
IPSA	Inverse Planning Simulated Annealing
ISBT	Interstitial Brachytherapy
OAR	Organs at risk
ORN	Osteoradionecrosis
PTV	Planning Target Volume
QoL	Quality of Life
TPS	Treatment Planning System
VOI	Volume of Interest

ABSTRAK

Brakiterapi memainkan peranan penting dalam rawatan kanser lidah mulut dengan menyampaikan dos radiasi tinggi secara terus ke tumor sambil mengurangkan pendedahan kepada tisu sihat di sekelilingnya. Inverse Planning Simulated Annealing (IPSA) ialah algoritma pengoptimuman automatik yang biasa digunakan dalam brakiterapi, namun keberkesanannya dipengaruhi oleh tetapan parameternya. Kajian ini bertujuan untuk membandingkan hasil dosimetrik antara Graphical Optimum (GrO) dan tiga set parameter IPSA yang berbeza dalam perancangan brakiterapi bagi kanser lidah mulut. Satu analisis retrospektif telah dijalankan, di mana parameter dose-volume histogram (DVH), khususnya Gross Tumor Volume (GTV) (D_{90}) dan D2cc bagi rahang, otot konstriktor farinks (PCM) dan kelenjar submandibula (SMG), dinilai merentasi pelan rawatan yang berbeza. Keputusan menunjukkan GrO mencapai purata Gross Tumor Volume (GTV) (D_{90}) tertinggi sebanyak 6.10 Gy, manakala IPSA 1, IPSA 2 dan IPSA 3 masing-masing mencatatkan 4.14 Gy, 4.68 Gy dan 5.37 Gy. Perbezaan yang signifikan secara statistik telah ditemui dalam GTV D90 dan D2cc mandibel antara pelan GrO dan IPSA. Namun begitu, bagi otot konstriktor farinks serta kelenjar submandibula kiri dan kanan dalam pelan IPSA 2 dan IPSA 3, tiada perbezaan dos D2cc yang signifikan berbanding GrO. Walaupun pengoptimuman IPSA mencapai kesesuaian dos yang boleh diterima, tiada set parameter IPSA yang mengatasi GrO dari segi liputan sasaran. IPSA 2 menunjukkan keseimbangan yang baik antara liputan sasaran dan perlindungan tisu normal. Sebagai had kajian, analisis ini hanya berdasarkan data satu fraksi rawatan bagi setiap pesakit akibat ketiadaan data untuk pecahan berganda, yang mungkin menjejaskan penafsiran keseluruhan. Kajian akan datang disarankan untuk mengumpul dan menganalisis data bagi beberapa pecahan rawatan bagi meningkatkan ketepatan dan

penilaian lebih menyeluruh terhadap prestasi pengoptimuman IPSA dalam brakiterapi kanser lidah mulut. Dalam kalangan pelan IPSA, IPSA 2 dikenal pasti sebagai konfigurasi parameter yang paling optimum kerana memberikan keseimbangan terbaik antara liputan dos terhadap tumor dan perlindungan terhadap organ pada risiko (OAR). IPSA 3, walaupun mencapai liputan dos tumor yang lebih tinggi, telah menghasilkan peningkatan dos kepada OAR, terutamanya kelenjar submandibular kiri dan kanan, sekali gus menekankan keperluan pengurusan imbangan yang teliti antara liputan sasaran dan pemeliharaan tisu normal dalam perancangan songsang.

ABSTRACT

Brachytherapy plays an essential role in the treatment of oral tongue cancer, providing a high radiation dose directly to the tumor while limiting the exposure to surrounding healthy tissues. Inverse Planning Simulated Annealing (IPSA) is an automated optimization algorithm commonly used in brachytherapy, but its performance can be influenced by parameter settings. This study aimed to compare the dosimetric outcomes between Graphical Optimization (GrO) and three different IPSA parameter sets in brachytherapy planning for oral tongue cancer. A retrospective analysis was conducted, where the dose-volume histogram (DVH) parameters, specifically GTV (D90) and D2cc for the mandible, pharyngeal constrictor muscle (PCM), and submandibular glands (SMG), were evaluated across different plans. The findings showed that GrO achieved the highest mean GTV D90 of 6.10 Gy, while IPSA 1, IPSA 2, and IPSA 3 recorded mean D90 values of 4.14 Gy, 4.68 Gy, and 5.37 Gy, respectively. A statistically significant differences were found in GTV D90 and D2cc mandible between GrO and IPSA plans. However, for the pharyngeal constrictor muscle, left and right submandibular glands, IPSA 2 and IPSA 3, there are no significance D2cc doses compared to GrO. Although IPSA optimization provided acceptable dose conformity, none of the IPSA parameter sets outperformed GrO in target coverage. IPSA 2 showed a favorable balance between target coverage and normal tissue sparing. As a limitation, this study only analyzed data from a single treatment fraction for each patient due to unavailable multi-fraction data, which may affect the overall interpretation. Future studies should consider collecting and analyzing data for multiple fractions to enhance accuracy and allow for more comprehensive evaluation of IPSA optimization performance in oral tongue cancer brachytherapy. Among the IPSA plans, IPSA 2 is identified as the optimal parameter

