Aus dem Zentrum für Zahn-, Mund und Kieferheilkunde
der Universität zu Köln
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"Comparative analysis of volumetric changes between resurrected oral tongue cancer and post operative radial forearm free flap" – a pilot study

Inaugural-Dissertation zur Erlangung der zahnärztlichen Doktorwürde
der Medizinischen Fakultät
der Universität zu Köln

vorgelegt von
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aus Detmold

promoviert am 11. Februar 2025

Gedruckt mit Genehmigung der Medizinischen Fakultät der Universität zu Köln
2025

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Danksagung

Zuerst gebührt mein Dank meinem Betreuer Privatdozent Dr. med. Dr. med. dent. Matthias Zirk, der mit seiner tatkräftigen Unterstützung zu jeder Zeit an meiner Seite stand. Für die hilfreichen Anregungen und die konstruktive Kritik bei der Erstellung dieser Arbeit möchte ich mich herzlichst bedanken.

Ich bedanke mich bei Herrn Universitätsprofessor Dr. med. Dr. med. dent. Christian Linz an der Klinik für Mund-, Kiefer und Gesichtschirurgie in Köln für die Möglichkeit meiner wissenschaftlichen Arbeit.

Außerdem möchte ich meinen Eltern und Geschwistern, die mich uneingeschränkt ermutigen und an mich glauben, danken. Besonders meiner ältesten Schwester Maryam Azarnia geb. Niknazemi, die mir diesen Weg überhaupt eröffnet hat.

Abschließend möchte ich mich bei meinem Ehemann bedanken, der mir mein Studium durch seine Unterstützung erleichterte und stets ein offenes Ohr für mich hatte.

Für meine geliebten Eltern

Content Summary

List of Abbreviations

RFFF	Radial forearm free flap
SCC	Squamous cell carcinoma
CT	Computed tomography
MRI	Magnetic resonance imaging
DOI	Depth of invasion

1. Summary

i. English

To determine whether the relationship of the volume of pre-operative oral tongue cancer and its corresponding post operative volume of RFFF (radial forearm free flap) is significant, 156 volumetric measurements were conducted within this retrospective pilot study using ITK-SNAP, a 3D segmentation software [1,2]. The timeframe considered within this investigation extended over a period of eleven and a half years from January 2009 until June 2021, whereby patient datasets with the relevant ICD10 Diagnosis (as summarized in Figure 4) admitted to the University clinic of Cologne were selected after specific inclusion criteria. Within these datasets an RFFF was planned for a total of 71 patients, of which 43 conducted their pre- and post-operative imaging within the University clinic of Cologne (radiology department). A final sum of 26 datasets were included after screening the remaining 43 patient files for post-operative complications, cancer remission and artefacts within the relevant imaging data. Via semi-automatic segmentation using the 3D segmentation software ITK-SNAP [1,2], the volumes of each tumor and its corresponding flap were calculated and summarized on SPSS. The analysis of these variables on SPSS showed a statistically significant correlation between the RFFF and its corresponding calculated tumor volume (‘p=0,769 (p <0.001)’[2]). A prediction of RFFF volume may be deducted moderately reliable using the tumor volume with 59.1% confidence (R-Qua: 0.591), by following a regression model that considers the below coefficients:

‘Flap Volume = 3241,633 + 1, 322 * Tumor Volume (mm^3)’[2]

Accurately predicting the volume of RFFF needed to cover the tongue defect in SCC, leads to more minimally invasive tissue extraction when obtaining donor tissue. This subsequently results in smaller tissue defects at the site of tissue extraction and a better prognosis for the healing or secondary coverage of this area. The data collected in this study may improve the understanding of the influence of volumetric changes to support decision making on treatment strategies, complications, follow-up and patient care by emphasizing the need for highly precise treatment plans by using tools to conduct digital mapping of structures. Study groups containing larger population samples of SCC of the tongue and reconstruction with an RFFF are required to draw more reliable conclusions. This investigation may serve as the basis for initiating further research within this field to improve digital planning protocols, better surgical treatment plans and subsequently lower post-operative complications by minimizing the extraction volume of the patient’s donor site.

ii. German

Im Rahmen dieser retrospektiven Pilotstudie wurden insgesamt 156 Volumenmessungen mit der 3D-Segmentierungssoftware ITK-SNAP [1] durchgeführt, um den Zusammenhang des Volumens eines präoperativen oralen Zungenkarzinoms und dessen korrespondierenden Radialislappens (RFFF ‚radial forearm free flap'‚) zu eruieren. Über einen Zeitraum von elf Jahren und sechs Monaten von Januar 2009 bis Juni 2021, wurden Patientendatensätze mit der relevanten ICD10-Diagnose (wie in Abbildung 4 zusammengefasst), die im Universitätsklinikum Köln behandelt wurden, sorgfältig selektiert. Ein RFFF wurde für insgesamt 71 Patienten geplant, von denen 43 ihre prä- und postoperative Bildgebung in der Radiologie der Uniklinik Köln durchführen ließen. Nach dem Screening der verbliebenen 43 Patientenakten auf postoperative Komplikationen, Rezidiven und Artefakte innerhalb der relevanten Bildgebung wurden insgesamt 26 Datensätze in die Studie mit einbezogen. Mit Hilfe der 3D-Segmentierungssoftware ITK-SNAP [1] wurde das Volumen jedes Tumors und des dazugehörigen Lappens durch semi-automatische Segmentierung berechnet und in SPSS eingepflegt. Die statistische Analyse dieser Variablen in SPSS zeigte eine sehr positive Korrelation zwischen dem kalkulierten Tumorvolumen und dessen korrespondierenden RFFF ($p=0{,}769$ ($p<0{,}001$)). Somit kann das RFFF-Volumen durch das entsprechende Tumorvolumen, mäßig zuverlässig mit 59,1% Konfidenz (R-Qua: 0,591) durch das Regressionsmodell mit den folgenden Koeffizienten vorhergesagt werden:

$$\text{Lappenvolumen} = 3241{,}633 + 1{,}322 * \text{Tumorvolumen}\ (mm^3)$$

Eine genaue Vorhersage des RFFF-Volumens, das zur Deckung des Zungendefektes bei SCC benötigt wird, führt zu einer weniger invasiven Gewebeentnahme an der Spenderregion des Patienten. Dies führt zu kleineren Gewebsdefekten an der Entnahmestelle und einer entsprechenden verbesserten Prognose für die Heilung oder sekundäre Deckung dieses Bereichs. Die Ergebnisse dieser Studie sollen das Verständnis über den Einfluss volumetrischer Veränderungen verbessern, um die Entscheidungsfindung in Bezug auf Behandlungsstrategien, Komplikationen, Nachsorge und Versorgung von oralen SCC Patienten zu unterstützen. Die Ergebnisse dieser Arbeit unterstreichen die Notwendigkeit hochpräziser Behandlungskonzepte durch den Einsatz von Tools zur digitalen, dreidimensionalen Darstellung von Strukturen. Um zuverlässigere Schlussfolgerungen ziehen zu können, sind Studiengruppen mit größeren Populationsstichproben von Patienten mit oralem SCC und Versorgung mit einem RFFF erforderlich. Diese Studie kann als Grundlage für weitere Forschungsarbeiten auf diesem Gebiet dienen, um digitale Planungsprotokolle zu verbessern, chirurgische Behandlungskonzepte zu optimieren und weniger postoperative Komplikationen durch Minimierung des Entnahmevolumen im Spenderbereich der Patienten zu erlangen.

1.1. Aim of this study

This feasibility study is aimed to indicate whether oral tongue cancer pre-operatively significantly relates to its corresponding RFFF volume post-operatively [2]. Designated patterns within these volumes could aid digital operation planning, leading to better time management and a potentially smaller RFFF. Successful treatment of oral tongue cancer hinges on a well-devised surgical plan that incorporates thorough interdisciplinary staging, a detailed strategy for addressing defects following tumor excision, and appropriate donor site management. Accurate planning that forecasts resection volumes is crucial, as it can significantly enhance the overall quality of patient care and reduce donor site complications [2]. More precise radial forearm free flap extraction may compromise the forearm less by decreasing the total required tissue volume from the site of the donor. Therefore, more precise predictions of required RFFF volumes within surgical treatment of oral tongue cancer would not only improve patient care but also optimize surgical treatment plans.

2. Introduction

2.1. Oral tongue cancer

The functions of the tongue muscle may be divided into sensory and motor functions, which fulfil crucial roles within the human body [2]. The tongue's motor functions entail actions such as grinding, grasping and moving the food bolus during chewing, in addition to facilitating language and speech. Sensory function is enabled by taste buds embedded in the tongue's specialized mucosa of the surface, which are responsible for the perception of taste. Additionally, the lingual tonsil serves as a protective barrier against pathogens that may enter through the oral cavity [3].
Confirmed cases of oropharyngeal cancer have continued to increase over time, being responsible for a yearly worldwide incidence of approximately 476,125 patients in the year 2020 [2,4,5]. Cancerous lesions of the tongue present themselves as the most frequent cancer within the oral cavity, being responsible for 30% of all malignant cancers [2,6,7].
The correlation of the well-known risk factors chronic alcohol abuse and tobacco consumption in Squamous cell carcinomas (SCC) were observed in over 90% of all oral tongue cancer cases. Most frequently this type of cancer occurs in men aged 55 to 65 and women between the age of 50 to 75 [8,9]. Among other risk factors for oral tongue cancer are diets consisting of low fruits and vegetables intake, certain inherited conditions, and poor oral hygiene [4]. Furthermore, oral tongue cancer may be related to exposure to certain chemicals or to human papillomavirus (HPV) infection [10].
Cancer of the tongue can be divided further by its location into the anterior two-thirds and the posterior third, which also commonly falls under cancer of the oropharynx. Despite the histological similarities of these two subtypes, malignancies arising at the base of the tongue must be approached differently in terms of prognosis and treatment [11]. Although many advances have been made in the detection, management and treatment over the past years, the advanced-stage SCC of the tongue still only present with a 5-year survival of 50% [12].

An increasing incidence of cancer within the head and neck region has been shown by past literature to be increasing with higher age [10]. More recent research has identified younger populations, who appear to have an increased incidence of disease [13]. These groups can be divided into high-risk HPV–associated oropharyngeal cancer patients, which do not present with common risk factors of smoking and alcoholism. The subjects within this group tend to be primarily male, white ethnicity and aged younger than 50 years. In comparison to HPV-negative oropharyngeal cancers, this group appears to have an improved prognosis [13,14]. The other group consists of oral tongue cancer patients, who also show an increasing incidence that is not related to the infection with HPV. The subjects within this group include young, white females, aged 50 years or below. There is no scientific evidence that oral tongue cancer has an association with HPV infection, whilst oropharyngeal cancer has been described to be HPV-associated [15-17].

The clinical manifestation of oral tongue cancer may vary from sores or ulcerations to palpable growths on the tongue, which do not heal within two weeks. Furthermore, these mucosal changes can be accompanied by a local inflammatory reaction. This can lead to pain or numbness in the tongue or difficulty while speaking, swallowing, or eating [18,19].

A reliable method to clearly differentiate SCC of the tongue from other resembling lesions such as Leukoplakia and Erythroplakia, is to examine the tissue sample histologically. The clinically white imposing plaque of Leukoplakia cannot be wiped away, with its most preferred treatment option being a simple excision due to its low risk of malignant transformation. Opposing to this, the erythematous plaque of Erythroplakia, mostly presents itself with significant dysplastic changes, which can even be as advanced as a carcinoma in situ. Thus, a much more extensive excision is often recommended for Erythroplakia due to the high risk of malignant transformation found within these lesions [19].

The critical distinguishing point between an invasive carcinoma and a carcinoma in situ is the interruption of the basement membrane [20]. Moreover, SCC of the tongue is also accompanied by multiple other histological characteristics such as keratin deposits and fibrotic nests of squamous cells [12]. Further factors influencing Staging, grading and prognosis of the carcinoma include the invasion of draining lymph nodes and vessels, perineural structures as well as the destruction or displacement of surrounding tissues. As the most significant histological determinant, the depth of invasion (DOI) plays a crucial role in determining individual prognosis thus impacting the treatment plan of each patient [12,20]. **Figure 1** illustrates how the DOI is measured. A carcinoma of the tongue with a depth of invasion, which exceeds 5-8mm is found to be at higher risk of lymphogenic metastasis even in the absence of clinical or radiological manifestation [20,21]. Due to the importance of this parameter in nodal metastasis and survival rates, it was included in the T stages of the '8th Edition of the American Joint Committee on Cancer (AJCC) TNM-Classification'[22,23] as seen in **Figure 2**. The AJCC, also known as the International Union Against Cancer (IUAC) provides a system which allows classification or staging of cancer in a simplified and uniform matter around the world. Using this system, the staging of a cancer can be carried out clinically before treatment (cTNM), using the pathology report after resection (pTNM) and at recurrence (rTNM) [2,22].

