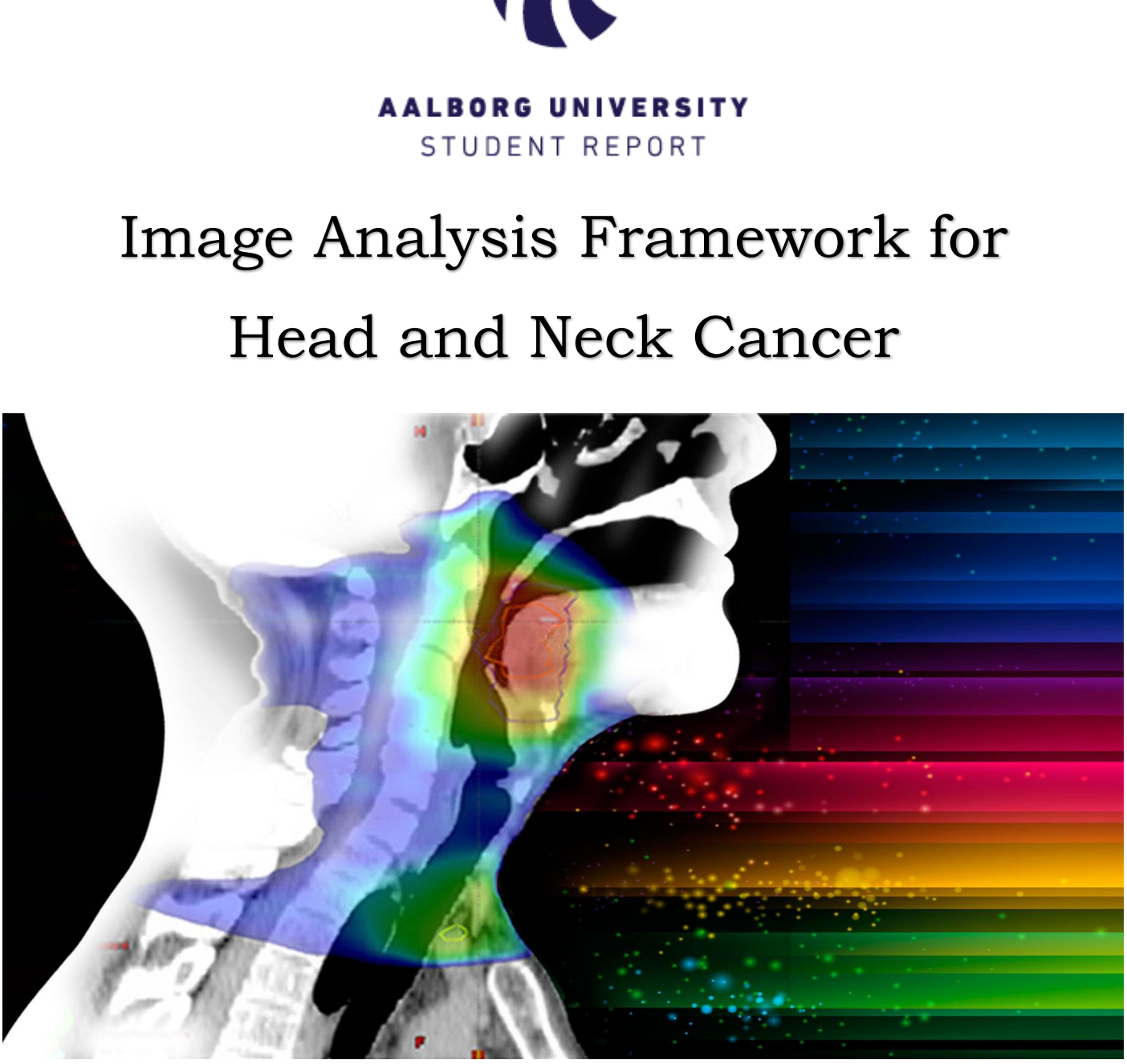

AALBORG UNIVERSITY
STUDENT REPORT

Image Analysis Framework for Head and Neck Cancer

Master of Science in Engineering,
Biomedical Engineering and Informatics

Master's thesis

Senthoopiya Achuthan Paramanathan

Autumn 2015

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STUDENT REPORT

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Abstract:

In Denmark, approximately 1500 new cases of head and neck cancers are diagnosed every year. Radiation therapy is the most common treatment for this type of cancer, and shall not be taken lightly. The side effects of such treatment could decrease the life quality of a patient.
Currently, physicians are manually delineating the tumor tissue location on images from computed tomography (CT) scanning. Besides being time inefficient this method also leads to intra- and inter-observer variation.
Having this as the motivation, the focus of this project is to develop a framework that segment tumor tissues based on head and neck cancer CT scanning images. This framework uses classification-based segmentation with texture information as input. The developed framework have first been cross-validated, and from this a trained-classifier have been created. Finally, the trained-classifier have been tested on new images from two patients. The results from the cross-validation showed a sensitivity of 66.58%, specificity 98.85%, and accuracy of 95.94%. The results obtained from the test using the trained-classifier, is as follows: sensitivity 22.8%, specificity 90%, and accuracy of 64%.

Contents

Danish Summary - Dansk Resumé

Hvert år bliver der diagnosticeret ca. 1500 nye hoved- og hals kræft tilfælder i Danmark. Hoved og hals kræft involverer mange vigtige organer. Derfor er det vigtigt at overveje, hvilke organer som kan blive påvirket af behandling. Der findes tre behandlingstyper, hvor den ene er strålebehandling. Strålebehandling er den mest anvendte behandlings form for denne type kræft. Denne behandlings type skal ikke tages let, da bivirkningerne kunne påvirker patientens livskvalitet.
Det er vigtigt at identificere og validere kræft mistænkte hurtigst muligt, således behandling kan begynde tidligt. For kræft celler kan vokse, sprede sig og skade de omkring liggende raske celler. Overlevelses prognose med hoved- og hals kræft afhænger af behandlings start tid og hvor meget kræften har spredt sig. Derfor, afsløring af en potentiel kræft placering en af de vigtigste del i undersøgelses fasen. Dertil kan der anvendes forskellige billeddannende modaliteter. Standard billeddannende modalitet på nuværende tidspunkt er computertomografi (CT). Kræft cellernes placering og dens størrelse kan identificeres ved lægerne indtegner manuelt på CT-scannings billeder. Dette er meget tidskrævende og kan fører til intra- og inter-observatør variation.
Dette projekt har som hoved fokus at udvikle et framework, som segmenter tumorvæv på hoved- og hals kræft fra CT-scanning billeder. Dette framework bruger classification-based segmentering metode, med tekstur oplysninger af billeder som input. Den udviklede framework er først blevet cross-valideret, og fra denne en trained-classifier er blevet oprettet. Derefter er den trained-classifier brugt til at teste nye billeder fra to patienter. Resultaterne fra cross-validering viste sensitivity på 66,58 %, specificity på 98,85 %, og accuracy på 95,94 %. De opnåede resultater fra testen på nye billeder med den trained-classifier viste sensitivity på 22,8 %, specificity på 90 %, og accuracy på 64 %.

Samlet set kan der konkluderes, at den udviklede framework kan med succes segmentere tumorvæv baseret på hoved- og hals kræft fra CT-scannings billeder. For en grundig statistisk analyse er der dog behov for at teste frameworket på flere billeder.

Preface

This project is done by Senthoopiya Achuthan Paramanathan from Aalborg University, studying Biomedical Engineering and Informatics on the 4^{th} semester of the master. The time period for the project is the 1^{st} of September 2015 to the 6^{th} of January 2016. The theme of the project is Applied Biomedical Engineering and Informatics.

Reading Guide
References are noted as number in square bracket and the complete information are listed in the bibliography. The bibliography include author name, year, title, journal name, pages, volume and web link. Figures and tables are numbered in accordance to chapter e.g. the fist figure in chapter 2 has the number 2.1 and second 2.2 etc. Figures and tables are provided with explanatory text.

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Chapter 1

Introduction

Head and neck cancer accounts for about 3% of all cancers in the United States. An estimate shows that in 2015 almost 59340 people will develop head and neck cancer and 12290 death estimate will occur from that count, [28]. The average life expectancy for this type of cancer is about five years, [28]. Currently, there exist three types of treatment for this cancer: (i) surgery, (ii) radiation therapy, and (iii) combination of surgery and radiation therapy. Cancer treatments shall not to be taken lightly, and the decision may have serious consequences and effect on the patient. The most commonly used treatment for the head and neck cancer cases is the involvement of radiation therapy, [28] and [34].