configuration, offering the best overall balance between tumour coverage and OAR protection. IPSA 3, while achieving higher tumour dose coverage, resulted in increased doses to the OARs, particularly the right and left submandibular glands, highlighting the need for careful trade-off management between target coverage and normal tissue sparing in inverse planning.

CHAPTER 1 : INTRODUCTION

1.1 Background of the Study

Oral tongue cancer is common, with an estimation of 826 new cases and 440 deaths in Malaysia within 5 years prevalence (Ferlay et al., 2024). Squamous cell carcinoma is the most common histological of oral tongue cancer with the tongue has been the most frequent site of occurrence. The occurrence of oral tongue cancer varies by habit, lifestyle, country and race. The main factors of the tongue cancer occurred are smoking tobacco and alcohol consumption. However, other factors such as excess body weight, low fruit and vegetable diet intake, age and gender also contribute to the occurrence of tongue squamous cell carcinoma (Rowden, 2023). Alcohol drinking coupled with tobacco use accounts for 70 to 80% of HNSCCs (Marziliano et al., 2020) (Nokovitch et al., 2023). Among the population of male and female, male tends to have high risk of oral tongue cancer with a ratio of 2:1. The incidence is higher in Asia. It may be due to different social habits such as chewing betel nuts mixed with lime and the habit of reverse smoking (Bagale et al., 2021). Low fruit and vegetable diet intake will be prone to lack of the antioxidant, anti-inflammatory, anti-angiogenic, and anti-proliferative properties that have a preventive role in the development of oral and other types of cancer (Rodríguez-Molinero et al., 2021). A study by Iyengar et al., in a retrospective cohort study which included 155 patients, a body mass index (BMI) of 30 kg/m2 or greater was associated with a five-fold increase in the risk of death from oral tongue SCC (Iyengar et al., 2016). The incidence of oral cancer in Japan is reported to be 1% of all cancers, and the number of patients is increasing with the age of the population. In Western

countries, the number of patients with oral cancer among young people and nonsmokers is on the rise (Steven et al., 2015).

The standard treatment of oral tongue cancer is surgery, then followed by the chemotherapy or the adjuvant external beam radiotherapy (EBRT) (Kim et al., 2022). Standard treatment is categorised into partial glossectomy, hemiglossectomy and total or subtotal glossectomy. In partial glossectomy or hemiglossectomy cases, reconstruction aims to preserve the function of the remaining tongue. In total or subtotal resections, the goal is to reduce the space between the reconstructed tongue and the palate to restore articulation and swallowing. In a study of Blatt et al., after primary curative treatment of OSCC, recurrence can be detected in about 20% of cases; 76% of recurrences occur within the first two years. Others even state recurrence rates of up to 86% within the first year (Blatt et al., 2022). For early and some selected locally advanced nonmetastatic tongue squamous cell carcinoma (TSCC), upfront surgery is the standard treatment. However, an organ-sparing approach using interstitial brachytherapy (ISBT) offers a comparable local control (LC) rate, meaning it effectively manages the cancer without the need for extensive surgical removal of the tongue (Musa et al., 2022).

Brachytherapy results in better dose distribution compared with other treatments because of steep dose reduction in the surrounding normal tissues. Excellent local control rates and acceptable side effects have been demonstrated with brachytherapy as a sole treatment modality, a postoperative method, and a method of reirradiation (Yamazaki et al., 2013). HDR brachytherapy is less time-consuming, treatment can occasionally be administered on an outpatient basis (Yamazaki et al., 2013) (Jameson et al., 2015). The successful of brachytherapy has been studied and reported such as for stage T1 tongue cancer, the 5-year

local control rate with low-dose-rate (LDR) brachytherapy is 79–93%. For stage T2, the rate is 70–83% (Bajwa et al., 2016). One study found an overall survival rate of 75.6% at 3 years and 59.1% at 5 years and the disease-specific survival rate of 82.3% at 3 years and 68.6% at 5 years (Ianoyski et al., 2020). High Dose Rate (HDR) Brachytherapy has shown its capability in achieving better local control with fewer side effects compared to the standard care for oral which is surgical resection, followed by the external beam radiotherapy beam (EBRT) (Choi et al., 2018). To achieve the aim of brachytherapy treatment goal, planning technique should come up better.