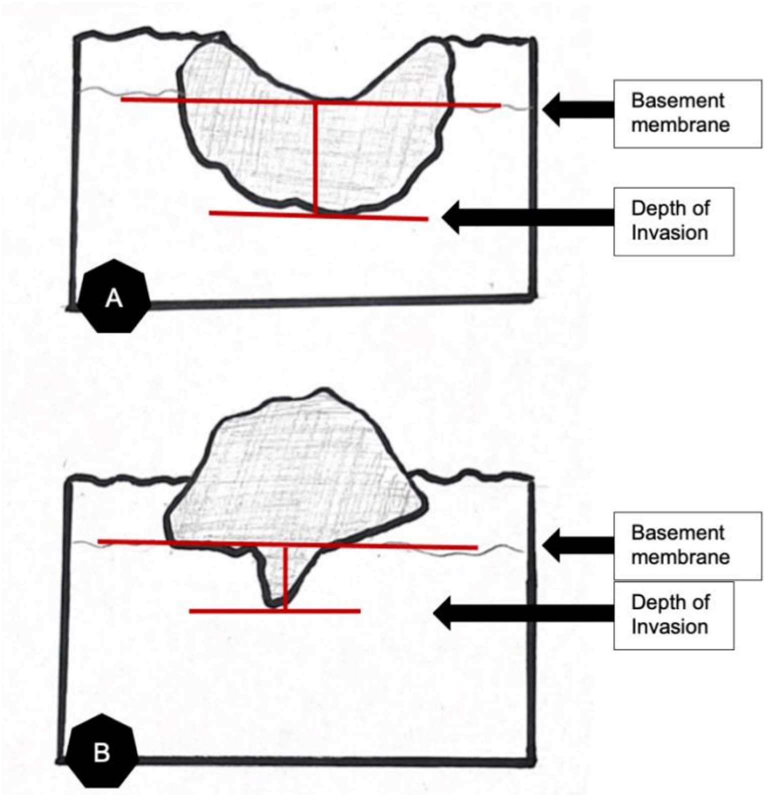


Figure 1: Measurement of DOI for ulcerative (A) and exophytic (B) tumors [2]. (based on [22,23]; drawing by: Mina Niknazemi)

TX	Assessment of primary tumor not possible
Tis	Carcinoma *in situ*
T1	Tumor ≤ 2cm and DOI ≤ 5mm
T2	Tumor ≤ 2cm, DOI > 5mm and ≤ 10mm ***or*** Tumor >2cm and ≤ 4cm and DOI ≤ 10mm
T3	Tumor > 4cm or any tumor with DOI > 10mm
T4: T4a **T4b**	Tumor invades adjacent structures only (e.g., through cortical bone of mandible or maxilla, or involves the maxillary sinus or skin of the face) Tumor invades masticator space, pterygoid plates, or skull base and/ or encases the internal carotid artery

Figure 2: **'**Primary tumor (T) for oral cavity cancers.[2]' (based on [22])

If suspicious lesions are identified during clinical examination, often within dental routine check-ups, histological testing is necessary to confirm the diagnosis of oral tongue cancer. A tissue sample may be deducted in various ways such as an incisional biopsy, an excisional biopsy, a needle biopsy, or an endoscopic biopsy [8]. The sample should always be taken from marginal areas of the tumor. During an incisional biopsy a small amount of the tumor is cut out, whilst an excisional biopsy involves the entire removal of the tumor. FNA (fine needle aspiration) and core biopsy are types of needle biopsies, whereby the FNA uses a very small needle to obtain a tissue sample. During core biopsy a slightly larger needle is used to extract a small cylinder of tissue, which allows the removal of a larger sample for examination. Both methods do not require cutting into the skin, which allows are more minimally invasive approach and can be carried out under local anesthesia ([8,24]). Additionally, a Panendoscopy should be carried out to check for further sites of tumor infiltration. Tissue samples can also be taken during this procedure [8].

Imaging tests such as Ultrasounds, X-rays or CT scans are recommended for analysis of the dimensions and magnitude of the initial tumor. To avoid possible distortions of the contrasting agent within imaging data, the tumor biopsy should be extracted after the image has been taken [8].

Once the tumor board has completed TNM Staging, a treatment plan can be created which may entail any combination of radiation, chemotherapy and surgery. The chosen combination of treatment depends on factors such as the location and T-stage of the cancer, but also the patient's overall health[2,21].

Oral tongue cancer treatment is mainly aimed to attain tumor management locally, with the aim to minimize esthetic or functional damage[2]. The most important functions to be preserved during tumor therapy are articulation, phonation, and masticatory and swallowing functions [8]. An interdisciplinary therapeutic plan should be drawn up and carried out according to the current guidelines by an experienced tumor board, which may consist of surgeons from maxillofacial and oral specialties, a throat, nose and ear medicine physician, oncologists, radiotherapy, pathology, and neuro- or plastic- professionals [2,8].

2.2. Surgical resection

2.2.1. Background

For curative treatment of the tongues squamous cell carcinoma (SCC), surgical removal with negative margins is crucial. This approach involves fully excising the primary tumor, ensuring no cancer cells remain at the resection site. Residual cancer cells characterize a resection with positive surgical margins and are related to a poor clinical outcome due to an increased risk for local cancer relapse [25-27].

The radical resection of cancer of the tongue may result in defects of the tongue muscle, with variations depending on the size of the primary tumor. The resulting defects may negatively impact appearance and function of the tongue and impact the living quality of the affected patients [27]. The main aim of the interdisciplinary tumor board is to produce a treatment plan for corresponding patients, which involves a resection followed by a tongue reconstruction to improve the quality of life of the patient by maximizing the recovery of the function of the tongue [17]. The currently available scientific evidence provides no consensus on the exact approach of how tongue defects should be repaired after radical surgery. Most authors describe the selection of different tissue flaps according to the characteristics of the defect. These include location, size, and surrounding tissue defects [17,25].

According to the treatment recommendations of the AJCC, surgical tumor resection is generally the preferred treatment of early stage (pT1-2, N0) SCC of the tongue [22]. Depending on certain co-factors an adjuvant radiotherapy may be performed. A combination of surgical resection and adjuvant radiotherapy is mostly chosen in cases where the invasion of perineural or lymphovascular structures, positive/close margins, or node positivity is observed. These co-factors are often detected in the postoperative permanent pathology report [15,28-30].

When a tongue defect caused by surgery cannot heal on its own, reconstruction may be carried out using either regional or free flaps. The choice of reconstruction technique and flap origin is influenced by several factors, such as the precise location, the defect's size, the type of tissue being replaced, and the institutional guidelines [2,8].

2.2.2. Neck dissection

Alongside the removal of the primary tumor by surgical intervention, a neck dissection could be conducted. This decision is mostly dependent on the TNM Classification of the cancer [8]. Next to the dimensions of the tumor within preoperative imaging procedures, lymph nodes of the neck are also classified as being either inconspicuous, suspect or highly suspected of tumor infiltration. Between 20-40% of lymph nodes that presented themselves as being inconspicuous within imaging data, contained histological occult recurrences of the cancer [8,31]. A DOI greater than 4mm is often in association with cervical lymphnode metastases on the ipsilateral side [8,31]. An elective neck dissection is performed if the lymph nodes appear to be clinically inconspicuous (at cN0-), whilst a curative neck dissection is the chosen method if at least one lymph node is suspected to be afflicted by tumor metastasis [8,32].

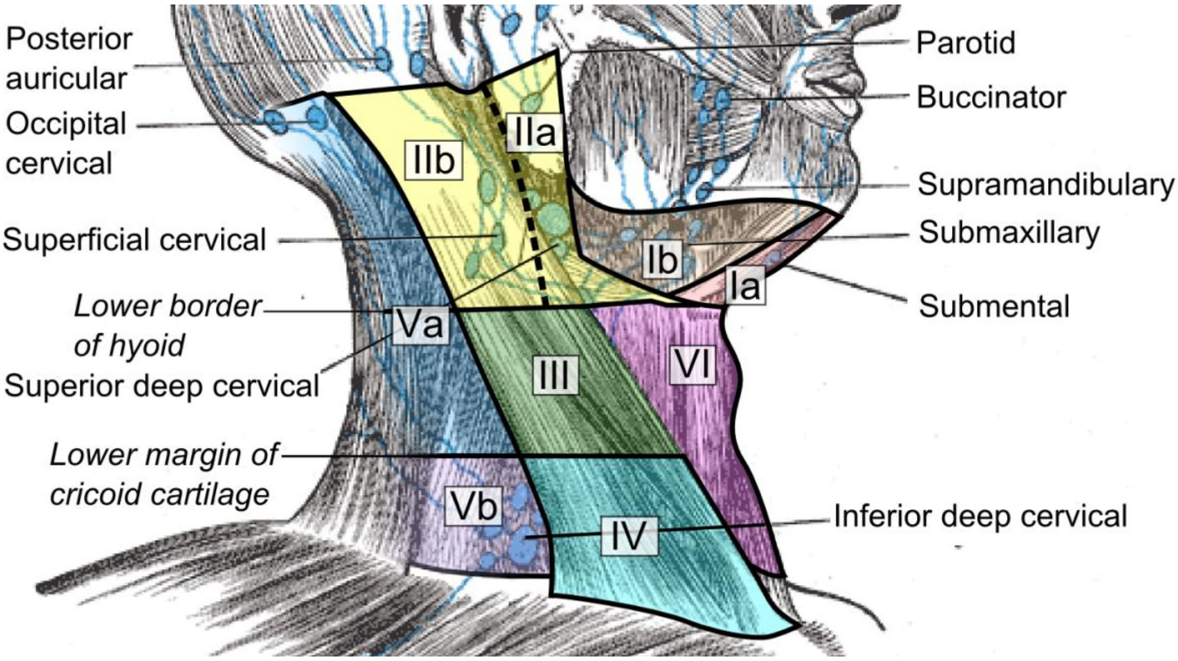


Figure 3: Cervical lymph nodes and levels (Creative commons license, [33] 43).

Neck dissection modifications are classified into several groups. **Figure 3** summarizes these groups and distinguishes between the levels shown in **Figure 4** [32,34].

Neck dissection modification	Clearance levels	Further structures
Radical neck dissection	Levels I-V	Additionally with clearance of the accessorius nerve, jugular vein and sternocleidomastoid muscle[32,34]
Modified radical neck dissection	Levels I-V	Preservation of one or more non-lymphoid structure [32,34]
Selective neck dissection	Fewer levels than I-V	Usually clearance of levels I-II
Extended neck dissection	Additional lymph node groups or non-lymphoid structures [32,34]	

Figure 4: Summary of Neck dissection modifications (based on [32,34]).

Due to the potential presence of hidden metastasis in apparently normal neck examination results (cN0), it is necessary to consider prophylactic neck lymph node dissection. However, there is currently no established risk threshold for this procedure, as no randomized studies have provided definitive guidance. As a result, it is not advisable to rule out an elective neck dissection in carcinomas within the oral cavity [35,36].
A substantial amount of evidence exists regarding the correct levels of the neck that need to be removed during an elective neck dissection in cases where obvious lymph node involvement signs are absent. In the context carcinomas of the oral cavity, various studies

have established that metastasis primarily occurs in levels I-III, whilst only 1% account for the involvement of level V [37,38].

In SCC of the tongue specifically, metastasis occurred into level IV more frequently, indicating an additional clearance of this level in tongue carcinomas [39]. In cases where the neck appears normal upon clinical examination, the likelihood of level IIB being affected is depending on the primary tumor location. Tongue carcinomas are almost always responsible of cases where level IIB is implicated, whilst elsewhere localized primary tumors rarely affect this level [40,41]. Thus, the Clearance of Level IIB infiltration is highly recommended for cases of tongue carcinomas, whereas cases of oral floor carcinomas without evidence of relevant lymph node infiltration must be carefully considered [42]. If the position of the primary tumor is either within the floor of the mouth or near the midline, the probability of metastasis to the contralateral side is increased [43,44]. Cases of selective neck dissections (levels I-III), during which the pathological analysis of the specimen reveals positive tumor infiltration, are extended subsequently to levels IV and V. Adjuvant radiotherapy may also be recommended in some cases [43,45].