In general, head and neck region includes many important organs such as brain, muscles, blood vessels, nerves, glands, nose, mouth, teeth, and tongue. These organs have several functional importance in a human body as these organs have direct access to the pathways of the vascular, lymphatic, nervous, respiratory, digestive and endocrine system. As of this, any radiation therapy that may include these organs must be avoided or treated with caution to avoid negative impacts on the life quality of the patient, [37].

The initial phase before a radiation therapy is the preparation of the treatment. One of the important aspect of this preparation is the calculation of the amount of radiation dose that is needed for a particular case, and the decision of which organ that can be risked by radiation therapy. These calculations and decisions are based on images from different imaging modalities. From these images different target volumes are identified according to the intensity of radiation and risk level. The importance of this task is that the definition of the target volumes have an effect on the outcome of the treatment, e.g., side effects and treatment complications, [4].

The golden imaging modality standard used in target volume identification for the head and neck cancer is Computed Tomography (CT) scanning, [4], [5] and [27]. Currently in clinical practice, the target volume definition consists of manual delineation

on images from CT scanning by physicians from different specialization. Despite this manual delineation is widely used among the physicians there is some drawback to it. The manual definition from physicians of the target volume from the CT scanning images are very time-consuming, and in most cases lead to intra- and inter-observer variation, [4] and [5].

Having this as the key motivation, this project aims at developing an image analysis framework that segment tumor tissues based on CT scanning images.

The remaining of this project is structured as follows, Chapter II outlines the important aspects of the head and neck cancer. In Chapter III the management of the head and neck cancer and the target volume identification are presented. In chapter IV the state of the art within the field of head and neck cancer segmentation methods is presented. Chapter V presents the objective of this project. Chapter VI present the developed image-analyzing framework, which can be used to segmentation of the tumor tissues from the CT scanning. Chapter VII presents a description of the materials, test and validation that were carried out on the developed framework. Finally, in chapter VIII and IX the results and conclusion of this project is presented.

Chapter 2

Head and Neck Cancer

This chapter briefly outlines the important aspects of the head and neck cancer. Head and neck cancer accounts for 3 % of all cancers in United States, [6]. In Denmark, approximately 1500 new cases of head and neck cancers are diagnosed every year, [35]. This type of cancer affects males three to five times higher compared to females, [6].

Head and neck cancer can develop in any tissues or organs in the head and neck region. In this region, there are over 30 different possible organs where cancer can occur. An example of these could be, around the lip, in the mouth (oral cavity), inside the nose (nasal cavity), the space behind the nose (paranasal sinuses), pharynx, larynx or parotid glands. Figure 2.1 shows different regions where cancer can develop, [21].

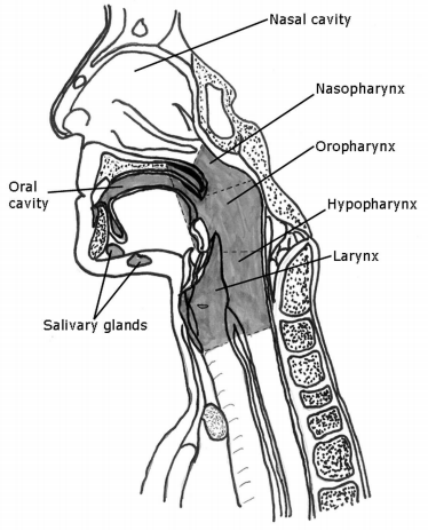


Figure 2.1: The different regions which are labeled in figure illustrate the possible location where the head and neck cancer can develop in a human body, [39].

The behavior of head and neck cancer depends on the organ it arises from. The site were the tumor arises is called the primary tumor. From the primary location, the cancer can be spread in three ways. The first that the cancer start growing from the primary site to the adjacent organs. The second, is through the lymphatic channels to lymph node. The third, is through the blood vessels to other sites in the body. The most common way the head and neck cancer spreads to other area is by the lymph nodes. When tumor spreads from the primary tumor to distant location in the body called metastasis, [31].
The lymph node are located along the major blood vessels found at each side of the neck, as shown in figure 2.2. The risk of cancer spreading to other organs of the body through blood vessels is related to whether the cancer is spread to the lymph node or not, [31].

The most common type of the head and neck cancer is squamous cell carcinoma. The less common type include the salivary gland tumors, lymphomas and sarcomas. In the section 2.1 these cancer types will be described. The key factor for head and neck cancer have a history from the use of tobacco products and exposure to the human papilloma virus (HPV). The prevention methods to reduce the risk of head and neck cancer is by vaccination against HPV and reducing the use of tobacco products, [16].

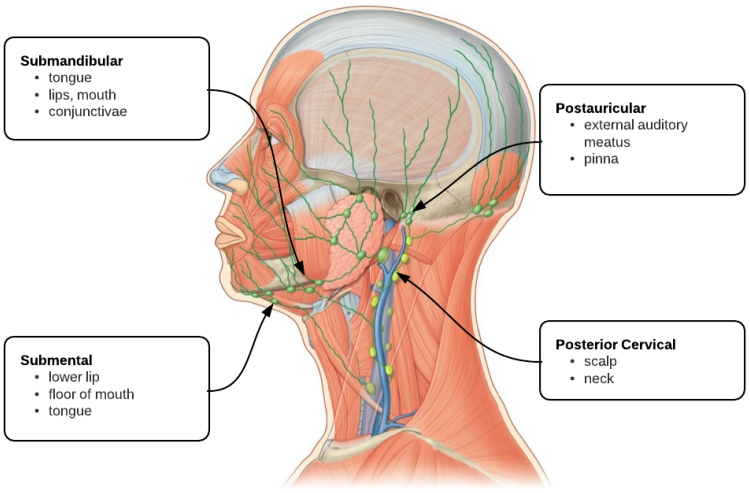


Figure 2.2: This figure illustrate the different lymph node and blood vessel which are found in the head and neck region, [12].

2.1 Head and Neck Cancer Types

Head and neck cancer can be divided into two groups. The first group is called head and neck squamous cell carcinoma (HNSCC), which is developed in mucosal mem-

branes of the upper aerodigestive tract. This group accounts for almost 90% of the total head and neck cancer diagnosis, [16]. The second group, arise in the thyroid and in the salivary glands, [16].

Head and neck squamous cell carcinoma
Squamous cell carcinoma arises from squamous cell, which is located in the outer layer of skin and in the mucous membranes. The mucous membranes or mucosa ensures that the underlying lamina propria of connective tissue remains moist. HNSCC develops in the mucous membranes of the mouth, nose, and throat. HNSCC can spread to other site of the body, e.g., to the lymph nodes or lungs. HNSCC is further classified by the location where it occurs, [16] and [39]:

- Oral cavity: if cancer occurs in the mouth
- Oropharynx: if cancer occurs in the middle part of the throat near the mouth
- Nasal cavity and paranasal sinuses: if cancer occurs in the space behind the nose
- Nasopharynx: if cancer occurs in the upper part of the throat near the nasal cavity
- Larynx: if cancer occurs in the voicebox
- Hypopharynx: if cancer occurs in the lower part of the throat near the voicebox

Thyroid Cancer and Salivary Gland Cancer
The thyroid cancer is common for women than men, and, the age group is often from 35 and to 39, [25]. This cancer type is more likely to occur people aged 70 years or over, [25]. Thyroid cancer can be divided into four different groups by the way the thyroid cell looks under a microscope, as mentioned below, [21] and [25].

- Papillary: The most common type of thyroid cancer. It is slow growing.
- Follicular: The type is less common.
- Medullary: This type is rare and can run in families.
- Anaplastic: This type os rare but fast growing and very difficult to treat. This is more common in people over 60 years.

The salivary glands keeps mouth moist and helps food slide down the gullet into the stomach. The salivary glands are found underneath the tongue, at the sides of the mouth in front of the ears and under the jawbone. This type of cancer is very rare. The causes of the cancer is still unknown, [21].

Chapter 3

Management of Head and Neck Cancer

In Denmark, the Danish Head and Neck Cancer Group (DAHANCA) organize the management of Head and Neck cancer. This group ensures a continuous development of diagnostics and treatment of this cancer based on results from a pool of randomized clinical trials. The group have national wide cooperation with other departments. Together, this group have developed evidence-based guidelines that are associated with quality assurance through a national wide clinical database. The group ensures that any further treatment of head and neck cancer is kept as the same throughout the country based on DAHANCA's nationwide guidelines. Figure 3.1 shows the flowchart of the head and neck cancer management, [34].