Graphical Optimization (GrO) is an interactive method where the planner manually adjusts the isodose lines (lines showing areas of equal radiation dose) to improve the treatment plan. By clicking and dragging the isodose lines with the mouse, the planner can increase or decrease the dose to certain areas, aiming to cover the tumour well while protecting nearby healthy organs. The dwell weights (radiation source strength at certain points) are automatically adjusted as the isodose lines are moved. After using GrO, the plan was also compared with other techniques like no optimization (NO), point optimization (PO), and point graphical optimization (PGO). (Azahari et al., 2021)

Inverse planning simulated annealing (IPSA) is a heuristic stochastic anatomy-based inverse optimisation method and a treatment planning technique that utilizes an automated algorithm to rapidly determine optimal dwell time combinations satisfying prespecified dose prescriptions and constraints (Fröhlich et al., 2019) (Cheung et al., 2022). IPSA provides a combination of source activation, dose normalization, dose optimization, and dose prescription (Fu et al., 2021). When paired with the Dwell Time Deviation Constraint (DTDC), IPSA creates robust plans by minimizing significant variations in dwell times,

resulting in optimal dose distribution with reduced planning time and fewer complex adjustments including a greater refinement in plan optimisation. In Inverse Planning Simulated Annealing (IPSA) for brachytherapy, dose constraints are integral to creating a treatment plan that ensures optimal tumours control while protecting surrounding healthy tissues such as tongue, mandible and other oral tissues (Choi et al., 2018). The constraints are applied during the optimization process to balance the dose delivery to the target volume and organs at risk (OARs). For oral tongue, in a study by Choi et al., the D_{90} of CTV is 15 Gy, the tongue is 5 Gy and the mandible is 3.5 Gy. However, other dose constraint of OARs like pharyngeal muscle constrictor and submandibular glands are unknown.

1.2 Problem Statement

Graphical optimisation technique is currently applied for the treatment of patients undergoing brachytherapy for interstitial tongue cancer cases (Choi et al., 2018) (Azahari et al., 2021). This technique is designed to optimize the delivery of therapeutic radiation directly to the tumour site, enhancing treatment efficacy while minimizing exposure to surrounding healthy tissues. However, despite its application, there remains a significant gap in the existing literature regarding established guidelines for dose constraints specifically tailored for interstitial tongue brachytherapy. This absence of standardized guidelines presents a challenge, particularly when considering the delicate nature of the anatomical structures involved.

The current implementation of IPSA in Oncentra planning systems relies on dose constraints applied primarily to the organs at risk (OARs). While the algorithm requires accurate contouring of the organs, there are no predefined dose constraints set for critical OARs such

as the mandible, pharyngeal constrictor muscles, and submandibular glands. The organs at risk (OAR) associated with interstitial tongue brachytherapy include critical structures such as the mandible, which is important for both structural support and functional activities like chewing and speaking; the pharyngeal constrictor muscle, which functions in the swallowing process; and the left and right submandibular glands, which are essential for salivary function and overall oral health (Ferda Yamic et al., 2024). This lack of specific dose constraints for these structures may lead to suboptimal treatment plans, increasing the risk of side effects such as mandibular necrosis, swallowing dysfunction, and salivary gland damage.

To address this issue, there is a need to study optimization methods for IPSA parameters, specifically focusing on the inclusion of new dose constraints for these critical OARs in oral tongue cancer cases. By creating and implementing a new set of IPSA parameters tailored for these structures, the aim is to enhance the effectiveness and safety of brachytherapy planning. This optimization would ensure that IPSA provides a robust and clinically reliable plan for oral tongue cancer, reducing treatment-related toxicity and improving overall patient outcomes.

1.3 Objective

1.3.1 Main Objective

To optimize the Inverse Planning Simulated Annealing (IPSA) parameter settings in brachytherapy treatment planning for oral tongue cancer patients.

1.3.2 Specific Objectives

1. To assess the dose conformity to tumour and the dose constraint to the mandible, pharyngeal constrictor muscle and submandibular glands with Inverse Planning Simulated Annealing (IPSA).
2. To compare and identify the optimal IPSA parameter set based on the dose-volume histogram (DVH) outcomes for tumour coverage and organ-at-risk sparing.
3. To establish the dose constraints for critical organs at risk (OARs), specifically the mandible, pharyngeal constrictor muscles, and submandibular glands, in oral tongue cancer brachytherapy.