2.2.3. Removal of the tumor

The act of swallowing and articulation heavily relies on the base of the tongue safeguarding the entrance of the larynx. Therefore, subsequent defects which occur after surgical resection of tongue carcinomas can lead to functional impairments. The extent and nature of these deficits are mainly determined by three factors: location of tumor defect, size of tumor defect but also the method of reconstruction [17,46]. The extent of functional impairments generally increases with a larger resection size. Specifically, in the case of the tongue, the loss of muscle volume carries greater functional implications than mucosal loss [43]. If the resection of the cancer leads to partial or total loss of the base or oral part of the tongue, microsurgical reconstruction procedures are therefore necessary to avoid extensive functional impairments. A reduction in tongue volume by 50% without appropriate reconstruction can result in significant functional issues [43,45,47].

Several complications and risks are associated with this surgery including a scarring tongue fixation with subsequent restrictions in speech, swallowing and chewing. Sensory defects within in coverage areas of the lingual and mental nerves, as well as wound dehiscence with secondary healing [45]. Further postoperative risks my include bleeding, hematoma, and oedema formation at the tongue base and laryngeal entrance, which could lead to the necessity of a tracheostoma [48].

A transoral approach was most frequently used as the surgical technique within T1 and T2 tumors [48]. After appropriate general anesthesia and a nasotracheal intubation, the areas of interest are presented using relevant surgical instruments. The first step includes an exposition, whereby the tongue is pulled forward by appropriate threads [48,49]. The second step involves the marking of the section to be resurrected, whereby a minimum of one centimeter distance from the tumor must always be adhered to. Using more pulling threads, the soft tissue can be expanded and marked precisely [48-50]. Once the marking is completed, the buccal side can carefully dissected. The tumor resection takes place from medial, whilst macroscopically controlling the incision. Smaller vessels are coagulated bipolar whilst bypassing where possible. The specimen should ideally be harvested in one piece. Reconstruction for smaller defects may be performed by forming a tongue flap and uniting it with the appropriate gingival flap [48,50]. Since this technique often results in a scarred tongue fixation, covering the defect with a microvascular re-anastomosed free graft, such as an RFFF, is recommended as an alternative [48].

2.2.4. Reconstruction of the tongue

The current literature has not agreed on a uniform consensus on how tongue defects after radical surgery should be reconstructed. Most authors recommend an analysis of size and location of the defect, combined with further soft and hard tissue involvements. The selection of the suitable reconstruction technique should be made according to this analysis, whilst keeping the functional maintenance of the tongue at focus [25]

There may be various reasons of functional restrictions after tongue resection such as insufficient structure of the remaining muscle, loss of mass, nerval damage scarring and fibrosis [51]. For this reason, the chosen restoration should focus on sustaining full mobility of the tongue for articulation, speech, mastication and swallowing to be restored. Thus, selecting the suitable reconstruction technique is crucial to accomplish these objectives [52]. Various approaches such as primary and secondary closure, skin graft, and tongue reconstruction using a regional or free flap. A specific amount of tongue mass is required to transport the food bolus along the oropharynx into the direction of the hypopharynx, whilst using the palate as an abutment. Many speech and correct pronunciation abilities are moreover dependent on the flexible interaction between tongue, palate, and alveolar processes [50,52-54].
Smaller tongue defects may be successfully taken care of by primary or secondary intention. Whilst these are not sufficient in restoring loss of tongue volume, regional or free microvascular reconstruction is required to replace any mass lost in the surgical tumor removal [53,54].

A large assortment of flaps have been described for the reconstruction of the tongue, as summarized in **Figure 5**[2]. These include the flaps such as the pectoralis major myocutaneous, nasolabial island, trapezius musculocutaneous, infrahyoid myofasciocutaneous, pedicled submental island, pedicled latissimus dorsi, tongue base island advancement, islanded facial artery musculomucosal, the myomucosal buccinator and the infrahyoid myofascial [2,53,55-59]. Fundamental influences for the selection of the type of flap depend on constitution of donor tissue, as well as the previously mentioned tongue defect size. If the vascular supply of the chosen locoregional flap is compromised due to for instance a previous neck dissection, the more advanced microvascular free flap should be preferred for reconstruction [53].

Over the past decades, surgical experiences with microvascular transplantations have advanced much further. As a result of this, the success rates of free flap transfers have risen to 94% - 96% [60]. Since these relatively high success rates allow reliable reconstructions of complex defects replacing increasingly wide volumes, microsurgical free flaps have established themselves as the standard for reconstruction of the tongue [60-63]. The ideal flap choice takes various factors into consideration. These factors include the morbidity of donor site, elasticity of flap tissue, defect size and geometry, other structures requiring reconstruction, as well as nerve development of the motor or sensory neo-tongue [64]. A range of free flap options have been described by various authors as displayed on **Figure 5**, such as the radial forearm free flap (RFFF), latissimus dorsi flap, ulnar forearm flap, lateral arm flap, trapezius island flap, rectus abdominis muscle or myocutaneous flap, tensor fasciae latae flap, and gracilis, fibula, scapula, and iliac crest flaps [2,65-69].

Local and locoregional flaps	**Free flaps**
• pectoralis major myocutaneous • trapezius musculocutaneous • pedicled submental island • pedicled latissimus dorsi • tongue base island advancement • infrahyoid myofasciocutaneous • islanded facial artery musculomucosal • nasolabial island • myomucosal buccinator • infrahyoid myofascial	• radial forearm free (RFFF) • ulnar forearm • lateral arm • rectus abdominis muscle or myocutaneous • latissimus dorsi • trapezius island • tensor fasciae latae • gracilis, fibula, scapula, and iliac crest

Figure 5: Summary of most frequently used free, local and locoregional flaps [2,53,55-59,65-69].

(1) Radial forearm free flap

When the primary goal of reconstruction is tongue mobility, the most commonly used microvascular flap for restoration is the RFFF [2,70,71]. Even when taking various donor site factors into consideration, including the strength of pinching and gripping, which lead to potential functional loss in the arm, or the need for coverage using a skin graft, the radial forearm free flap (RFFF) still surpasses other free flaps in terms of functionality [2,71,72].
Originally the RFFF was known as the "Chinese Flap", where it was initially described in 1981 by Yang et al [73]. It supplies a consistent anatomy, a lengthy vascular pedicle that is flexible, as well as an extensive capacity for microvascular anastomosis, also allowing high potential for reinnervation [2,25,53]. These characteristics justify why the RFFF is also referred to as the "Work-horse" of reconstructive surgery [74].

Performing an intraoperative Allen test when harvesting the RFFF, ensures proper infusion of the donor forearm by the ulnar artery after the RFFF cubicle is lifted [75]. According to the authors Cai and Mühlbauer, the RFFF shape is marked according to defect size and prepared with the cephalic vein in central position. The initial cut along the marked position should reach the surface of the deep fascia superficially and involves lifting the myomembranous surface from distally to proximally. Once the cephalic vein is identified, as much as possible subcutaneous connective tissue containing communication pathways of the cephalic vein to the preserved flap. Special caution should be taken safeguarding the aponeurosis, which contains the microvascular connections of the radial and carpal flexor so that the radial artery and the flap are protected [72,75]. An anterograde dissection should be performed for the radial artery and perforating vessels in between the veins. The blood supply of the flap should remain active in the donor region until the recipient area is ready for the transplantation. The removal of the flap should be performed gradually, whilst cut off and ligation of the cephalic vein and the radial artery may be conducted distally of the flap [75]. To ensure proper flap reattachment in the donor area, a dissection of the pedicle at the cubital fossa should be performed whilst preserving subcutaneous tissue in the surrounding area of the vein. Determination of the pedicles exact position is conducted using the vascular pedicle length. This procedure should be done whilst preserving the median nerve. Finally, the wound must be properly disinfected. A pressure drainage tube may also be inserted [72,75]. Depending on the extent of the defect, a secondary forearm coverage may be performed using for instance an abdominal skin graft [76]. Attachment of the RFF may be performed on various recipient vessels such as facial arteries or veins, superior thyroid arteries and external jugular veins [77].

The survival rate of the RFFF may also be influenced by proper choice of recipient neck vessels and its venous drainage system for microvascular anastomosis [49].
When analyzing various venous outflow patterns that employed either a single or dual venous anastomoses, it was observed that the use of dual anastomoses resulted in a significantly reduced occurrence of venous insufficiency. These findings suggest that utilizing two separate venous drainage systems leads to improved outcomes [49,78].
When choosing the recipient vessels, several factors should be considered. These include characteristics of the cancer such as neck dissection type and location, but also patient age, risk factors including smoking and previous radiation therapy and health conditions affecting vascular constitution such as diabetes [60,77,79-81].
Possible recipient arteries showing good clinical results include several the superior artery of the thyroid, which is the most commonly used recipient. But also external artery branches of the carotid have shown good results. Furthermore, good clinical outcome has been established for facial, lingual, superficial temporal, transverse cervical arteries or hypoglossal arteries. The external carotid artery itself may also be used as an end-to-side anastomosis [66,77]. Although the superior thyroid artery can be dissected and positioned during neck dissection, complications may be encountered during micro-anastomosis due to the occurrence of small-diameter vessels. These vessels provide a diameter smaller than <1.5 and should be carefully considered during recipient vessel selection [77,82].

When considering possibilities for venous anastomoses, different options include the internal jugular vein as well as its branches, the facial, lingual, superior thyroidal, superficial temporal, hypoglossal veins. Additional veins may include the anterior and external jugular, and certain cervical veins [77,83,84]. Good clinical survival rates have been published for venous anastomoses, which involve the recipient being the internal jugular vein. It is possible to connect even more than one anastomosis due to its stable anatomy and many easy to access side branches [84]. Slower flow rates and smaller anatomical features have been associated with the external jugular vein. It has shown to be connected to a higher risk of insufficiency due to easier venous compression depending on the patient's position [77] (86).

It has been shown that radiation therapy in the patients' medical history is associated with somewhat deleterious neck vessels. The blockage of vessels may be caused by specific anatomical changes of the vessels followed by the effects of radiation. These may involve endothelial damage, microthrombus formation and fibrin deposits [85]. These structural changes of vessels are directly related to the timeframe between surgery and radiation, as well as the fractions and total radiation dosage [85,86]. Roughly 60 Gy has been observed as the smallest dose of radiation to influence neck vessels [85,86]. Some authors occasionally describe the

occurrence of a “vessel-depleted neck”. This condition describes a patient case, whereby it is not possible to use proper vessels for micro-anastomosis despite the presence of absence of an earlier performed neck dissection. A systematic review recommends the utilization of contralateral neck vessels for these cases. Alternatively, the superficial temporal vein from the ipsilateral side and lastly the transverse cervical vessels may be substituted [87].
Since the success of the flap and thus the tongue reconstruction is greatly dependent on the selection of the recipient vessels, proper preoperative planning is indispensable for flap survival. Individual patient risk factors, such as previous neck dissections or radiation therapies should be included in the assessment [88].

(2) Ulnar forearm free flap

The UFFF (ulnar forearm free flap) is like the RFFF extracted from the forearm. Both these flaps share many characteristics, which make them suitable for reconstruction of soft tissue within the oral cavity [55-59]. RFFF extraction includes the radial artery dissection, which serves as the main vascular supply of the hand and often requires an additional vein graft after lifting the flap to ensure proper vascular supply of the hand [89]. Extracting the ulnar artery does not necessitate reconstruction with an additional vein graft, thus presenting as an excellent alternative to the RFFF. In addition to the myocutaneous ulnar artery forearm flap, parts of the ulnar bone may also be harvested [89,90].

2.2.5. Postoperative Flap volume

To account for the commonly observed reduction in volume of free flaps after surgery, a slightly larger amount of tissue is taken from the donor site to compensate this post-operative shrinkage. [91-93]. Several factors can affect the volumetric changes of a free flap, including muscle atrophy in muscular flaps caused by loss of nerve supply, adjuvant radiotherapy [94], ischemia [95,96] , as well as hematoma, edema and inflammation after surgery [51,97] . Moreover, the chosen recipient vessels as well as their quality may further have an effect on the flap shrinkage [85].

2.3. Imaging methods

The most frequently utilized imaging methods to aid classification of the tumor within the TNM System in terms of primary tumor, lymph invasion and recurrences include dental panoramic

imaging, CT and MRI. If up to date dental panoramic images were taken during dental check-ups and treatments, these should also be made available by the dentist to aid proper diagnosis. Whilst a CT is often used to evaluate the bone invasion extension caused by the tumor, MRI images provide more detail on soft tissue invasion [98].
To track tumor recurrences, a contrast-enhanced CT is the first choice used [8]. A combination of various methods may be chosen to complement each other and provide answers to specific clinical questions. Depending on the overall health of the patient, the imaging method must also be amended accordingly. The MRI tube requires more compliance by the patient, whereby lying down still for a longer amount of time is crucial for high quality imaging data. Depending on the area to be examined, the duration of a CT may average between ten to thirty minutes. On the other hand, the duration of an MRI may vary from fifteen up to ninety minutes. Although there is no radiation being exerted on the patient during an MRI, the CT is still known as the workhorse [99].