The first suspicion of head and neck cancer occurs most often through consultation at the general practice or in specialist practice. From there, the general practitioners refer the patients to a specialist in the field of ear, nose and throat diseases. Based on investigation, the specialist decides to follow a specific guideline and tailor a treatment fitted to a patient. As a preparation for a treatment, the specialist begins by investigating relevant imaging modalities and biopsy of the patient. If the cancer is still under suspicion, then the patient is referred to a department with specialized personals, where a conference consisting of ear-nose-throat surgeons, oncologists, radiologist, nuclear medicine and, pathologists will be held. During this conference the current situation will be discussed and a treatment plan for the patient will be developed, [34].

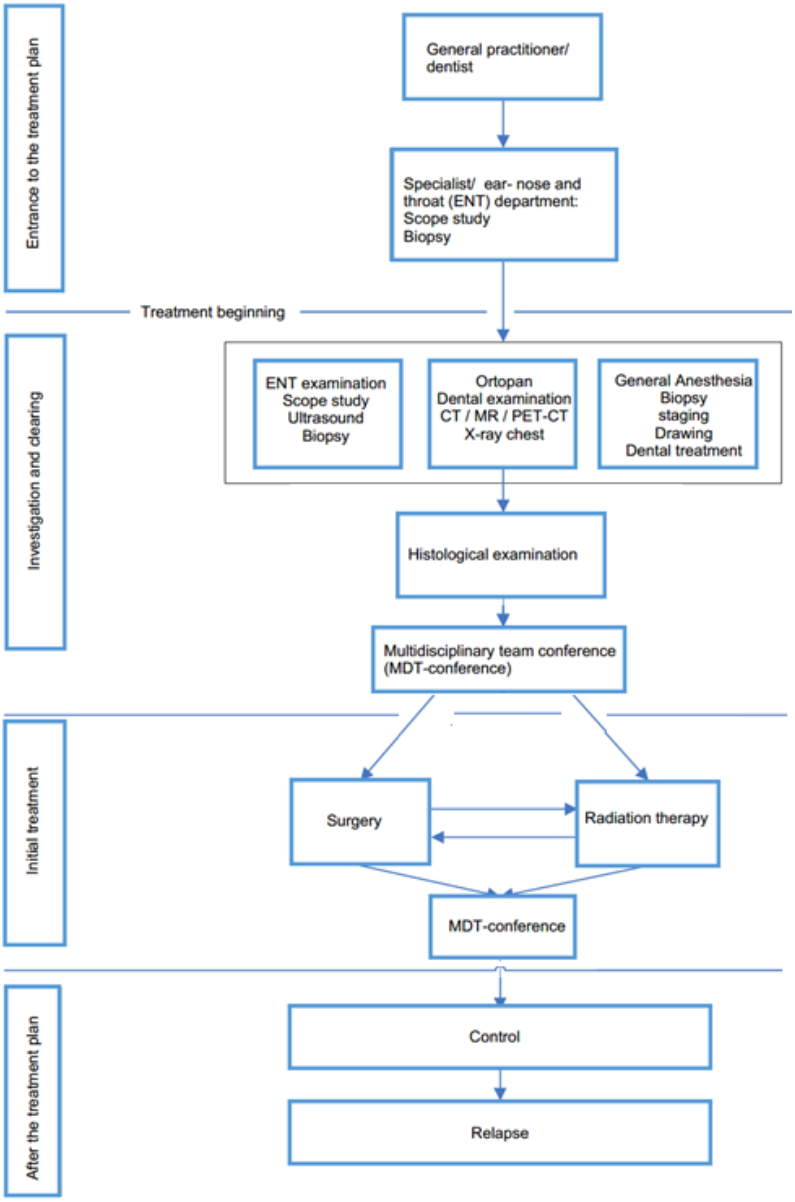


Figure 3.1: The flowchart of the head and neck cancer management from suspect of head and neck cancer to treatment. This images is modified from [34].

It is important to start the cancer treatment as early as possible, one of the reason is that there is a chance for the tumor tissues to grow and spread into the surrounding normal tissues. There is evidence that shows that the survival prognosis of the patient depends on when the treatment was initiated, [34].

Almost 75 % of head and neck cancer patients are treated with external radiation therapy and, if necessary, the treatment can also be given with a combination with chemotherapy, [34]. About 40% of the patients get surgery and, in combination with

radiation therapy, [34]. If relapse occurs, it occurs predominantly with in $1\frac{1}{2} - 2$ years after the treatment. Therefore, patients are called for control every $3^{rd} - 4^{th}$ months during the first 2 years and, every six months for another 3 years. Usually the treatment of patient closes after 5 years, [34].

3.1 Staging

There are different examination phases during the investigation of the head and neck cancer. These different phases are illustrated under the title Investigation and Clearing as seen in Figure 3.1. Among these different phases, staging the tumor is an important phase.

Head and neck cancer, similar to other cancer type, can be staged by the Tumor-Node- Metastasis (TNM) system. TNM system has three components for each letters. The first letter T for primary tumor extension, second letter the N for secondary tumor extension or lymphatic involvement and, finally M for distant metastasis. There are more subcategories for each letters. The letter T have subcategories from Tx to T4. Letter N have subcategories from Nx to N3 and M have M0 to M1. The tables 3.1, 3.2 and 3.3 shows more detailed description of the different subcategories, [16], [22] and [39].

	Primary tumor (T)
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension
T2	Tumor with parapharyngeal extension (posterolateral infiltration of tumor)
T3	Tumor involves bony structures of skull base and/or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, or orbit, or with extension to the infratemporal fossa/masticator space

Table 3.1: This table include the definition of subcategories from the primary tumor, [16], [22] and [39].

	Regional lymph nodes (N)
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph nodes = 6 cm in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral retropharyngeal lymph nodes = 6 cm in greatest dimension (midline nodes are considered ipsilateral nodes)
N2	Bilateral metastasis in cervical lymph nodes = 6 cm in greatest dimension, above the supraclavicular fossa (midline nodes are considered ipsilateral nodes)
N3	Metastasis in a lymph node > 6 cm and/or to the supraclavicular fossa (midline nodes are considered ipsilateral nodes)
N3a	> 6 cm in dimension
N3b	Extension to the supraclavicular fossa

Table 3.2: Table include the definition of subcategories from the regional lymph nodes, [16], [22] and [39].

	Distant metastasis (M)
M0	No distant metastasis
M1	Distant metastasis

Table 3.3: The definition of subcategories from the distant metastasis, [16], [22] and [39].

A combination of T, N and M defines the various stages of the head and neck cancer. The head and neck region has a complex lymphatic system with many lymph nodes, as shown in figure 2.2, which may result in some complications on the staging of head and neck cancer. The staging is different depending on the anatomical location of a tumor, [16], [22] and [39]. Different imaging techniques can be used to staging the tumor. In next section, these will be described.

3.2 Imaging Techniques

Various imaging techniques are used in the evaluation of head and neck cancer patients before, during and, after the treatment, [16] and [39]. Many head and neck cancer arises from the mucosal lining. The histological diagnosis will be available from the endoscopic biopsy results before a patient referred for imaging. In most cases, imaging gives primarily supplying information on the submucosal extension depth of the primary tumor, including its relation to surrounding structures, the presence of regional and/or distant metastasis, or information about the second primary tumor. The most commonly used radiographic techniques are Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET), [16].

3.2.1 Computed Tomography

CT scanning creates a three dimensional image of the inside of the body. The CT scanning system produce the image in cross sectional or slices. A computer software uses these image slices and combines these into a cross sectional view. The CT scan is used to show any abnormalities, tumors and to measure the size of the tumor. To get a better detail on the image the patient is given a contrast medium before the scan. The contrast medium improves the visibility of a specific organ, blood vessel or tissue. The contrast medium can be injected into the vein of the patient or given as a liquid form, [27]. An example of axial dimension of a CT scanning image is shown in figure 3.2.