1.4 Significance of Study

This study is important because it focuses on improving the quality of brachytherapy treatment planning for oral tongue cancer patients. Oral tongue cancer is challenging to treat with brachytherapy due to the complex structure of the oral cavity and the close location of important organs like the mandible, pharyngeal constrictor muscles, and submandibular glands. It is essential to deliver enough radiation to the tumour while protecting these organs from high doses. Inverse Planning Simulated Annealing (IPSA) is a technique used to automatically plan brachytherapy treatment. However, the success of IPSA depends on selecting the right parameter settings. Currently, there is limited information on how to adjust these parameters specifically for oral tongue cancer. This study is significant because firstly, it can help improve treatment outcomes by creating better, more personalized brachytherapy plans. Not only that, but it also aims to achieve good dose coverage to the tumour while reducing the dose to nearby healthy organs. Furthermore, it provides useful information for

future brachytherapy planning guidelines and research, and it supports the goal of improving patients' quality of life by reducing side effects from treatment.

CHAPTER 2 : LITERATURE REVIEW

Oral Tongue

Oral tongue cancer is a form of squamous cell carcinoma that arises from the anterior two-thirds of the tongue, an area known for its rich vascular and lymphatic supply. According to the World Health Organization (WHO), oral cavity cancers constitute a significant portion of head and neck malignancies globally, with tongue cancer representing a considerable proportion of these cases. (Aghiorghiesei et al., 2022). In Malaysia, the National Cancer Registry reports an increasing trend of oral cancer incidence, with the tongue consistently being the most commonly affected intraoral subsite (Chan et al., 2023). Oral tongue cancer often presents as an ulcerative or exophytic lesion, typically characterised by rapid local invasion and potential for early nodal metastasis due to the anatomical features of the region (Bugshan et al., 2020)

Oral Tongue Cancer Treatment

The management of oral tongue cancer depends largely on the stage at diagnosis. Early-stage disease (Stage I–II) can often be managed with single-modality therapy, either surgery or radiotherapy. Advanced cases typically require a combination of surgery, radiotherapy, and chemotherapy (Meccariello et al., 2022). Brachytherapy has established itself as a valuable treatment modality, particularly for early-stage and residual disease following surgery, due to its ability to deliver high radiation doses directly to the tumour while limiting exposure to surrounding healthy tissue. The mobility of the tongue and its proximity to critical structures such as the mandible, submandibular glands, and muscles involved in speech and swallowing present significant challenges in achieving optimal dose distribution without compromising

organ function (Kutuk et al., 2024). Thus, advancements in brachytherapy planning techniques are essential in improving both oncologic outcomes and quality of life for patients.

Brachytherapy

Brachytherapy is a form of internal radiotherapy where radioactive sources are placed in close proximity to or within the tumour volume, allowing high doses of radiation to be delivered locally with rapid dose fall-off in surrounding normal tissues. In the treatment of oral tongue cancer, interstitial brachytherapy using flexible catheters or needles is the most commonly employed technique. Catheters are inserted under anaesthesia and positioned parallel to one another across the tumour-bearing area of the tongue. The prescribed dose is typically delivered through high-dose-rate (HDR) brachytherapy using an iridium-192 (Ir-192) source, which is remotely controlled through an afterloading device. (Akino et al., 2024)

The success of brachytherapy requires extreme conformity, with delivery of a high radiation dose directly to the tumour while sparing surrounding normal tissues via rapid radiation dose fall-off beyond the implanted tumour volume (Sturdza et al., 2022). In brachytherapy, radioactive sources are placed inside or very close to the tumour. The goal is to deliver a high dose of radiation to the tumour while protecting the nearby healthy tissues. The radiation dose is strongest close to the source, meaning the tumour gets the maximum dose needed to kill cancer cells effectively. The dose of radiation drops quickly as you move away from the source. This is called rapid dose fall-off. It happens because radiation intensity decreases sharply with distance. Dose conformity means shaping the radiation dose to match the tumour's size and shape. This ensures that the tumour receives enough radiation to destroy cancer cells and the healthy tissues around the tumour—like the mandible, submandibular

glands, and pharyngeal constrictor muscles—receive very little radiation to avoid damage. Better conformity may help in delivering minimum dose to organs at risk (OARs) and maximum dose to planning target volume (PTV) (Atiq et al., 2017). Conformity measures estimate how conformal the prescription dose it to the target volume, some of them also include doses organs at risk (OARs) (Björn et al., 2021). Conformity Index (CI) describes how well the reference isodose encompasses the target value and excludes non-target structures (Azahari et al., 2021).