2.3.1. CT

CT images are obtained by the conversion of mobile electrons into X-ray photons. These photons are produced by an X-ray machine and passed through an object at differing angles through 360 degrees. They are then converted back into electrons, whilst measuring these X-ray photons. Using a formular that is based on the concept of the number of X-rays passing through a specific object being inversely proportional to density of that object, two-dimensional images are produced. A computer processor combines many slices of two-dimensional images to produce three-dimensional objects. Since the human body consists of many parts with various densities, an image on a screen may be produced.
The CT is currently the most frequently utilized imaging modality amongst all medical indication groups [100]. It is used for patients suffering from oral tongue cancer preoperatively, to classify the degree of invasion and identify possible extension towards the bones of the jaw. Mild and subtle enhancements are generally shown for SCC. Modern multidetector scanner only take a few minutes to obtain CT imaging of the oral cavity. The raw imaging data may be used for reconstruction of the coronal and sagittal axis. When evaluating hard tissue such as the mandible, the CT is the most superior method to analyze cortical bone invasion [100]. Limitations within evaluations of oral cavity tumors, arise due to the beam hardening artefacts from metallic dental works within the oral cavity. Metallic artefacts from dental restorations more often mask the surrounding anatomy due to displaying a more disturbing signal on an CT scan than the artefacts created during an MRI scan[101].
CBCT (cone beam computed tomography) offers a variation of the traditional CT with a lower radiation dose and at lower costs. Whilst initially CBCT examined smaller volumes during the

sectioning procedure than a standard CT, it was originally limited to diagnostics within the dental area. Further technical developments have allowed larger volumes to be represented, thus justifying the use of CBCT in higher volumes such as for instance within temporal bone imaging [102,103]. Due to a lot of imaging noises the CBCT is not suitable for soft tissue diagnosis [104].

2.3.2. MRI

MRI uses a strong magnetic field to align randomly orientated protons in an object. Specific sequences of rapidly repeating radiofrequency pulses are produced by the MRI scanner and cause an ‘excitation’ and ‘resonance’ of the protons [105]. The removal of the exerted radiofrequency pulse causes the protons to realign with the magnetic field and release a radiofrequency signal, which can be transformed into an image by the processor. Within MRI, two types of signals may be detected depending on the speed of proton realignment or dephasing. The T1 signal considers how fast the protons realign with the magnetic field and show a greater T1 signal, the faster the protons realign. This pattern is characteristic for fat tissue, thus producing high T1 signal within fatty tissues of the body. The T2 signal considers how fast the protons dephase and show greater T2 signal, the slower the dephasing takes. Since protons in water dephase slowly, a high T2 signal is characteristic for water in body tissue [106].

Providing the subject is able to remain still, without exerting any movement including swallowing over the required period, an MRI scan displays more precise differentiation of the tumor from surrounding muscle tissue. Specifically for oral tongue cancer patients, MRI provides a highly reliable method to diagnose the extension within the complexity of the tongue musculature [105,106]. This evaluation may otherwise be problematic on mere clinical examinations of patients. On T1 weighted images, the SCC is isointense to muscle and tends to show a high T2 signal, where a mild to moderate homogeneous enhancement is observed. Due to the characteristics of protons within soft tissue, an MRI can illustrate tumor/muscle interface and differentiate potential peri-neural spread of the tumor. To obtain an adequate MRI within the cavity of the mouth, an average time of 30 minutes may be expected. Additional imaging data of the neck region may require further 30 minutes. MRI may be rendered non diagnostic if sudden movements such as swallowing are carried out during the imaging period. This may represent itself as a limitation for patients with bulky tumors with secretion, causing more frequent swallowing reflexes [105,106].

2.4. Volumetric analysis

2.4.1. ITK SNAP

The standard for the level of information required from medical imaging, rises increasingly. Due to constant further developments, the amount of imaging data being processed currently takes its peak. Processing large volumes of data manually, requires more time and effort by the physician. Automatic and semi-automatic segmentation processes therefore gain increasingly more popularity within this field. The open-source software ITK-SNAP[1] (Penn Image Computing and Science Laboratory) was initially 'developed and subsequently certified, for morphometric and volumetric analysis of the nucleus of the brain'[1]. This interactive tool was developed in the early 2000's and supports the common medical file formats such as NIFTII And DICOM [1,107]. Interactive features within the software allow the navigation through various dimensions. Sagittal, coronal, and axial slices are merged to display an image in all three dimensions[2]. The three-dimensional view of images is used for image navigation or segmentation of tissues and structures, as well as volumetric calculations in cubic millimetres. All images are acquired with voxels of equal size in each plane (isotropic spatial resolution)[2], to ensure unity across multiple imaging files. Within each thumbnail of a specific view, a 'crosshair line' is used for orientation and positioning. The intersection of this cross shows the same position amongst all views [107]

There are three different visualization options for multiple imaging modalities: Firstly, a tiled layout. Within this option coronal, axial and sagittal slices may all display identical slices through all loaded images. Secondly, thumbnails with one image are focused by occupying most of the window and the other modalities are shown as small thumbnails. By clicking on these modalities, it is possible to switch the focus to a different image. And thirdly, selected modalities showing partially opaque overlays on top of other images.

Via manual, automatic or semi-automatic segmentation the desired structures can be identified. Semi-automatic segmentation is most frequently used for tissue delineation as the computerized repeatability using an automatic detection process combined with a manual correction in case of imaging inaccuracies, provides a combination of advantages of automatic and manual segmentation.

3. Material and Methods

3.1. Data summary

This pilot study considers data of a sum of 52 datasets, accounting for 26 patients (19 males, 7 females) being treated at the University clinic of Cologne, who fulfilled the appropriate criteria to be relevant for this retrospective study [2]. The selection of suitable candidates was carried out by considering the relevant criteria in ***Figure 6.***

Study inclusion	Study exclusion
Operation date within the period of: 01.01.2009 – 01.06.2021	
Pre- and post-operative treatment within the University clinic of Cologne (including in-House imaging via MRT or CT)	Pre- or post-operative Imaging not within the University clinic of Cologne
ICD10 Diagnosis: C01, C02, C04, C06, C14	
TNM Classification of T1 and T2 with surgical treatment plan	TNM Classifications of T3 or T4 with no surgical treatment plan
Flap from the radial forearm region	Flap from other regions
Imaging data without artefacts in relevant areas	Imaging data with artefacts in relevant area
RFFF survival	RFFF Failure

Figure 6: Standard criteria necessary for study inclusion and exclusion

ORBIS is the internal data and information management system of the University hospital of Cologne and was used to extrapolate relevant Patient data. Using the study inclusion and exclusion criteria, a search was conducted displaying all patients admitted to the University hospital of Cologne within the timeframe of 01.01.2009 – 01.06.2021, with a confirmed diagnosis of oral tongue cancer (ICD10: C01, C02, C04, C06, C14)[2]. The displayed results of 570 possible patients were then filtered using surgical plans and tumor board reports to include all patients who had undergone surgery within their treatment plan.

All relevant patient and surgical reports were carefully analyzed and narrowed the initial pool of 105 patients down to 70 patients, who were supplied with an RFFF after resection of the tumor[2].

The medical imaging software of the University Clinic of Cologne was utilized to filter the remaining datasets based on pre- and post-surgical (MRI or CT) diagnostic imaging conducted by the clinic's radiology department. From the initially selected patients, 42 subjects had both pre- and post-operative imaging conducted at the institution. 16 datasets were excluded due to artifacts in the images, post-surgical complications such as hematomas or fistulas, or failure of the flap that necessitated early removal. This selection resulted in a final number of 26 cases. Clinical diagnostics, including CT or MRI scans, were carried out within the department of radiology within University Clinic of Cologne[2].

3.1.1. Statistical analysis

The datasets were originally recorded using Excel and subsequently analyzed with IBM SPSS Statistics for MAC (version 28.0.1.1(14); IBM, Armonk, NY). A frequency and mode evaluation was carried out for categorical variables. The Mann-Whitney-U test was employed to assess patterns of distribution across gender and age for independent variables. Numerical variables, including tumor and flap volumes, were analyzed by calculating the mean, median, standard deviation, and percentiles. An assessment for normality of distribution revealed one outlier in the tumor volume data. After verifying the plausibility of this elevated value in relation to the patient's disease extent, the outlier was retained, resulting in a non-normal distribution. Consequently, the Spearman correlation test was applied to evaluate the null hypothesis. To ensure accuracy in repeated measurements of tumor and flap volumes, the Friedman test was used. Regression analyses were performed to explore correlations among non-normally distributed variables. Statistical significance was determined at a 95% confidence level, with results deemed significant if $p < 0.05$[2].

3.2. Volumetric measurements

Pre- and post-operative imaging series that were relevant to the study were identified, with their DICOM datasets anonymized and subsequently exported. These datasets were then uploaded into ITK-SNAP (Penn Image Computing and Science Laboratory), an open-source software for further analysis. By removing all of the patients personal date, the imaging data was fully anonymized before volumetric quantification[2]. ITK-SNAP, which was initially developed and subsequently certified for ‘volumetric and morphometric analysis of the caudate nucleus of the brain’[1], offers interactive features within the software, which allow the navigation through various dimensions within frequently used imaging techniques such as MRI and CT. The three-dimensional view of images is used for image navigation or segmentation of tissues and structures, as well as volumetric calculations in cubic millimeters. Via manual, automatic or semi-automatic segmentation the desired structures can be identified. Semi-automatic segmentation is most frequently used for tissue delineation as the computerized repeatability using an automatic detection process combined with a manual correction in case of imaging inaccuracies, provide the most accurate results.

Within ITK-SNAP [1] the dimensions of sagittal slices, coronal slices, and axial slices were used to generate a three-dimensional image. MRI and CT scans were performed using isotropic spatial resolution, ensuring voxels were of equal size in all planes. Semi-automatic segmentation of the presurgical images delineated the tumor, and its volume was determined using ITK-SNAP in cubic millimeters. To minimize measurement errors, each segmentation was repeated three times on the same imaging dataset, following a standardized protocol to ensure consistency across three independent instances, ensuring a minimum of 48 hours of time passed in between each. To avoid manipulation of measurements due to remembrance of similar structures, an adequate time interval was kept in between the measurements. further statistical analysis was conducted using the mean values of the datasets[2].

The same standard was carried out for the patients corresponding post-operative images, by conducting semi-automatic segmentation to calculate the RFFF volume. The measurements were further validated by two surgeons with maxillo-facial specialization at isolated occurrences [2].

The Ethics Committee of the University Hospital Cologne approved this study under the Ref.: 23-1444-retro. The 1964 Helsinki declaration and its later amendments are in accordance with all procedures performed in this study[2].