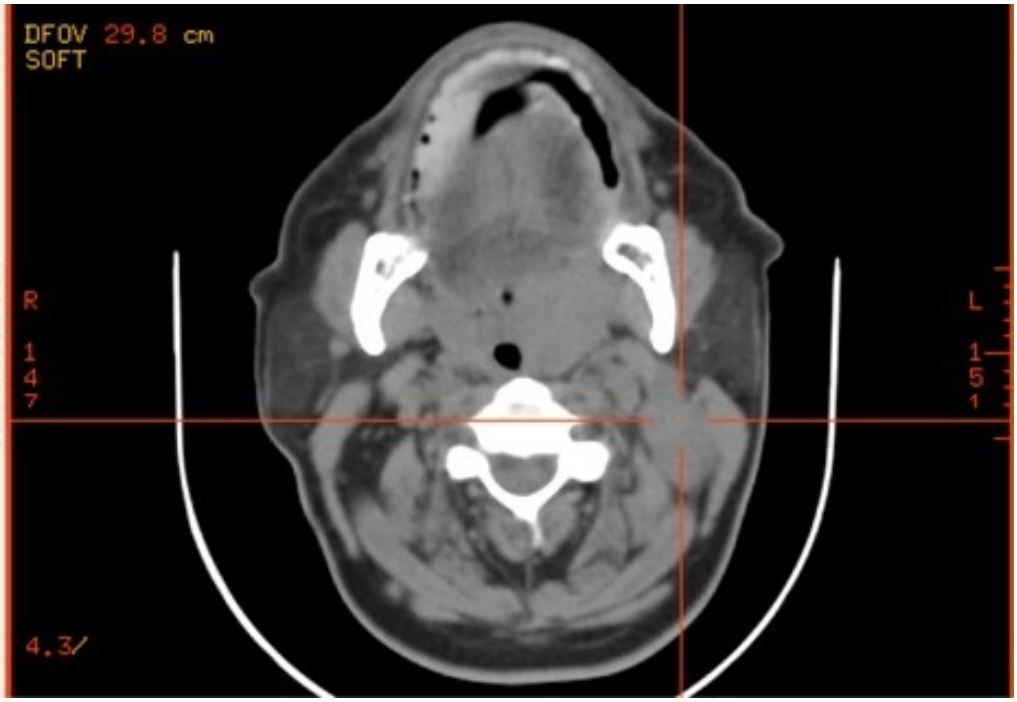


Figure 3.2: Axial dimension of a CT scanning image of head and neck cancer. The centerline shows the location of the primary tumor tissue. This images is modified from, [33]

3.2.2 Magnetic Resonance Imaging

MRI uses magnetic fields and radio waves to produce cross sectional detailed images of the body. Figure 3.3, shows one of the example of the MRI image of head and neck cancer. MRI can be used to measure the size of the tumor. To get a better detail on images the patient is given a contrast medium before the scan. MRI devices works by an electric current that passes through some coiled wires and, create a temporary magnetic field around the body of the patient. A transmitter/receiver in the machine sends and receive radio waves and these signals are used to produce digital images of the area of interest, [27].

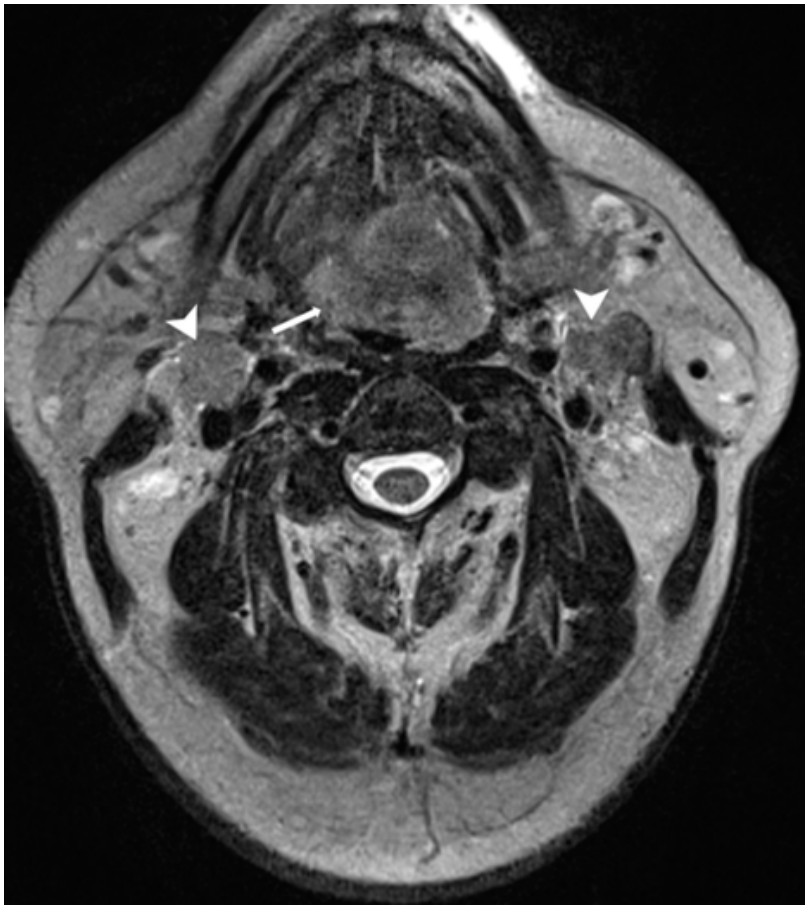


Figure 3.3: An axial dimension of a MRI scanning image of head and neck cancer. The long arrow found in the center shows the location of the primary tumor tissue. This images is modified from, [3].

3.2.3 Positron Emission Tomography

A PET scan is another way to create detailed image of organs and tissues inside the body. Before scanning, the patient gets injected with a small amount of a radioactive sugar substance. This sugar substance apogee the cells which use the most energy. The cancer cell tends to use energy actively. Therefore the injected radioactive substance absorbs more by the cancer cell. The scanner detects this substance to produce images of organs and tissues inside of the body. The cancer cell in the body will be visible in the images, [27]. Figure 3.4 illustrated an example of PET scanning image.

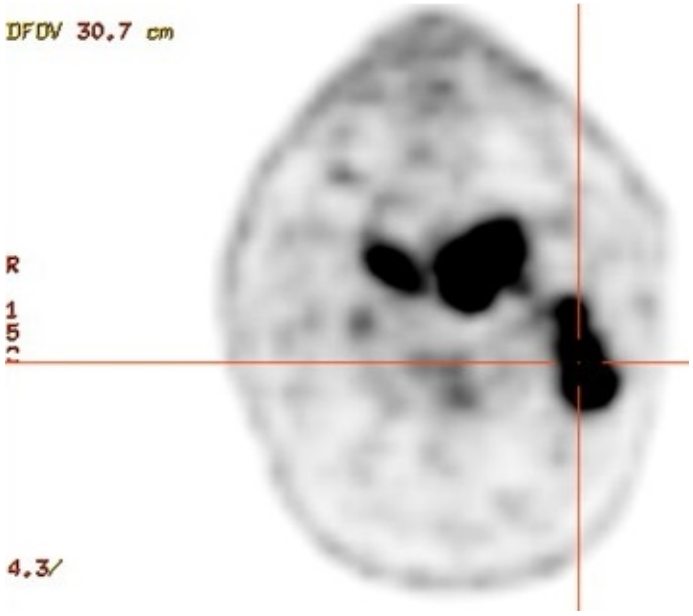


Figure 3.4: PET scanning image of head and neck cancer. The centerline shows the location of the primary tumor tissue. This images is modified from, [33].

These images from the different imaging techniques will be analyzed and in a team conference, where the decision of the patient treatment will be determined. Further, in this conference the TNM staging will be discussed. The TNM staging is used to select the treatment type for head and neck cancer. The purpose of the treatment is to cure patients with minimal impairment. Furthermore, it is useful to know the sensitivity of a tumor early as possible, which help the treatment planning, [9]. One of the most used in head and neck cancer treatment is radiation therapy. In following section, this type of treatment will be described.

3.3 Radiation Therapy

If the radiation therapy is selected as the treatment of head and neck cancer, then the target volume, size, shape and location of the tumor have to be identified. The therapy scanning images are used for radiation treatment planning. The International Commission on Radiation Units and Measurements (ICRU) have prepared recommendations for definition of the different volume to account in therapy scanning, [4] and [11].
In a study Wang et al., [37], pointed out that there are evidence show that dose of radiation improves local control of the head and neck cancer. The risk of increase toxicity level in the body and treatment complication will rise when the level of radiation dose is high. The toxicity increase have negatively impacts on the life quality of patient, [37].

The radiation dose and fractions depends on the target volume, size and location. In general, the dose that is given to a patient is divided in 33-34 fractions during a complete head and neck cancer treatment. Six fractions are given during five days in a week, [19].
The radiation dose is defined as the absorption of one joule of radiation energy per one kilogram matter. The unit uses for this is gray (Gy), [7]. The dose level for the primary tumor is 66Gy. If the tumor tissue is bigger than 4cm then gives 68Gy. The organs found near by the primary tumor gets 60Gy and the organs found in distant get 48-50Gy, [19]. To find the level of radiation dose, the different target volume have to be defined. In the following section the different volume and target-volume delineation based on different imaging will be described.