Brachytherapy Treatment Planning

Treatment planning for brachytherapy involves defining the gross tumour volume (GTV), clinical target volume (CTV), and organs-at-risk (OARs) using computed tomography (CT) or magnetic resonance imaging (MRI). The prescribed dose is then distributed through an arrangement of dwell positions and dwell times for the radioactive source within the implanted catheters. Traditional forward planning relies heavily on the expertise of the planner, who manually adjusts dwell positions and times to achieve desired dose distributions. However, this method is laborious, time-consuming, and can lead to suboptimal or inconsistent outcomes, particularly in complex anatomical regions like the oral cavity. These limitations have driven the development of advanced optimisation techniques, such as Inverse Planning Simulated Annealing (IPSA), to improve treatment planning efficiency and dosimetric quality.

Types of Brachytherapy

In most radiotherapy departments, manual afterloading and LDR BT were largely replaced in the late 19_{90}s by HDR BT and automatic afterloading techniques. HDR BT (dose rate ≥ 12

Gy/h) has a greater biological effect than LDR BT, and this effect is greater in late-reacting normal tissues than in cancer tissue, which explains the lower therapeutic ratio. This is why HDR BT requires a fractionated approach. In general, switching from LDR to HDR increases the likelihood of side effects for a given level of cancer control, particularly in interstitial applications. Therefore, it is important to select the optimal number of fractions and total dose of HDR BT to achieve the same effects on the tumour and normal tissues as achieved with LDR BT. (Tuček et al., 2022) Brachytherapy is characterized by its steep dose gradient, which ensures excellent sparing of surrounding tissues, delivers high doses to the tumour centre, and involves a short overall dose delivery time that helps prevent the accelerated proliferation of tumour stem cells. (Babu & Krishnan, 2025)

Inverse Planning Simulated Annealing (IPSA)

Inverse Planning Simulated Annealing (IPSA) is a computerised optimisation algorithm designed to automate the brachytherapy treatment planning process by determining the optimal distribution of dwell times at specified dwell positions within the implanted catheters. Unlike forward planning, where planners manually assign dwell times based on trial and error, IPSA utilises a mathematical approach to iteratively adjust dwell times with the aim of achieving predefined dosimetric objectives. These objectives typically include ensuring adequate dose coverage to the clinical target volume (CTV) while limiting the dose received by nearby organs-at-risk (OARs). The algorithm operates by generating multiple random solutions, evaluating them against an objective function, and progressively refining them towards a global optimum solution through simulated annealing—a probabilistic technique that allows occasional acceptance of suboptimal solutions to avoid entrapment in local minima. (Cheung et al., 2022)

The implementation of IPSA has been extensively validated in various clinical settings, most notably in prostate and cervical cancer brachytherapy. In these applications, IPSA has demonstrated significant improvements in dose conformity, homogeneity, and OAR sparing compared to manual and graphical optimisation techniques (Srivastava et al., 2022). The algorithm's ability to handle complex geometries and competing dose constraints makes it particularly suitable for anatomically challenging regions like the head and neck. However, despite its advantages, IPSA planning is highly sensitive to the input parameters defined by the planner, such as dwell time deviation constraints, dose penalties for the target and OARs, and dwell position constraints. Fine-tuning these parameters is crucial in achieving optimal plan quality, especially in sites with high anatomical variability like the oral tongue.

Recent studies have explored the application of IPSA in brachytherapy, reporting dosimetric outcomes. For instance, Srivasta et al. (2022) demonstrated that IPSA improved target dose conformity while maintaining acceptable OAR doses in cervix cancer brachytherapy. Not only that, the study compared IPSA with graphical optimisation (GrO) in tongue cancer and noted there was no significant difference, however the planning times for IPSA were greatly reduced compared to GRO and plans were dosimetrically similar. These findings highlight the potential of IPSA to enhance dosimetric quality in oral tongue cancer brachytherapy. However, limited literature exists on optimising IPSA parameters specifically for this site, emphasising the need for studies like the present one to systematically assess and refine parameter settings for improved clinical outcomes.

Dose constraint

In oral tongue brachytherapy, achieving a high D_{90} is essential to ensure adequate tumour control. However, excessive radiation exposure to adjacent critical structures can result in significant morbidity, including osteoradionecrosis of the mandible, xerostomia from submandibular gland damage, and dysphagia due to pharyngeal constrictor muscle injury.