4. Results

This retrospective analysis was conducted in the University Clinic of Cologne and included 105 patients, who received surgery after the diagnosis tongue cancer or floor of the mouth cancer [2]. Within the extracted dataset, 70 patients received an RFFF. Alternative grafts included the pectoralis major, latissimus or split skin. These files were filtered within the medical imaging program of the University Clinic of Cologne according to pre- as well as post-operative (CT or MRI) imaging being accessible[2]. The pre-surgical and post-surgical images were available for 42 patients in total, who had these taken within the university clinic of cologne. Of these, 16 datasets were omitted from the study due to various reasons such as imaging artefacts, bad display quality or premature removal of the flap due to transplantation failure[2]. A final selection of 26 datasets were included in this study, after application of the exclusion criteria. The age within this group started at 32 years for the youngest age at the time of the surgery and extended to a maximum age of 84 years. The subsequent mean age was 64 with a standard deviation of (± 14,9 SD). The age distribution of patients with the diagnosis oral tongue cancer, who received an RFFF is displayed on **Figure 7.**

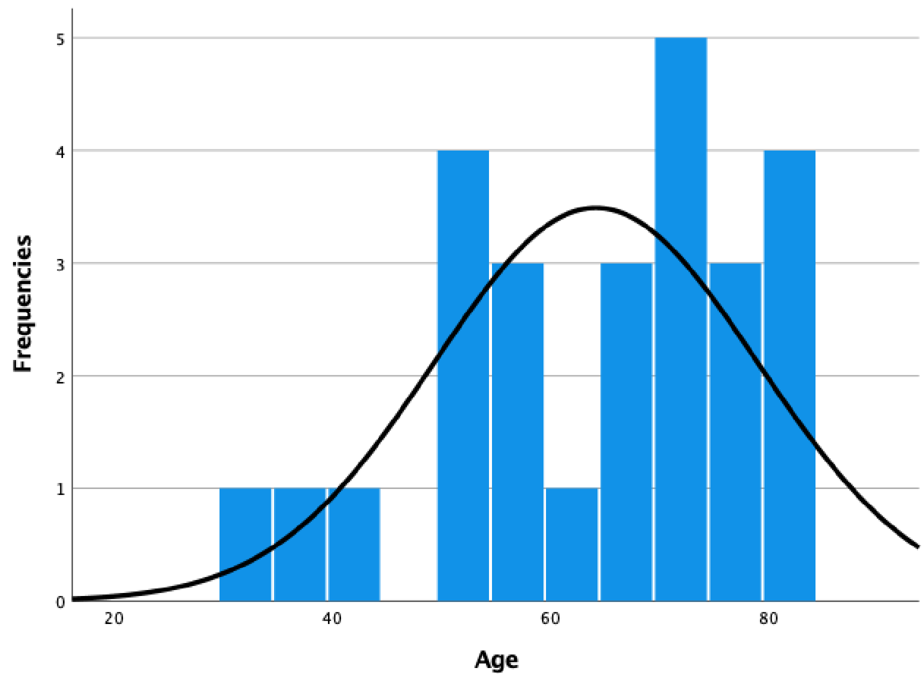


Figure 7: Age distribution of patients with the diagnosis oral tongue cancer, who received an RFFF displayed on a Histogram**.**

The analysis of the gender distribution displayed a strong tendency towards the male gender subjects. In sum, 19 subjects (73,1%) were observed to be male, whilst only 7 female subjects (26,9%) were registered[2]. The distribution of gender can be found within **Figure 8.**

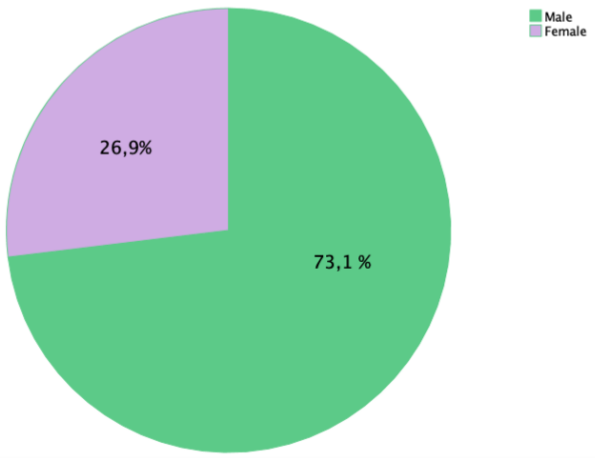


Figure 8: Pie chart displaying the distribution of gender.

Using a side-by-side boxplot the distribution of age in accordance with gender is illustrated[2] within **Figure 9**.

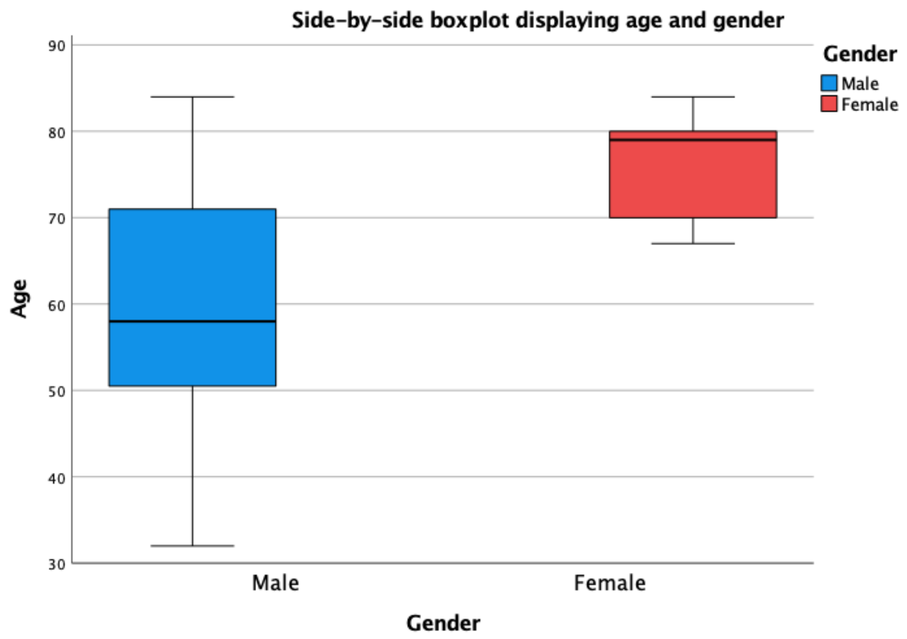


Figure 9: Side by side boxplot displaying age and gender.

To determine if there were statistically significant differences in age distribution between male and female subjects, the Mann-Whitney-U test was employed for independent samples. Assuming the null hypothesis of identical age distribution across genders, the results indicated a rejection of the null hypothesis (p = 0.015)[2]. Consequently, the study displayed a predominance of male participants, as illustrated in **Figure 10**.

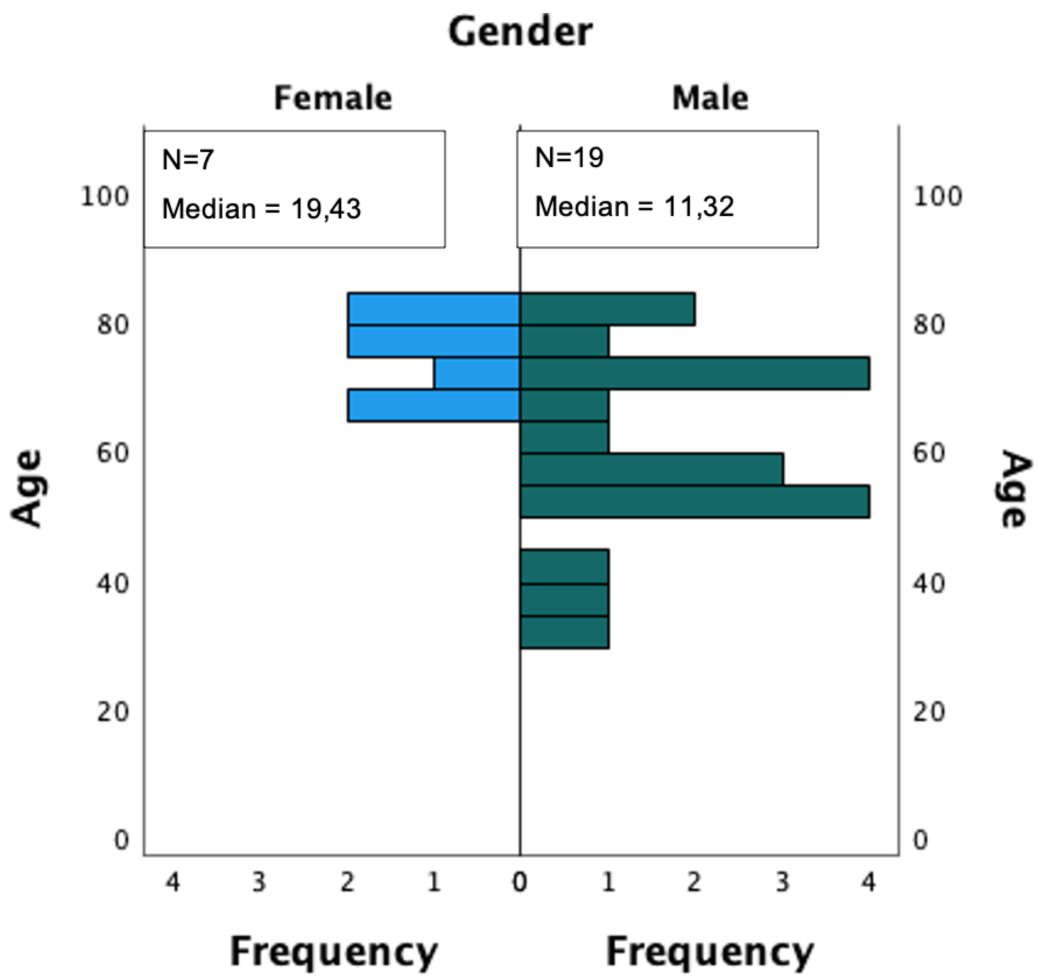


Figure 10: Age distribution of male and female.

The localization of the tumor was mostly situated within the body of the tongue for 20 (76,9%) of the subjects, whilst the remaining 6 (23,1%) were located in the floor of the mouth. The cancer originated on the right side in 17 (65,4%) cases and 9 (34,6%) times on the left side. The bar charts of **Figure 11** and **Figure 12** display these distributions graphically.

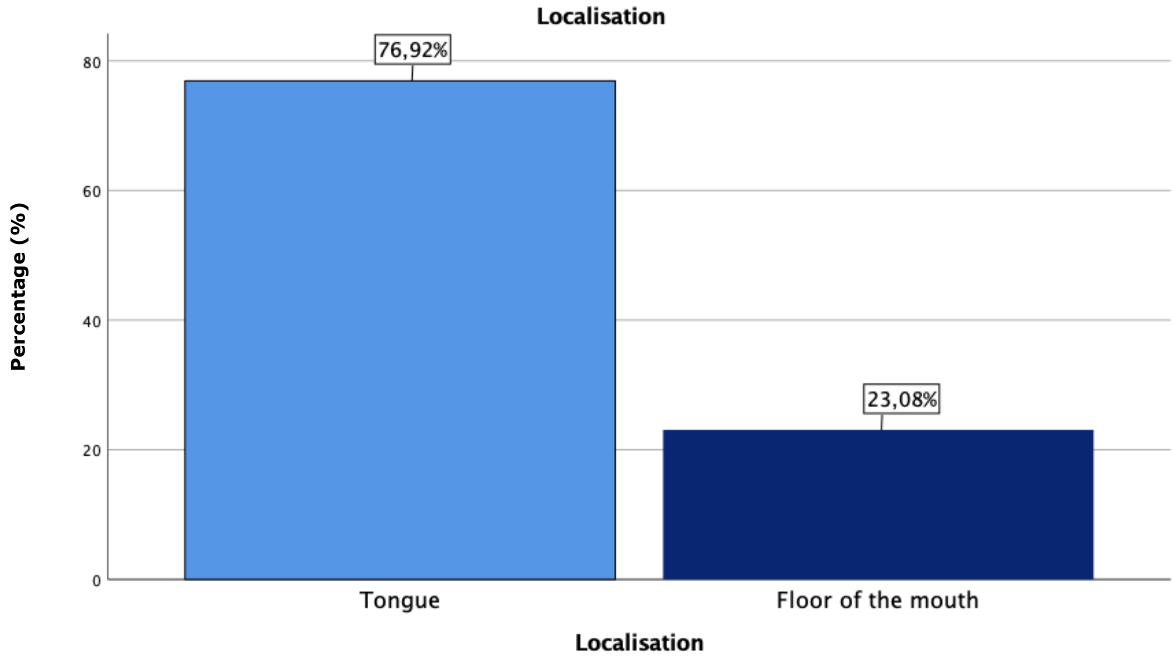


Figure 11: Localization of the tumor.