3.3.1 Target Volume Definition

The preparation of radiation treatment planning includes the definition of different volumes. These volumes are used to calculate the amount of dose and, which organ that can be risked by radiation therapy. In this section, some important volume and the definition of them will be described. The overview of the different volume are as follows, [4]:

- Gross Tumor Volume (GTV)
- Clinical Target Volume (CTV)
- Organ at Risk(OAR)
- Planning Target Volume(PTV)

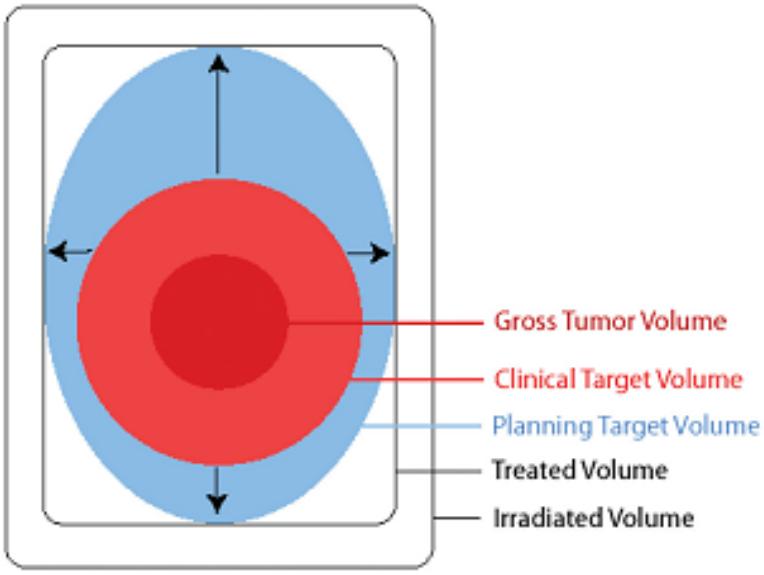


Figure 3.5: This figure illustrate the different target volume locations, [4].

Figure 3.5 shows an illustration of the different volume mentioned above. More detailed description are found in following sections.

Gross Tumor Volume (GTV)

GTV is the gross visible extent and location of the tumor growth. GTV is further divided in three subcategories T,N and M. The GTV may consist of primary tumor (GTV-T), metastatic lymph involvement (GTV-N), or other distant metastases (GTV-M). The density of the tumor cell is high, therefore the radiation therapy dose must be delivered to the whole GTV to obtain tumor control. The GTV can be identified by the imaging modalities and clinical examination. Determination of the GTV have to agree with the requirements for staging the tumor according to the clinical TNM and, American Joint Committee on Cancer (AJCC) systems. Using e.g. surgery the tumor has been completely removed from the body, then the GTV will not be visible in any of the imaging modalities, [4].

Clinical Target Volume (CTV)

The clinical target volume (CTV) is the volume that contains a demonstrable GTV and surrounding volume of tumor tissue that contain sub-clinical or microscopic disease. This volume has to be considered for radiation therapy. If this volume is included, then it should be radiated sufficient to achieve the cancer control. As GTV the CTV is also divided in CTV-T for primary tumor and, CTV-N for metastatic lymphadenopathy and CTV-M for distant metastases. If the same dose is prescribed for two such CTVs and, if they are close to each other, they can be labeled CTV-TN. If different doses are prescribed, there will be one CTV-T and one CTV-N, respectively, [4].

Organ at Risk

Organ at Risk (OAR) is the normal tissue, which can be at risk from the radiation therapy. The organs that are in risk can be organized in functional sub-units. The concept of functional sub-units are serial, parallel and serial-parallel organization of the normal tissues. Figure 3.6 show the different sub-units. The spinal cord has a low dose tolerance limit, which means that even a small volume of the spinal cord involved the risk may be harmful to the lungs, [4].

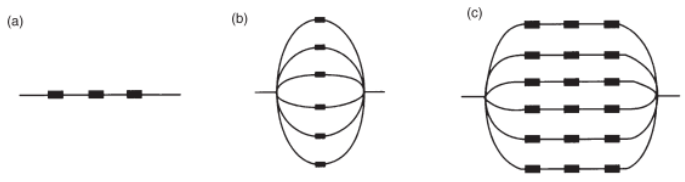


Figure 3.6: (a) serial of functional sub-units (e.g. the spinal cord), (b) parallel of functional sub-units (e.g. the lungs) and (c) serial-parallel of functional sub-units (e.g. the heart), [4].

Planning Target Volume(PTV)

Planning Target Volume (PTV) is a geometrical concept, introduced for treatment planning and evaluation. The geometrical concept include, e.g., patient motion and treatment setup differences. It is a recommended tool to shape dose distributions that ensure a clinically acceptable probability that an adequate dose will actually be delivered to all parts of the CTV, [4].

Treated Volume and Irradiated Volume

Treated volume shown in figure 3.6, is the whole volume (GTV, CTV and PTV) that receives radiation. This volume is important for local control of the tumor. Irradiated volume shown in figure 3.6, is the volume that receives a high radiation dose in relation to the normal tissue tolerance. This volume include treated volume, [4].

3.3.2 Target Volume Delineation based on CT

One of the imaging modality that is used to target volume definition is CT scanning. However, the CT scanning of radiation therapy, and diagnostic CT scanning are different. In therapy, the medical status of the patient should be evaluated using all the relevant diagnostic modalities that are available for the current situation. The therapy CT scanning images will be evaluated and target volume will be manually contoured by the experts in the field, and discussed in therapy team conference. In the case where the tumor is not clearly visible on the diagnostic CT scanning, the target volume delineated by use of other available information such as clinical examination, MRI and PET scanning images, [4] and [11]. In many studies mentioned that the CT scanning considered to be the gold standard in the radiation therapy planing, [4], [5] and [27]. One of the reason that the CT scanning images are used is that the information from CT scanning can be transferred into an electron density map. The electron density information is applied to the radiation dose calculation. However, the CT scanning represents the anatomic information of both tumor and normal tissues i.e. the CT scanning images not highlight the tumor tissues. This complicate the differentiation the tumor tissues from the normal soft tissues, [27]. In addition, in a study by Wang et al., [37], mentioned that CT scanning images alone to tumor definition is not sufficient. This study pointed out that if the primary tumors size is small then identification of the primary tumor from the CT scanning images is difficult, [37]. Furthermore, there exists inter-and intra-observer variability in target-volume delineation based on CT scanning. In the section 3.3.5, the inter- and intra-observer variability is detailed, [4] and [27].

3.3.3 Target Volume Delineation based on PET images

Another imaging modalities that can be used in the target volume definition is PET. The PET with ^{18}F-fluorodeoxy-glucose (FDG), includes high-contrast resolution that enables the tumor localizations to be identified with high sensitivity. In figure 3.4

from section 3.2.3 a FDG-PET scanning image is shown, and the dark region of the image is the location of the tumor. The dark region differ clearly from the surrounding normal tissues. However, having identified the tumor localization is only the first part, the tumor boundaries needs to be identified as well, which in this case may be proven to be a difficult task. One of the reason behind the difficulties in identifying the tumor boundaries can be targeted at the spatial resolution of FDG-PET images, which is low, and the images have blurry appearance, [32]. From a paper by Foster et al., [14], the challenges in segmentation of PET images are described. The paper agree with the above-mentioned issue. The low resolution issues decrease the contrast between the object and its boundary, [14].
Various methods using FDG-PET to target-volume definition are currently available. The most used method is visual interpretation by physician. Visual view is susceptible to the window-level settings which requires a high level of configurations and it allow a more subjective evaluation. There are found more objective methods using the thresholding algorithms. Although these several methods which exist for target volume delineation, the choice of method may influence the purpose of the radiation therapy, [32].

3.3.4 Target Volume Delineation based on integrated PET/CT images

Target volume can also be defined by use of integrated PET/CT images. Several studies have shown that the combination of PET and CT can improve the target volume delineation. In figure 3.7 an example of the integrated PET/CT images, corresponding CT and PET scanning image are shown, [29] and [37].