To minimise these risks, dose constraints for organs-at-risk (OARs) are established based on clinical tolerance data. The mandible, for instance, is highly sensitive to radiation, with Dmax thresholds typically recommended to remain below 70–73.5 Gy in maximum dose. The submandibular glands are responsible for the majority of unstimulated salivary flow, and their preservation is critical for maintaining oral moisture. Studies by Bisello et al. (2022) recommend limiting the D_{mean} to these glands to reduce the risk of xerostomia. Similarly, the pharyngeal constrictor muscles play an essential role in swallowing, and dose constraints are necessary to prevent late dysphagia. Guidelines suggest keeping the D_{mean} below 50 Gy.

Organ	Dose-Volume Constraints
Bone mandible	V_{50Gy} < 31-32% or V_{50Gy} < 31 cm^3 D_{MAX} < 70–73.5 $Gy_{(mandatory)}$ $V_{55\ Gy}$ < 20%$_{(optimal)}$
Pharyngeal constrictor muscles	D_{MEAN} < 50 Gy
Submandibular Gland	D_{MEAN} < 35 Gy

Table 2.1: The general dose–volume constraints for adult patients (organ nomenclature based on the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG) contouring guidelines (Bisello et al., 2022)

Organs	Imaging technique	Anatomical Description
Bone mandible	CT-bone window	Consider the entire mandible bone, from the temporo-mandibular joint to the symphysis mandibular. Exclude the teeth from the contour.
Pharyngeal constrictor muscles	-	Include the whole muscle constrictor structure, such as the superior, middle, and inferior pharyngeal constrictor muscle. Cranial edge: pterygoid plates (caudal limit) Caudal edge: arytenoid cartilages (caudal limit). Posterior edge: pre-vertebral muscle. Lateral edge: medial pterygoid muscle (cranially); hyoid bone and thyroid

		cartilages (caudally). Anterior edge: pterygoid Hamulus
Submandibular gland	-	Cranial: Medial pterygoid muscle, mylohyoid muscle. Caudal: Fatty tissue. Anterior: mylohyoid muscle, hyoglossus muscle. Posterior: Parapharyngeal space, sternocleidomastoid muscle. Lateral: medial pterygoid muscle, mandibular bone, platysma. Medial: mylohyoid muscle, hyoglossus muscle, superior and middle pharyngeal constrictor muscles and digastric muscles. Contour each gland separately. *Glnd_Submands* can be considered as sum of

		two volumes for dosimetric purposes

Table 2.2 : the anatomical description of organs at risk (organ nomenclature based on the Global Quality Assurance of Radiation Therapy Clinical Trials Harmonization Group (GHG) contouring guideline (Bisello et al., 2022)

In the context of IPSA planning, these constraints are incorporated into the optimisation process as penalty functions, where deviations from the prescribed dose limits result in increased penalties. Balancing these competing objectives—maximising tumour dose while sparing OARs—is one of the primary challenges in oral tongue brachytherapy planning. Establishing evidence-based dose constraints specific to oral tongue brachytherapy is therefore crucial, and forms one of the key objectives of this study.

Importance of Inverse Planning Simulated Annealing

The effectiveness of IPSA in brachytherapy planning depends heavily on the appropriate selection and fine-tuning of its optimisation parameters. These parameters serve to instructions guiding the algorithm to prioritise dose delivery to the target volume while respecting dose constraints for surrounding organs-at-risk (OARs). The key parameters typically involved in IPSA include the minimum and maximum dose objectives for the target and OARs, the dwell time deviation constraint, and the relative importance or weighting factors assigned to each objective. Each of these parameters can significantly influence the resulting dose distribution, making their optimisation a critical aspect of the treatment planning process.

Another important aspect of IPSA parameter setting involves defining dose objectives for the clinical target volume (CTV) and organs-at-risk (OARs). These objectives typically include both minimum and maximum dose levels, expressed as a percentage of the prescribed dose.