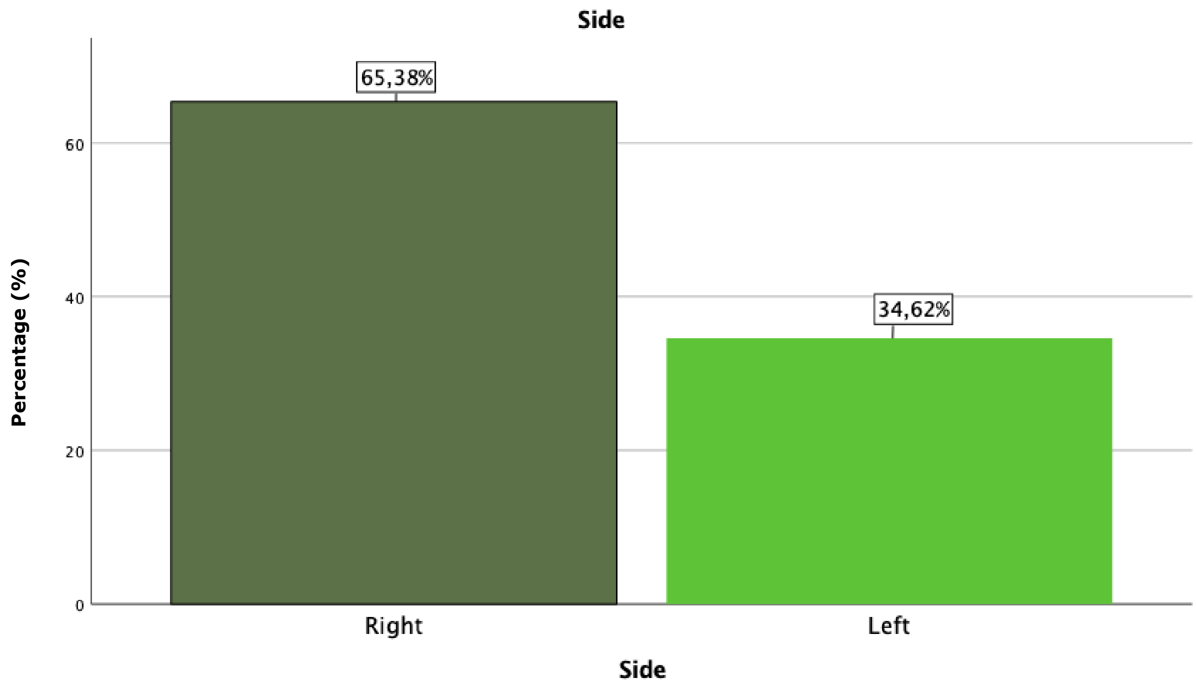


Figure 12: Side of tumor origin.

To illustrate the time interval (in months) between the scans of tumor pre-operatively and the flap post-operatively, the pie chart in **Figure 13** is used. 60% of the subjects accounted for 16 subjects in total, who were issued their post-surgical scan within 6 – 12 months after their pre-surgical scan being taken[2].

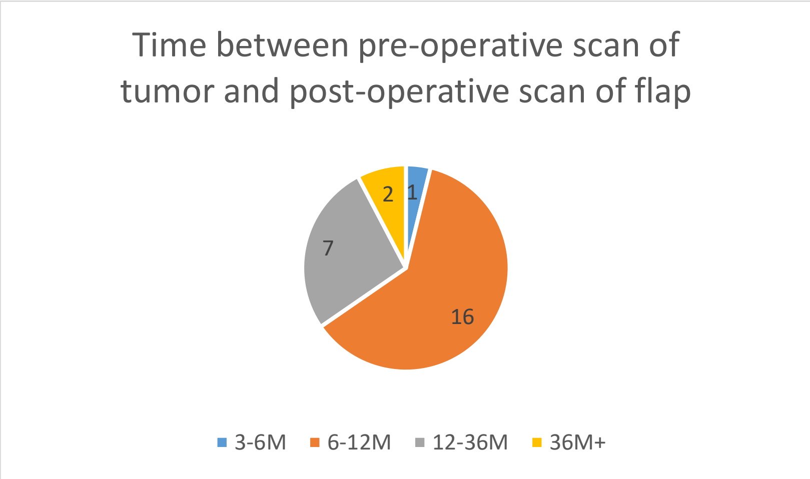


Figure 13: ‘Time between pre-operative scan of tumor and post-operative scan of flap in months (M).’ [2]

With regards to the TNM-Classification, this study included 10 subjects with T1 and 16 subjects with T2 classifications[2].

For each patient, pre-surgical imaging data was evaluated across various dimensions. The sections displaying the most distinct tumor boundaries were selected, converted to DICOM format, and evaluated using ITK-SNAP. Via semi-automatic segmentation, the initial volume of the tumor was determined before resection. To enhance accuracy, each dataset underwent three separate measurements, with a minimum gap of 24 hours between each. Furthermore, two additional clinicians independently validated the measurements to ensure reliability [2].

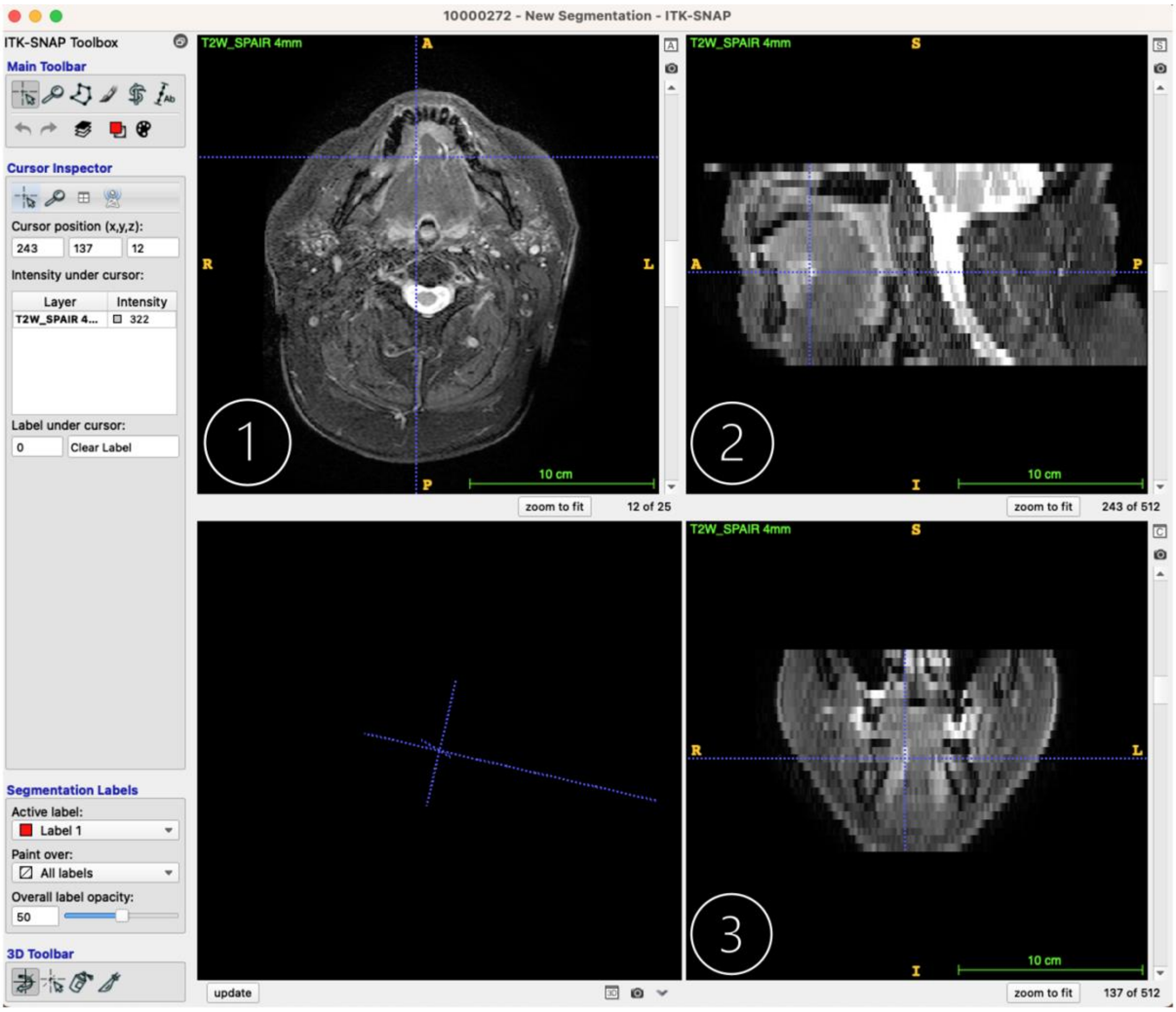


Figure 14: **'**Editorial view of a pre-operative imaging dataset on ITK-SNAP. Each window represents another plane: 1- transversal, 2- sagittal, 3- frontal.'[2]

Through semi-automatic segmentation the mass of the tumor was identified in all planes and the subsequent total volume of cancer, before surgery was estimated through the "Volumes and Statistics" tool on ITK-SNAP[2].

Volumes and Statistics - ITK-SNAP

Label Name	Voxel Count	Volume (mm3)	Intensity Mean ± SD (T2W_SPAIR 4mm)
Clear Label	6550644	6.872e+06	49.0463±82.9470
Label 1	2956	3101	185.2338±68.7037

Figure 15: Volumes and Statistics Toolbar within ITK-SNAP. "Label 1" represents the total cancer volume (mm³) marked in red.

The "active contouring" tool was used to separate the mass of the tumor from adjacent anatomical structures, thereby displaying it in seclusion. In this specific viewing mode, the extracted mass can be rotated and examined from multiple perspectives within ITK-SNAP[2].

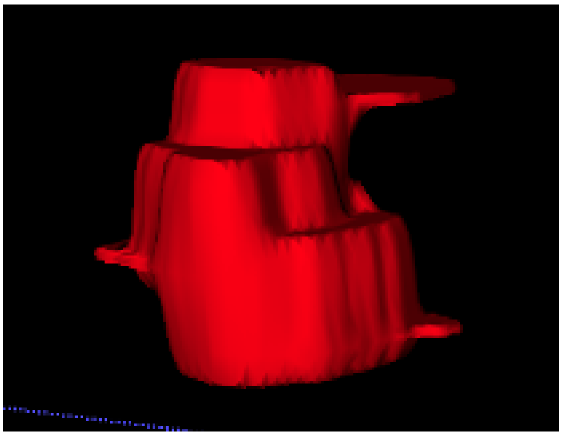


Figure 16: Snapshot of 3-Dimensional tumor representation after semi-automatic segmentation.

The calculation for maximum, minimum and mean Volume, as well as Variance and Standard deviation (SD) was conducted, after obtaining all pre-operative tumor volumes for all 26 patients[2].

		VolTumor1	VolTumor2	VolTumor3	MeanVolTu
N	Valid	26	26	26	26
	Missing	0	0	0	0
Mean		4347,96	4551,42	4606,62	4502,0008
Median		3587,50	3452,50	3875,00	3716,8350
SD		2572,668	2932,010	2829,595	2743,78291
Minimum		1496	1208	1742	1527,00
Maximum		13250	14220	15050	14173,33

Figure 17: ‘Summary of results for tumor volumes (in mm^3) prior to operation.’[2]

Figure 17 summarizes the minimum, maximum and mean tumor volumes. By determining variance and standard deviation (SD), the mean value for tumor volume resulted in a mass of 4502,00 (± 2743,78 SD) mm^3 [2].

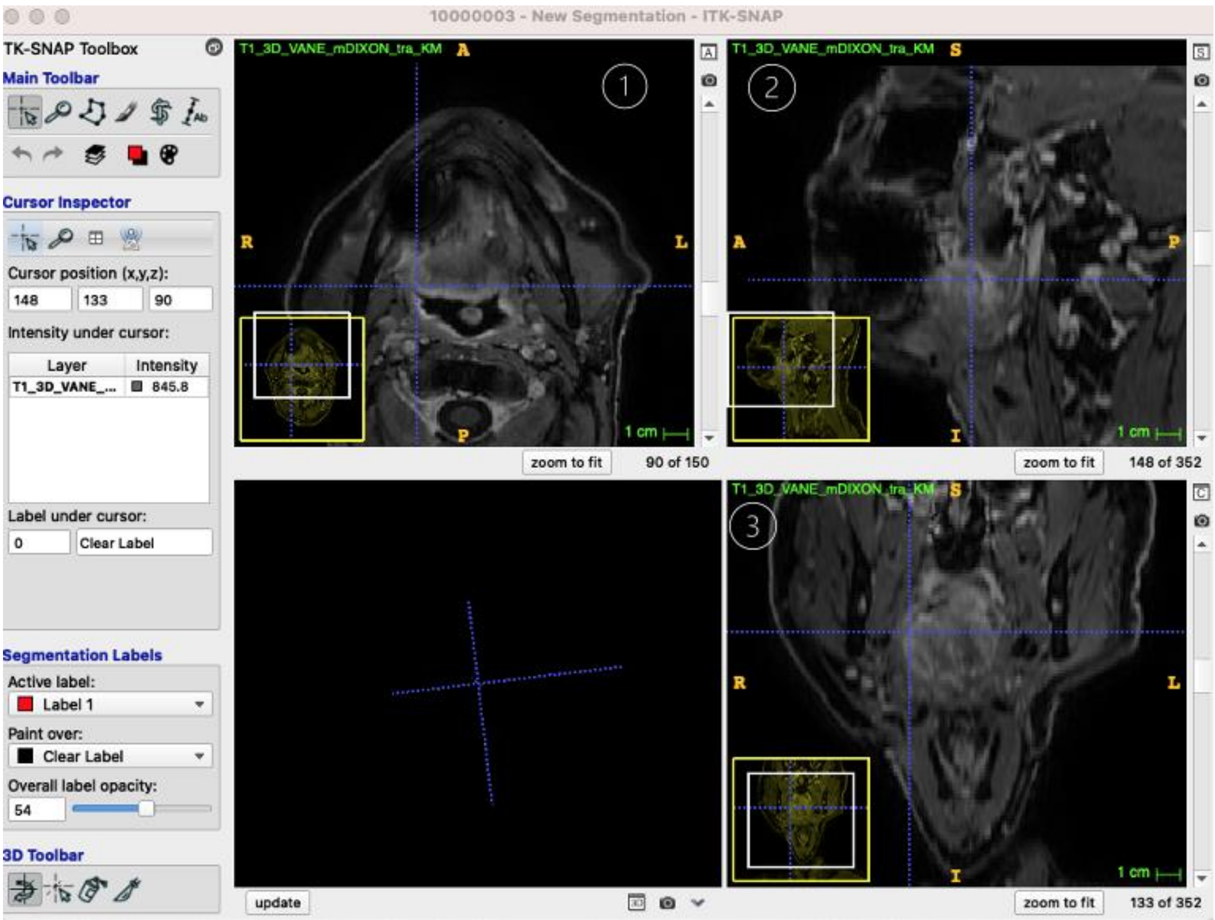
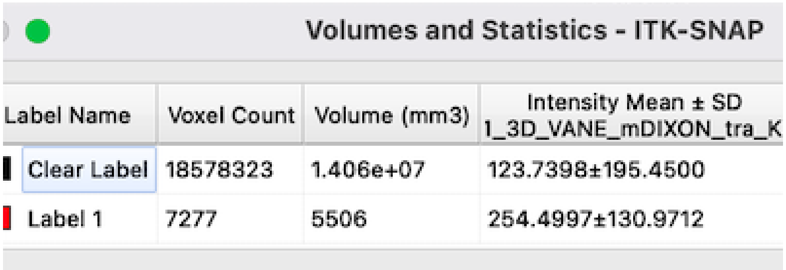