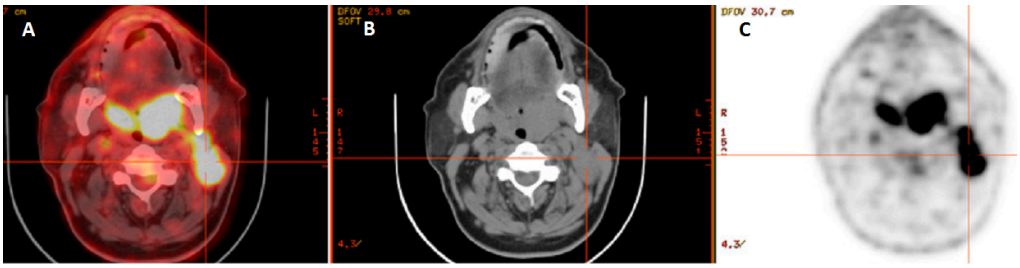


Figure 3.7: The first figure(A),integrated an head and neck cancer image from a PET/CT scanning. Figure(B), shows the image from a CT scanning. Figure(C) shows the image from a PET scanning, [33]. The primary cancer location is found in the center of the red line on all three images.

In a study by Paidpally et al., [29], the results shows that PET/CT combined can improve the sensitivity and specificity compared with MRI or CT alone in target volume identification. In a study by Kovalchuk et al., [20], which describes the effect of integrated PET/CT on target volume delineation, PET have a significant influence on CT based tumor definition. Using both PET and CT on target volume delineation, reduce the risk of geographic misses, minimizing dose to normal tissue

and impact the treatment plan, [20]. The study by Wang et al., [37], mentioned that the integrated PET/CT provide diagnostic advantages, positive impact on target delineation and precision of radiation therapy. Furthermore, this study also conclude that the integrated PET/CT is useful for the treatment planning and tumor staging, [37].

3.3.5 Observer Variability in Target Volume Delineation

Identification of target volume is important during radiation therapy treatment planning. However, the target volume definition remains subjective and least consistent variable in order to deliver the accurate radiation therapy. Many factors involves when considering the precision of target volume identification, such as the chosen imaging modalities, the resolution, contrast level and patient position in co-registered scans. These factors lead to the difficulty of the target volume identification and high observer variability. Currently, the target volume is defined manually, [2].

In a study by Anderson et al., [2], one of the target volume gross tumor volumes (GTV) identification using three imaging modalities(CT,PET/CT and MRI) are compared in order to analyze the inter-observer variability. They use data from 14 patients with head and neck cancer. Three radiation oncologists contoured GTV on these three imaging modalities. The results show that GTV definition by CT has largest variation by standard deviation between the observer is 35%. The observer variation PET/CT has standard deviation of 28% and for MRI 27%. However, the volume overlap ratio means that the greatest inter-observer agreement during GTV identification found in PET/CT (46%), for MRI 36% and finally CT 34%, [2]. Figure 3.8, shows the observer variation of the studies three imaging modalities.

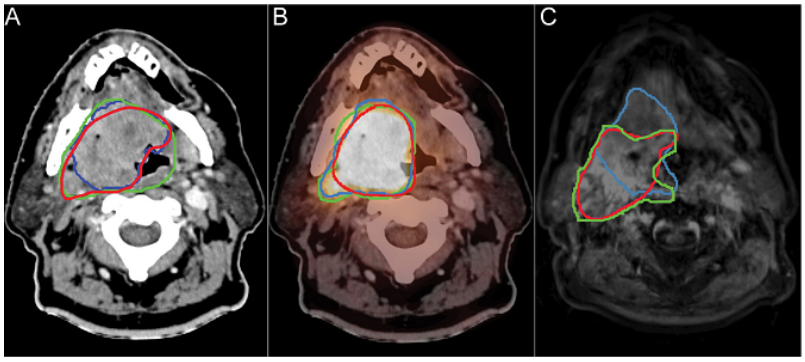


Figure 3.8: This figures illustrate the observer variability from three observers. The three different color drawing represent each observer. Figure(A) shows the image from CT scanning. Figure(B) shows the integrated PET/CT scanning images. Figure(C) shows the MRI scanning, [2].

In addition, a study by Cooper et al. analyzed the GTV identification by four neuroradiologists and four radiation oncologists on 20 sets of CT scanning images from 20 different head and neck cancer patients. The result from this study shows

that the average degree of agreement found in 53.2% of cases. However this study concluded that the estimation of GTV shape is imprecise even for the experienced physicians, [10].

Furthermore, in the study by Mukesh et al., [24], it is mentioned that to reduce the inter- and intra-observer variation on GTV definition can imaging modalities PET and MRI include to the CT scanning. Furthermore, multidisciplinary team contouring and using guidelines can reduce the inter-and inter-observer variation, [24].

Chapter 4

Segmentation Approaches

This chapter describes the state of the art within the field of head and neck cancer segmentation methods.

4.1 Currently Available Methods

Several segmentation methods are available in order to segment the tumor from imaging modalities. In a Ph.d. thesis by Huan, [39], these segmentation techniques are divided into four classes: (i) Threshold-based segmentation, (ii) Edge detection segmentation, (iii) Region-based segmentation, and (iv) classification based segmentation. In the following these four classes are detailed, [39].

Threshold-based Segmentation

This segmentation method is commonly used and simple to implement. The implementation is based on a global threshold value. This method may have a satisfying performance if sufficient contrast between the interest objects and the background is provided in the image. However, if the object is heterogeneous then this method will be unsuitable as a single threshold value is not sufficient for a detailed segmentation. Furthermore, this method will fail if the interest object have two or more overlapping intensity levels. The method standardized uptake value (SUV) of 2.5 around the tumor on PET images belongs to this type of segmentation. This type of segmentation method have a tendency to overestimate the target volume, [8], [14] and [39].

Instead of using a global threshold there are other threshold based methods available, e.g., fixed threshold of the maximum signal intensity and threshold that is adaptive to the signal to background ratio. In a fixed threshold method, the selection of threshold is given by an expert or learned in training of images. The threshold value may differ from image to image, this means that, the threshold value depends on the properties of the image, namely, scanner type, reconstruction and image noise.

Additionally, this method also has a tendency to overestimate the target volume. The adaptive threshold is based on image quality only and may fail if the interest object is of a complex shape, [14].

Edge Detection Segmentation

This edge detection method uses the gradient information of the image to segment the connected region. The segmentation methods based on gradient information are e.g. watershed, level set and active contour model. The thesis by Huan, [39], points out that many studies are working on these different edge detection segmentations. These methods need an observer to select the bounding box, thresholding of gradient etc. and this will introduce the observer variability in order to define the tumor volume.These methods have a satisfying performance in order to identify and segment a normal structure such as the liver, ventricles and vessels. Furthermore, this method gives successful results, if the background of tumor is uniform and the tumor edges are easy to distinguish from normal tissues. This scenarios occur in liver and brain tumor, [14] and [39].

Region-based Segmentation

The region-based method detects the connected regions/voxels that have different intensity from the region around the connected region. One of the simplest region-based segmentation is region growing method. This method starts from a predefined point or a seed point in the image and examines the neighbor pixels either by adding the neighbor pixels to region of interest or not. The criteria for adding the neighbor pixels could be pixel intensity, gray-scale texture or color. This method works well on normal structure segmentation or if the tumor region is homogeneous and is easy to distinguish from the boundaries, [39].

Classification-based Segmentation

In this segmentation method the images have been divided in blocks, region or voxels. After the division, they will be classified according to the corresponding group. The group could, e.g., be tumor and normal. In order to classify each image blocks into the corresponding class, the different features or information from the image blocks need to be calculated. These features could be gray levels information, local textures or color component. The thesis by Huan, states that this method has been used in several studies to segment prostate cancer, breast cancer and pulmonary cancer. These studies uses the texture information to classify normal and tumor tissues, with good results, [39]. In addition, a review by Jalalian et al., [18], analyses the computer-aided detection/diagnosis (CAD) systems that are developed for breast cancer. They found that the texture features are one of the feature that is used in several studies to discriminate the normal and tumor region, [18]. The following section describes the this feature.

4.2 Texture Feature

In this section, the texture information from an image will be described. This information will be used as an input for the classification based segmentation of head and neck cancer.
The texture analysis is a tool to analyze the heterogeneity within the tumor in medical imaging, [9]. The texture analysis describe the relationships between the gray level intensity of pixels within an image.