Fine-tuning these values enables planners to balance competing goals — achieving adequate target coverage while minimising OAR doses. The relative weighting assigned to each objective further modulates the optimisation outcome. A higher weight for the CTV minimum dose objective ensures better tumour coverage, whereas increasing the weight for OAR constraints enhances organ protection. In practice, achieving the optimal balance often requires iterative adjustments and dosimetric evaluations, a process known as parameter fine-tuning. A study by Yang et al. shows the different IPSA condition plans and how each condition plans will affect the target dose, the fitness of target dose curve, and the exposure dose to surrounding organs. The result showed that the IPSA condition plan of using the received optimisation parameter conditions combined with clinical practise manual adjustment to optimize the low dose of cervical segment, so as to further optimize the dose and fitness of target area and the dose of OARs within an acceptable range (Yang et al., 2022). Another study is by Cheung et al., dose hotspots were mitigated by setting a maximum dose penalty to the inside of the target volume. A small weight was applied to this penalty to avoid compromising target coverage. (Cheung et al., 2022)
IPSA was found to be superior in terms of homogeneity and conformity as compared with GrO plan (Jamema et al., 2011). Homogeneity means the radiation dose is spread evenly within the tumour, avoiding overdosed or underdosed areas. IPSA uses advanced algorithms to calculate the best positions and times for the radiation source, making the dose distribution more uniform. For conformity, IPSA shapes the radiation dose more precisely to match the tumour's size and shape, while reducing the dose to nearby healthy tissues. In contrast, manual planning relies on experience and trial-and-error, making it harder to achieve the

same precision. The plans generated by IPSA were more conformal than manual planning B (Kannan et al., 2015).

The D_{90}, representing the minimum dose received by 90% of the gross tumour volume (GTV) or clinical target volume (CTV), is a widely accepted indicator of target coverage and tumour control probability in brachytherapy. For organs-at-risk, D_{2cc} is essential for assessing the risk of radiation-related toxicities. In oral tongue brachytherapy, where the mandible, submandibular glands, and pharyngeal constrictor muscles are in close proximity to the target, controlling these OAR dose parameters is particularly challenging yet crucial.

Fine-tuning Inverse Planning Simulated Annealing

The present study builds upon this approach by fine-tuning IPSA parameters through an iterative process involving multiple test plans for each patient. The initial parameter settings are derived from established protocols in the literature and clinical practice guidelines. These settings are then modified systematically based on graphical optimisation (GrO) feedback and DVH analysis to achieve the desired dose conformity and organ sparing. The optimisation process is guided by both quantitative metrics — including D_{90} for the GTV and Dmean or Dmax for OARs — and qualitative assessments of isodose distributions on CT images. By comparing these outcomes with plans generated using manual graphical optimisation, the study aims to determine the most effective IPSA parameter configurations for oral tongue brachytherapy.

Evaluating and comparing brachytherapy treatment plans require comprehensive dosimetric analysis to quantify the quality of dose distribution delivered to both the target volume and the surrounding organs-at-risk (OARs). One of the primary tools for such evaluation is the

dose-volume histogram (DVH), which graphically represents the relationship between the volume of a structure and the dose it receives. DVH analysis enables planners to assess target coverage, dose conformity, and OAR sparing quantitatively and is considered a standard component of treatment plan evaluation in brachytherapy. In this context, key dosimetric parameters derived from the DVH, such as D_{90} for the tumour and D_{2cc} for the OARs, for comparing different treatment plans.

Inverse Planning Simulated Annealing Parameters

A study by Choi et al. a plan optimization was conducted using the Inverse Planning Simulated Annealing (IPSA) algorithm. As shown in Table 2.3, the initial IPSA parameters were applied, and the optimization process was iteratively performed by adjusting the initial constraints to evaluate dose values and weighting for normal tissues such as the mandible and tongue. The maximum allowable values for normal tissue constraints were determined within a specified range to ensure at least 90% of the Clinical Target Volume (CTV) received 100% of the prescribed dose for all patients.

					Surface			Volume		
	Margin				Min	Max		Min	Max	
ROI	Usage	(cm)	Actv.	Weight	(Gy)	(Gy)	Weight	(Gy)	(Gy)	Weight
CTV	Target	0.5	0.5	100	5	15	100	5	10	50
Tongue	Organ	0	0	50		5	50			
Mandible	Organ	0	0	80		3.5	80			

Table 2.3 : Inverse planning simulated annealing (IPSA) optimization algorithm parameters.

In this study, dosimetric comparison is conducted by generating DVHs for each treatment plan, extracting relevant parameters for the GTV and OARs, and statistically analysing the

differences. Specific attention is given to comparing D_{90} values for the tumour and D_{2cc} values for the mandible, submandibular glands, and pharyngeal constrictor muscles between IPSA-optimised plans and those created using graphical optimisation. The statistical significance of these differences is assessed to identify whether IPSA, with fine-tuned parameter settings, provides superior or equivalent outcomes compared to manual optimisation techniques. This dosimetric comparison forms a core component of the study's methodology and directly addresses the third objective of identifying optimal IPSA parameter sets based on DVH outcomes.