Figure 18: ‘Editorial view of a post-operative imaging dataset on ITK-SNAP. Each window represents another plane: 1- transversal, 2- sagittal, 3- frontal.’[2]

The post-operative flap volume was determined using the tool "Volumes and Statistics" on ITK-SNAP. The results were obtained by performing semi-automatic segmentation of the transplanted RFFF in an analog manner to the initial tumor volume as described above[2].


Volumes and Statistics - ITK-SNAP

Label Name	Voxel Count	Volume (mm3)	Intensity Mean ± SD 1_3D_VANE_mDIXON_tra_K
Clear Label	18578323	1.406e+07	123.7398±195.4500
Label 1	7277	5506	254.4997±130.9712

Figure 19: Volumes and Statistics Toolbar within ITK-SNAP. "Label 1" represents the total flap volume (mm^3) marked in red.

"Active contouring" on ITK-SNAP was used to extract the total volume of the RFFF in isolation from surrounding anatomical structures. In analogy to the snapshot of the tumor, the flap max also be displayed and analyzed in all three dimensions[2].

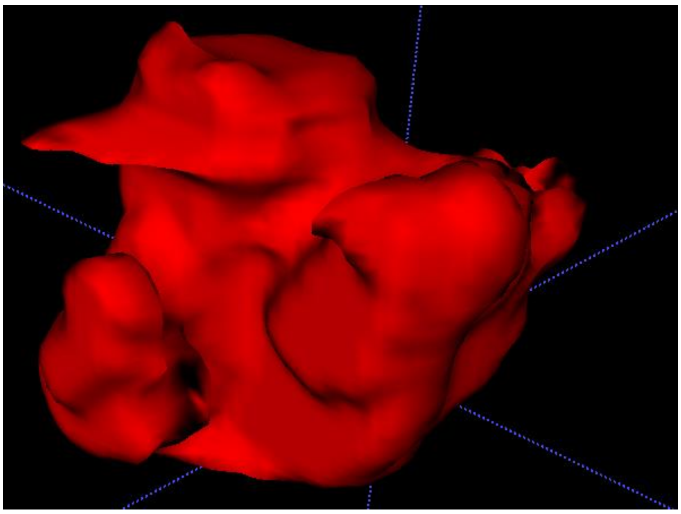


Figure 20: Snapshot of 3-Dimensional RFFF representation after semi-automatic segmentation.

The mean volume was determined, once all post-operative flap volumes were determined[2].

		VolFlap1	VolFlap2	VolFlap3	MeanVolFlap
N	Valid	26	26	26	26
	Missing	0	0	0	0
Mean		9200,31	9162,42	9214,46	9192,3981
Median		8701,00	8700,50	8953,00	8735,1700
SD		4823,667	4823,945	4635,198	4716,16564
Minimum		3086	4359	3660	3701,67
Maximum		23110	24720	24110	23980,00

Figure 21: **'**Summary of results for RFFF volumes (in mm³) after the operation.' [2]

In **Figure 21**, the values for the minimum, maximum, and mean flap volumes, accompanied by the variance and SD (standard deviation) are summarized. The analysis determined the mean flap volume to be 9192,40 mm³ with a corresponding standard deviation of ± 4716,17 mm³ [2].

To assess the validity of averaging the volumes of VolTumor1, VolTumor2, and VolTumor3, the Friedman test was in cooperated. The results indicated no significant difference between these tumor volume measurements (p=0.341). The identical statistical method was applied to confirm the consistency of using average values for VolFlap1, VolFlap2, and VolFlap3, with results displaying no significant variations among them (p=0.962). Therefore, mean values for both tumor and flap volumes were deemed suitable for subsequent correlation and regression analyses [2].

Using SPSS, a robust positive correlation of 0.769 ($p < 0.001$) was found between MeanVolTu and MeanVolFlap, indicating a direct relationship where an increase in tumor volume is associated with an increase in flap volume. To investigate if flap volume could be predicted based on tumor volume, regression analysis was conducted, treating MeanVolFlap as the dependent variable and MeanVolTu as the independent variable. The analysis suggested that variations in MeanVolTu could moderately predict changes in MeanVolFlap with a confidence level of 59.1% ($R^2 = 0.591$). Furthermore, the ANOVA test supported the statistical significance of the regression model in forecasting MeanVolTu ($p < 0.001$), confirming a reliable fit of the model to the observed data [2].

Coefficients[a]					
		Non-standardised coefficients		Standardised coefficients	
Model		Regression-coeffizient B	SD	Beta	T
1	(Constant)	3241,632	1176,309		2,756
	MeanVolTu	1,322	,224	,769	5,893

a. Dependent Variable: MeanVolFlap

Figure 22: Table summarizing coefficient values for the regression Model.

Figure 22 outlines the coefficient values within the regression tests, allowing the prediction of RFFF flap volume using the tumor volume. Using the following algorithm, the mean flap volume (MeanFlapVol0) may be forecasted:

'MeanVolFlap0 = 3241,633 + 1, 322 * MeanVolTu' [2]

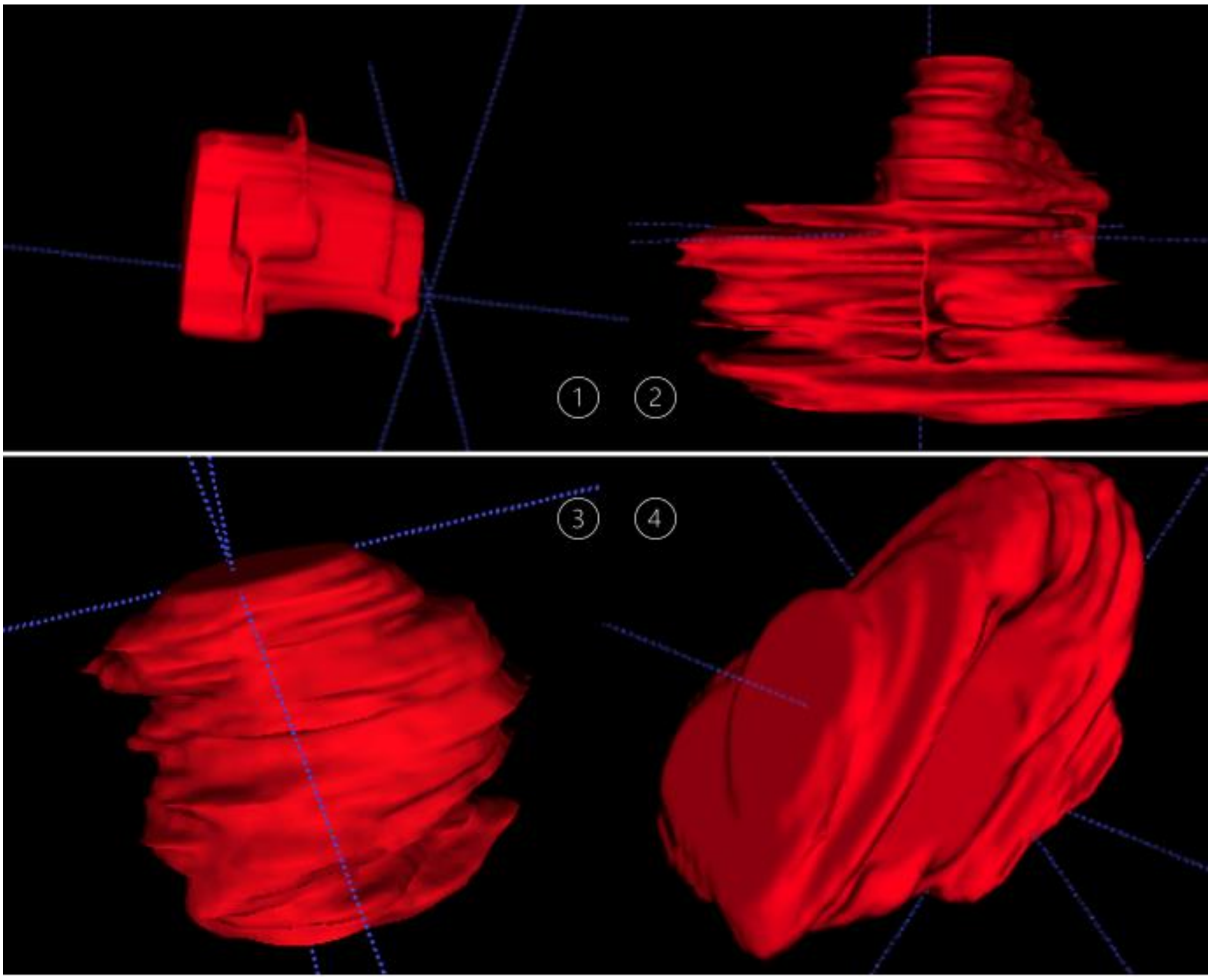


Figure 23: **'**Snapshots of segmentation images: 1- RFFF, 2 – tumor, 3 & 4 – different angles of the same RFFF.'[2]

5. Discussion

This pilot study analyzed 26 imaging datasets in sum, focusing on tumor volume prior to surgical removal and the corresponding flap volume after surgery. To enhance the reliability of these results, each CT or MRI dataset was measured on three independent occasions. Validation of these measurements was further supported by two additional maxillofacial surgeons conducting separate assessments[2]. The process involved using ITK-SNAP for semi-automatic segmentation to identify the relevant structures and calculate their volumes. Segmentation using a semi-automatic mode has been demonstrated to be an accurate and reproducible method for the quantification of tumor volume[1]. This approach has not been previously used for tumor and flap quantification of tongue cancer[2]. It has been applied to accurately quantify volumes of soft, as well as hard tissue in cases of retrobulbar hematoma[108], MRONJ (medication-related osteonecrosis of the jaw) lesions[109] and also for analyzing hemodynamics using 4D flow MRI angiographic data[110].

Although evaluation of borders within delineated structures using ITK-SNAP may show slight variations based on the individual evaluator, the semi-automatic segmentation approach significantly enhances reproducibility[1]. This specific technique benefits from the combination of precision and automated efficiency, allowing for corrections of computerized errors, such as those caused by imaging artefacts. Gau et al. demonstrated that semi-automatic segmentation achieved the best precision in quantifying resected volumes of areas within the brain whilst requiring a moderate level of human intervention, outperforming both fully automated segmentation and manual methods on ITK-SNAP[111].

As an increased sample size allows more precise and accurate conclusions, each reading was repeated three times with a minimum interval of 48 hours between each session. Allowing sufficient time between evaluations helps reduce cognitive bias by enabling the reassessment of imaging data with a fresh perspective rather than relying on memory of previous measurements[2].