Texture feature can be divided into two categories: (i) statistical (ii) structural, [39].
Category I: The statistical approach can further be divided into first-order (one pixel), second-order (two pixels) and higher order (three or more pixels) statistics, [39], [9]. The first-order of statistical method describes the global textural features that are related to the gray level frequency distribution within the image. These first-order textural features are based on histogram analysis, e.g. the parameters, which can be calculated are mean, minimum and maximum intensity, standard deviation, skewness and kurtosis, [9]. The first order textural features are based on the absolute intensity values of the individual pixels or voxels. This feature did not include the surrounding spatial information of the pixels or voxels. In the second-order of statistical method describes the local texture features. They are e.g. entropy, energy, contrast, homogeneity, dissimilarity and correlation. The local texture features are calculated by e.g. co-occurrence matrices, [9].
Category II: The structural approach includes the information about the texture edges, orientation, shape, size and symmetry of the image. This information are not useful for the consideration when the purpose is to distinguish between normal and tumor tissue, [39].

Huan et al., [40], have worked on target volume discrimination using texture analysis. One of their studies concludes that segmentation using texture analysis has the potential to provide accurate delineation of the target volume. By this method, the inter-observer variability can be reduced, [40].

Haralick et al. [15], have defined 14 different texture features. Which includes, (1) Angular second moment(ASM) or energy, (2) Correlation, (3) Contrast, (4) Sum of Square Variance, (5) Homogeneity, (6) Sum Average, (7) Sum Variance, (8) Sum Entropy, (9) Entropy, (10) Difference Variance, (11) Difference Entropy, (12) Information Measure on Correlation 1, (13) Information Measure on Correlation 2 and (14) Maximal Correlation Coefficient, [15].
Not all the above-mentioned features are relevant to discriminate normal and tumor tissue. In tumor tissues, more gray level variation may occur than in normal tissues. The features energy, contrast, homogeneity, entropy and sum average from above-mentioned 14 features, can be useful to distinguish these two type of tissues, [26], [36] and [39]. The texture information from the remaining features are not clear in the

clinical aspect to tumor identification, [1].
A review by Jalalian et al. analyze the computer-aided detection/diagnosis (CAD) systems that is developed for breast cancer. This review include many studies, which uses textural information to discriminate normal and tumor tissue. In these studies, one of the classification methods is the support vector machine (SVM), [18].

Chapter 5

Project Objectives

In order to find the key objectives of this project, the most important aspect, which are mentioned in previous sections, are briefly outlined, followed by the objectives and project delimitations.

As mentioned earlier, then head and neck cancer involves many important organs. Among these organs, some are at a higher risk when considering radiation therapy treatment. As a part of the treatment flow, imaging modalities are used. Imaging modalities may take many important roles as part of a treatment flow when considering management of this cancer type. Two of these roles are for example, (i) identifying those organs at risk (ii) to locate the primary cancer tissue.

In section 3.3 the different target volume definition together with the use of different imaging modalities to identification of the target volumes are described and discussed. It is known at this point that the standard imaging technology, which is widely accepted in the field, is CT. Different target volume segmentation methods are introduced in the literatures using this imaging modality.
In chapter 4, the state of the art, within the field of tumor segmentation method is mentioned. Many studies are using the classification-based segmentation to segment the normal and tumor tissues. These studies use the texture information from image as an input feature to distinguish normal and tumor tissues.

Based on those different studies, mentioned earlier, this project will be focusing on the classification segmentation method for head and neck cancer. In order to use the classification segmentation method the texture information is used as well.

This project will focus on the segmentation of the primary tumor region called gross tumor volume (GTV) in the head and neck cancer using CT scanning images. Based on this, the project objectives can be formulated as follows:

- Present an image analysis framework for head and neck cancer based on CT scanning
- Extract features that characterize head and neck cancer
- Classification and segmentation of GTV based on CT scanning images of head and neck cancer
- Test and validation of the segmentation

5.1 Limitation

The CT scanning is the standard technique, which are used in this field. This project only uses images from CT scanning. Each patient under suspicion of head and neck cancer, have some amount of CT scanning image slides. These CT scanning images are found in three dimensions, (i) axial, (ii) sagittal, and (iii) coronal. The axial dimension of the CT scanning images are selected for further analysis. Physicians have manually delineated the tumor tissues from these images. These manually selected tumor region, or more specifically, the gross tumor volume (GTV) is the region of interest in this project. Furthermore, only four slices with tumor tissue from each patients are selected to develop the image analysis framework. In order to classify the region of interest the texture information is used as feature. During development of the framework, only the texture information found inside of the manually delineated locations are used as cancer. The texture information similar to the delineated locations found outside of the delineated locations will be removed from the dataset.

Chapter 6

Development of Image Analysis Framework

Having the objective and the delimitation as mentioned in the previous chapter, the software framework for head and neck cancer based on CT images is developed, this chapter details the development steps. The development of the framework is illustrated in figure 6.1. Each block in this flowchart will be described in the following sections. This algorithm is written in MATLAB 2015b software.

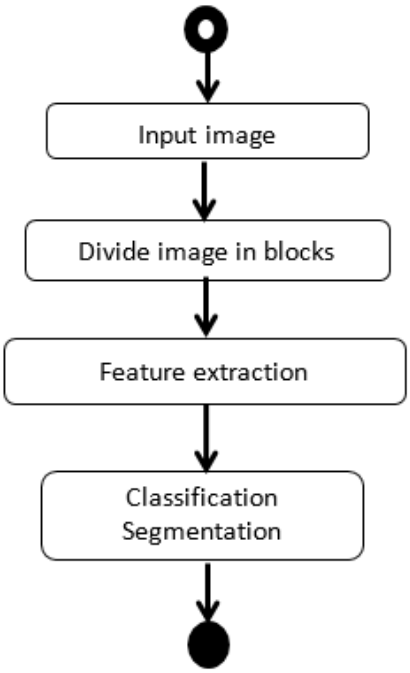
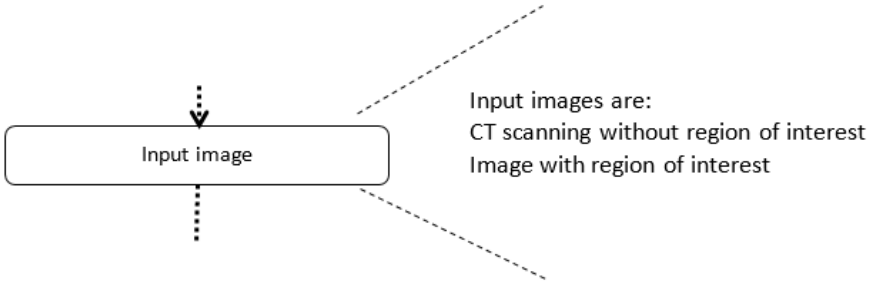


Figure 6.1: Overall flowchart of the developed framework.

6.1 Input Image



This algorithm is developed for two input images, (i) the CT scanning of head and neck cancer patient and (ii) the outlined region of the interest image. The outlined region of interest image will be referred as “mask”. The steps are the same for each images.

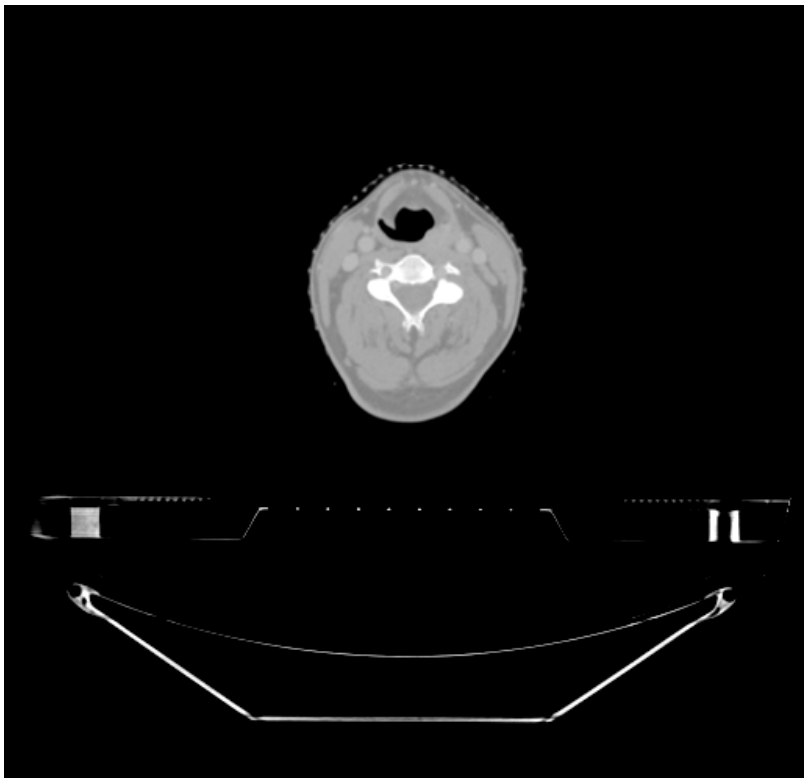


Figure 6.2: One of the original CT scanning image.