The importance of dose conformity

The importance of dose conformity and protection of organs at risk includes Quality of Life (QoL) considerations. Beyond mere survival, it is essential to evaluate treatment outcomes in terms of post-therapy quality of life. The functional integrity of preserved organs significantly impacts long-term patient well-being and determines the overall success of organ preservation strategies. Xerostomia and dysphagia rank as major post-treatment complications and are crucial determinants of diminished quality of life. Dysphagia, characterized by difficulty in swallowing, arises from structural or functional abnormalities that can occur anywhere from the lips to the gastric cardia. Among patients with advanced head and neck cancer, swallowing dysfunction frequently manifests as a significant complication directly related to the effects of radiation therapy, irrespective of the specific chemoradiotherapy protocols employed. (Kundu et al., 2025) Chronic xerostomia is a multifactorial process which can affect quality of life profoundly. The process includes reduced salivary output, decreased salivary pH and increased viscosity of the saliva. This may result in the unpleasant sensation of dry mouth, altered taste, dysfunction of mastication,

swallowing dysfunction and difficulties with speech (Onjukka et al., 2020). Osteoradionecrosis (ORN) is defined as necrotic bone exposed through a wound in the overlying skin or mucosa, without evidence of tumour recurrence, with a duration of at least six months. (Daniel et al., 2023)

CHAPTER 3 : MATERIAL AND METHODS

This is a retrospective study of 20 oral tongue cancer patients that undergone the HyBIRT treatment. In Oncentra MasterPlan, the manual graphical optimisation treatment plan for each patient is a retrospective treatment plan. Next, three inverse planning treatment plans with proper dose constraint are prepared. The DVH of GTV (D_{90}) and OARs (D_{2cc}) are analysed by using SPSS version 30.0.

3.1 Human Research Ethical Clearance

The ethical clearance for this study was granted by the Human Research Ethics Committee of Universiti Sains Malaysia (USM), or known as Jawatankuasa Etika Penyelidikan Manusia (JEPeM). The application process involved submitting the research proposal via email, followed by an online presentation session where the study's objectives, methodology, and ethical aspects were thoroughly reviewed. Approval was given once the committee confirmed that the research adhered to USM's ethical guidelines for studies involving patient data. The official approval letter is included in Appendix A. This ethical approval ensured that participant rights, safety, and well-being were appropriately safeguarded throughout the study.

3.2 Patient Selection

15 patients from 2021 until 2024, treated at Advanced Medical and Dental Institute (AMDI) for oral tongue cancer with high-dose rate (HDR) interstitial brachytherapy (ISBT) were selected for this retrospective study. This patient had undergone external beam therapy (EBRT) and high dose rate ISBT in Radiotherapy and Oncology Department of AMDI. All the patients selected based on the following criteria:

A. Inclusion Criteria

i. Patients with squamous cell carcinoma undergone the HyBIRT treatment

B. Exclusion Criteria

i. Patients with squamous cell carcinoma did not undergo the HyBIRT treatment

3.3 Treatment Scheme

The patient who had diagnosed and treated for oral tongue cancer undergone of HyBIRT treatment with prescribed doses of 20 Gy in 5 fractions. For IPSA treatment plans, there were 3 templates established from literature with different dose constraint as shown in Table 3.

		Surface				Volume			
Plan	ROI	Min Dose Weight	Min Dose (Gy)	Max Dose Weight	Max Dose (Gy)	Min Dose Weight	Min Dose (Gy)	Max Dose Weight	Max Dose (Gy)
IPSA 1	GTV	100	4.0	100	15.0	100	4.0	100	10
	Mandible			100	3.5				
	PMC			50	2.0				
	RT SMG			50	2.0				
	LT SMG			50	2.0				
IPSA 2	GTV	100	4.0	100	15.0	100	4.0	100	20
	Mandible			100	3.5				
	PMC			50	2.0				

	RT SMG			50	2.0				
	LT SMG			50	2.0				
IPSA 3	GTV	100	4.0	100	15.0	100	4.0	100	30
	Mandible			100	3.5				
	PMC			50	2.0				
	RT SMG			50	2.0				
	LT SMG			50	2.0				

Table 3.1 : IPSA1-3 weighted dose constraints

3.4 Brachytherapy planning by using Oncentra Masterplan Treatment Planning System

Treatment planning system is part of the process in deciding the most effective way to deliver radiation doses to the target tumour and organs at risk. Additionally, it aims to produce reproducible setups and ensure the patient's comfort throughout the treatment. In treatment planning, physicists are responsible for adjusting the treatment plans if there are any changes in the patient's condition.