The tumor volume values are influenced by a variety of factors such as patient age, the tumor's T-stage according to the TNM classification, gender, and many more clinically relevant variables [101,104,112]. Equally, flap volume is positively correlated with initial tumor volume as underlined in the findings of this study. Therefore, rather than focusing solely on individual numeric values, the cases were compared through correlation analysis. Factors that may impact this correlation include the tumor's progression rate, the interval between preoperative imaging and the surgical resection of the tumor, as well as the time gap between surgery and postoperative imaging for flap volume assessment[101].

Future research in this field would benefit from inclusion of a expert radiologists to determine initial tumor volume. Ensuring consistency in measurements by selecting a standardized layer would improve comparability, thereby minimizing discrepancies that arise from using different axes[2].

Additionally, it is important to consider the variations in the time intervals between surgery and postoperative imaging for individual cases. Factors such as patient-specific circumstances, their level of cooperation, and the scheduling availability in the relevant department can extend this waiting period. A prolonged delay between surgery and follow-up imaging may result in reduced flap volume due to postoperative flap shrinkage[97,113].

The volume of the tumor derived from pathological reports could not be directly compared with imaging data due to the nature of R0 resections, which require surgical margins to be microscopically free of tumor cells. This results in a larger resected mass volume compared to the actual tumor volume, thus causing discrepancies between pathological volume measurements and the tumor volumes calculated from imaging datasets. These safety margins are incorporated to account for uncertainties in determining the final size of resection. Conversely, unpredictable contraction of flaps leads to inconsistencies in the opposite direction, with postoperative imaging showing reduced flap volumes compared to the original resected mass. This reduction is attributed to individual healing variations, including edema reduction and the natural shrinkage of flaps used in reconstructive surgery[97].

Initially making an entrance within plastic surgery of the breast, the concept of SDM or ‘shared decision making’ plays a great role in aiding decision making by enhancing the quality of the decision, decreasing conflict and increasing satisfaction [114,115].

Patients' personal aesthetic preferences, particularly regarding the appearance of donor site scars, can significantly shape their overall perception and satisfaction with reconstructive surgery outcomes [116].

This study has detailed the time interval, measured in months, between the pre-surgical tumor imaging protocol and the post-surgical imaging protocol of the flap to enhance the clinical relevance of our findings. Providing that the follow-up duration impacts flap volume loss, future studies would benefit from implementing a standardized protocol for imaging instances. Due to the retrospective design of this feasibility study, which aimed to explore the plausibility of this approach, volumes documented in pathological reports were excluded from analysis[2].

Furthermore, radiotherapy in advanced cases of tongue cancer contribute to additional volume loss, not only of the flap but also of the tissues in the surrounding areas[117-119].

An investigation by Kim et al. examined the impact of postoperative radiation on flap volume. Their findings displayed no significant variation in flap volume between 3 and 24 months after surgery. As a result, given that all postoperative imaging for the patients in our study was performed within this same 3-month to 3-year timeframe, the influence of radiation was not included[120].

The significance of esthetic and functional outcomes when planning coverage of the primary defect occurring within the donor site is increasing further[121], with the RFFF achieving outstanding results within the past years [122]. An STSG (split-thickness skin graft) is mostly utilized to cover the primary defect. Covering defects using skin grafts in extensive surgical procedures may exhibit a failure rate as high as 28%. This coverage type is however, also associated with complications, including prolonged healing durations, exposure of flexor tendons, and potentially even additional surgeries at the donor site[123,124]. Doubtlessly the ability to predict flap size more precisely, may lead to extraction of smaller flap volumes from the donor site, thus decrease donor site morbidity. With respect to the volumetric masses influencing esthetic and functional outcomes, the justification for more research in this field is certainly available[121].

Due to the lack of direct evidence available on volumetric analysis of SCC of the tongue before surgery and the RFFF after surgery, it is not possible to draw immediate conclusions from previous studies on this specific topic. Numerous research has been conducted on different structures for volumetric quantifications using ITK-SNAP. In combination with the research available on defect coverage using an RFFF, the below outlined investigations are aimed to provide an overview of the up-to-date literature in this area[2].

The recent systematic review conducted by Ranganath et. Al. in 2022, considered subjects receiving an ALT (anterolateral thigh) or an RFF (radial forearm free) flap, whereby various factors such as aesthetic and functional, morbidity after surgery and health-related quality of life among oral tongue cancer patients was investigated[2,125]. According to the findings within this study, flap survival rates or the incidence of complications related to the flap, display no noteworthy difference[125]. ALT flaps are brought in association with a significantly reduced risk of morbidity of the donor site and higher patient satisfaction regarding donor site aesthetics. The systematic review indicates that ALT flaps offer comparable oral function and flap survival rates to RFF flaps, with the added benefit of reduced donor site morbidity. The authors further recommend that future decisions on donor site selection should consider additional factors relating to specific patient and surgical requirements not covered in this meta-analysis[2,125].

The study from Bozec et al. reported that reconstruction using the radial forearm free flap (RFFF) in combination with radical ablative surgery yielded encouraging functional and oncological outcomes in patients with oral tongue cancer. Out of the 132 patients included in their study, only three experienced RFFF failures, highlighting the technique's reliability in oral cancer reconstruction[2,112].

Younis et al. recently investigated the difference in flap shrinkage between the radial forearm free flap (RFFF) and the anterolateral thigh free flap (ALTF). Although both flaps exhibited a visible shrinkage, a significantly higher percentage of volume reduction was demonstrated by the RFFF compared to the ALTF[126]. Based on their findings, the authors recommend sizing the extraction volume of the ALTF by the factor 1.4 compared to the initial surgical defect and the RFFF by a factor of 1.5. This algorithm is particularly recommended for cases of hemiglossectomy, to accommodate for the expected shrinkage [2,126].

The comparative analysis conducted by Xu et al. used data from five studies focused on donor-site outcomes between the radial forearm free flap (RFFF) and the ulnar forearm free flap (UFFF). The complication rate at the donor site within this investigation revealed a significantly lower value for the UFFF compared to the RFFF. Based on these findings, the authors propose that the UFFF could serve as a promising alternative to the RFFF in oral tongue reconstruction. The authors emphasize the need for larger study samples with more relevant long-term follow-up data to validate these preliminary results[2,127].

Thiem et al. reported in contrast to the findings of Xu et al., that both the radial forearm free flap (RFFF) and ulnar forearm free flap (UFFF) display comparable flap survival rates and outcomes in terms of functionality, with favorable perfusion dynamics post-surgically[127,128]. In terms of functional grip and pinch strength, wound healing, or perceived impairment in daily activities (as measured by the DASH score), their investigation demonstrated no significant differences between the UFFF and the RFFF at both 4 and 24 weeks postoperatively[128]. These results suggest that both flap types may be equivalently suggested for reconstruction of the tongue by offering similar clinical outcomes [2].

The key focus in tongue reconstruction using free flaps is not only to restore the organ's mobility but also to sustain its dynamic muscle activity. The use of innervated flaps, like the infrahyoid pedicled muscle flap, provides a dual advantage: it not only fills the defect but also integrates with the surrounding tissues, promoting better functional recovery. By preserving neuromuscular integrity, rehabilitation is faster, sensory feedback is better, and control of oral functions is enhanced compared to non-innervated flaps. The replacement of resected parts of the tongue muscle using vital innervated muscle flaps maximizes the function [129].

Function and aesthetic outcomes are affected by the loss in volume of flaps may be observed for up to 3 years after the reconstruction takes place[130]. While surgical reconstruction using free flaps in oral tongue cancer surgery is conducted using a common approach, estimation of the flap volume obeys no commonly accepted, standardized protocol[106].

Numerous studies are available on volumetric calculations using semi-automatic segmentation within ITK-SNAP[2].

One study showed the use of an RFFF together with a split-thickness skin graft as less susceptible to infection in comparison to other tissue transfer methods. A smaller tissue transfer was also associated with a smaller infection rate. [131].

A retrospective analysis by Zirk et al. evaluated volumetric differences in osteolytic lesions associated with medication-related osteonecrosis of the jaw (MRONJ). The study identified the mandible as the most commonly affected site. Notably, female patients exhibited a higher incidence of lesions in the maxilla compared to their male counterparts. Using semi-automatic segmentation with ITK-SNAP for volumetric assessment, the research also revealed that male subjects had a significantly greater absolute volume of osteolysis, suggesting potential gender-related variations in MRONJ lesion characteristics [2,132].

Ritschl et al. used ITK-SNAP to conduct a comprehensive analysis of bone volume behavior in free flaps of the fibula and iliac crest. Across 113 cases, their findings indicated that both flap types maintained overall stability. Particularly, iliac crest flaps experienced a greater reduction in bone volume compared to fibula flaps. Key factors that significantly impacted bone volume included the time between surgery and follow-up CT imaging, gender, patient age, the specific reconstruction method used, and the number of fibula segments involved[101]. These results emphasize the need to account for these variables when planning bone flap reconstructions to optimize outcomes [2,101].

The larger the volume of tumor resection, the greater the required flap volume and subsequent defect and impairment created at the site of the donor. An increase of artefacts generated within actual resection margins of soft tissue and estimated resection margins based on radiographic data currently serve as the major restrictions of volumetric projections using a three-dimensional imaging software such as ITK-SNAP[1,2]. An R0 resection must always be performed within cancer-free tissue, meaing that estimated volumes usually end up being greater than anticipated initially[2]. Additionally, surgical complications of procedures on soft tissue may cause tissue volume changing effects, such as edema or rebuilding complex anatomical conjunctions such as the floor of the mouth, as well as prioritizing the repair of tongue length to achieve functional reestablishment of movement of the tongue. Moving past these discrepancies could potentially define preoperative tumor margins more precisely and subsequently support more accurate flap planning. Thus, causing smaller donor site volumes of extraction and decreasing flap failure as well as donor site morbidity[2].

A comprehension of the three-dimensional structure using virtual planning tools improve the pre- and intraoperative conditions, particularly for more complex cases. An opportunity to reconstruct a simulation of individual models for each patient, allow surgeons to optimize surgical outcome, time and anticipate potential complications [133-135].

In conclusion, the data obtained reveals a strong correlation between preoperative tumor volume and the postoperative flap volume ($p = 0.769$, $p < 0.001$)[2]. However, limitations of this study include the lack of comparative studies for direct reference. In addition to this, the relatively small sample size affects the robustness of the findings. At present, it is not possible to reliably determine a definite measurable constant to predict the required flap size using preoperative tumor volume, due to the small sample size within this study. Increasing the sample size could enhance the dependability of the statistical correlations and provide more precise predictions of flaps based on the preoperative size of the tumor[2]. Therefore, additional research is needed to explore potential correlations between tumor volume, particularly in the tongue, and the corresponding flap volume. Developing a numeric prediction for this relationship could improve surgical planning. Additionally, minimizing the volume of radial forearm free flap extraction reduces forearm impairment and leads to better donor site outcomes. These findings highlight the need for further clinical studies in this field[2].

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6. Figures

7. Publications

Zirk M, Niknazemi M, Riekert M, Kreppel M, Linz C, Lentzen MP. Comparative analysis of volumetric changes between resection volume of oral tongue cancer and post operative volume of radial forearm flaps. Clin Oral Investig. 2024 Aug 25;28(9):498. doi: 10.1007/s00784-024-05885-y. PMID: 39182195; PMCID: PMC11345318.

8. Curriculum Vitae

Date	Employer	Job title
Oct 2024 - current	AllDent Zahnzentrum Köln	Vorbereitungsassistenz
Apr 2023 – Sep 2024	University Clinic Cologne	‘Wissenschaftliche Mitarbeiterin’ in the ‘Poliklinik für zahnärztliche Prothetik im Zentrum für Zahn-, Mund- und Kieferheilkunde ‘
Jul 2022 - current	Bausch GmbH, Cologne	OccluSense Consulant
Apr 2022 - May 2022	Zahnarztpraxis Zahneule, Cologne	Macroscopic anatomy student assistant
Dec 2020 - current	University Clinic Cologne	Doctoral candidate in the ‚Zentrum für Mund-, Kiefer- und Gesichtschirurgie‘
Sep 2017 - Dec 2022	University clinic Cologne	Dentistry student ‘Staatsexamen Zahnmedizin’
Feb 2015 - Aug 2020	Amoria Bond GmbH, Cologne	Senior Sales Consultant
Nov 2013 - Dec 2014	Cantab Marketing Services, London	Google EMEA Junior Project Manager & Marketing Consultant
Sep 2010 - Jul 2013	Queen Mary University of London	University student Bachelor of Science - Biomedical Sciences
Nov 2006 - 2010	Copthall School, London	Student at secondary school
2002 - 2006	Anno Gymnasium, Siegburg	Student at Secondary school