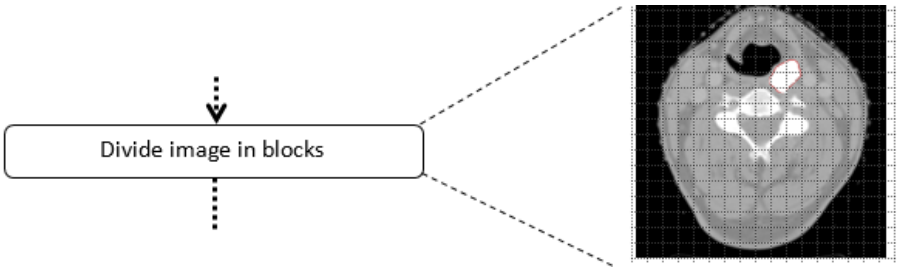
Figure 6.2 shows one of the original image. Each image have a background region as shown in figure 6.2, which are not relevant for further analysis, as of this, the CT scanning is visualized and the unwanted regions needs to be identified and

removed as part of a pre-processing step. Figure 6.3 shows three images, where image (a) the unwanted region have been removed as part of pre-processing. Image (b) shows the image without the manually drawn tumor region, where the removed part is illustrated in color. Finally, image (c) shows the tumor region which have been separated from the original image, denote that the tumor have been manually identified and drawn by a specialist.

Figure 6.3: (A) shows the image where the unwanted region is removed. (B) shows image without the tumor. The purple colored region is where the tumor was located. (C) shows the tumor region.

CT scanning have to represent the inside of the body structure of the patient, as mentioned in chapter 3.2, CT scanning consist of many slides. Not all of the slide that includes the relevant cancer region. To find those slides that includes the cancer region, the mask image is used. Mask is the image where a physician who is specialized in analysis of head and neck cancer image, have outlined the region of interest of the different CT slides. As mentioned in chapter 3.3, there are many different target volumes that needs to be accounted for in a radiotherapy CT scanning. In this project, the GTV volume is the region of interest. CT scanning are in three dimension, axial, sagittal, and coronal. All the dimension parts contain the same cancer cell information but they are represented in different dimensions. To simplify the developing algorithm only axial part of the images are used in this project. One patient could have more than one image slides with cancer cell. It will be time consuming to analyze all the slides with cancer. Therefore, four slides with cancer will be used to further analysis. It is important to identify both the wanted and the unwanted region from the input images. An image should only have one region, this means that, either an images without cancer region, or an image with the region of interest. To prepare these two images the mask image is used. In MATLAB, regions that are not to considered in analysis, have to be “not a number (NaN)”.

6.2 Image in Blocks



The input images contain many pixels information. To get the most information as possible the input image is divided in small blocks. When selecting block size, one have to account for what the purpose of the image blocks are. In this case, the purpose of the image blocks is to extract texture features. If the block size is too large then the image block might contain many different objects, which might lead to a negative influence on the final result. If the image block size is too small, then it may not effectively reflect the characteristics of the image, once again leading to a negative influence of segmentation results, [38]. The cancer region could be very small therefore each blocks size is decided in to block size of 3x3 pixels as illustrated in figure 6.4. By this way, the distance from the interest pixel to its neighbors is one pixel.

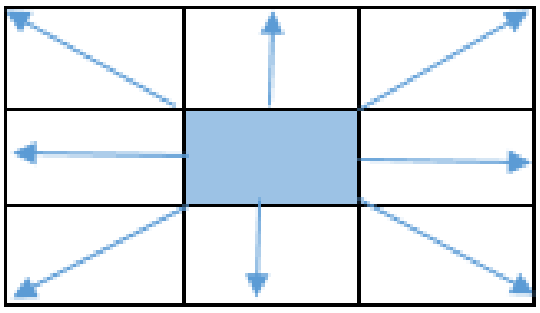
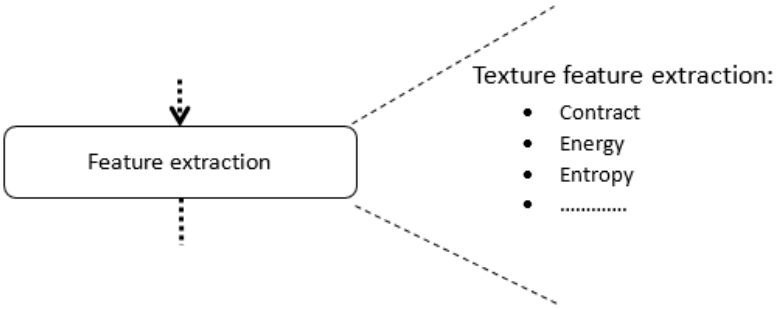


Figure 6.4: Center pixel is the interested pixel

6.3 Feature Extraction



Every image blocks are used to calculate the texture features. These calculated values are used to classify normal region from cancer region. As mentioned in section 4.2 the texture features can be used to classification of the different region. To find texture feature the gray-level co-occurrence matrix (GLCM) needs to be calculated as a first step. The GLCM is found by calculating how often pairs of pixel with specific values and in a specified relationship occur. In other words, the GLCM is created by calculating how often pixel with the intensity value i occurs horizontally adjacent to a pixel with the value j. Therefore each element (i,j) in the GLCM that specifies the number of times that the pixel with value i occurred horizontally adjacent to a pixel with value j. The integers, which specify the distance between the pixel of interest and its neighbor is shown in figure 6.5. The function called graycoprops is used to calculate the texture features from GLCM, [23]. The same procedure is used for the remaining image blocks.

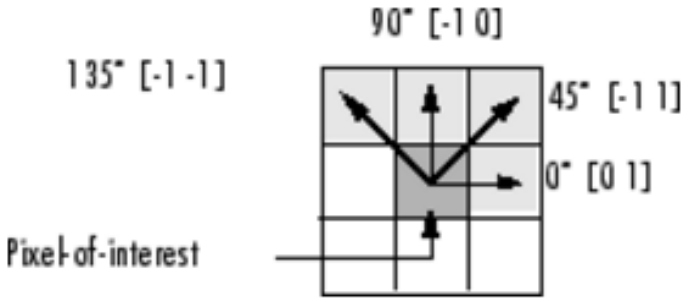
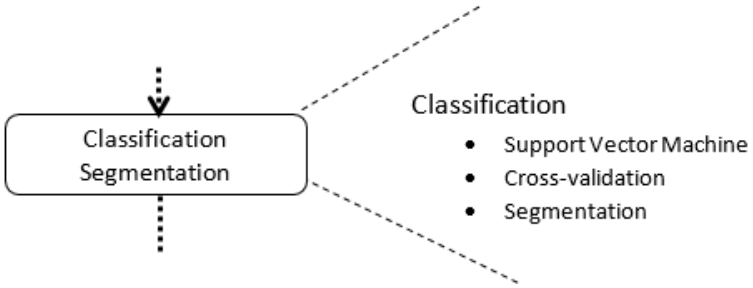


Figure 6.5: The distance between the pixel of interest and its neighbor, [23].

As mentioned in the 4.2 the features energy, contrast, homogeneity, entropy and sum average can be useful to distinguish normal and tumor tissues, [26], [36] and [39] In addition, to above-mentioned features the sum average, sum variance, and sum entropy are used in this project. However, the texture information from these features are not clear in the clinical aspect, [1].

6.4 Classification-based Segmentation



Feature extraction results from last section is used as input in the Support Vector Machine (SVM). SVM is one of the classifier algorithm that is used in this report. The aim of SVM is to find the optimal hyperplane that separates different classes from each other. There are two sections in SVM, first section is the training section and the second section is the classification section. In the first section, training samples are used to find the hyperplane. The hyperplane is the maximum distance from the nearest training samples between two classes. The data points that are close to the separating hyperplane is called support vectors. These support vectors create boundary for the hyperplane margin.
In second section, the hyperplane is used to classify new data points (classification section), [13]. In this project, normal and cancer patches of head and neck cancer have been used. The image blocks are classified according to which group they belongs to, i.e., the image blocks belongs either to the normal or cancer image group. Figure 6.6 illustrate an example of this concept.

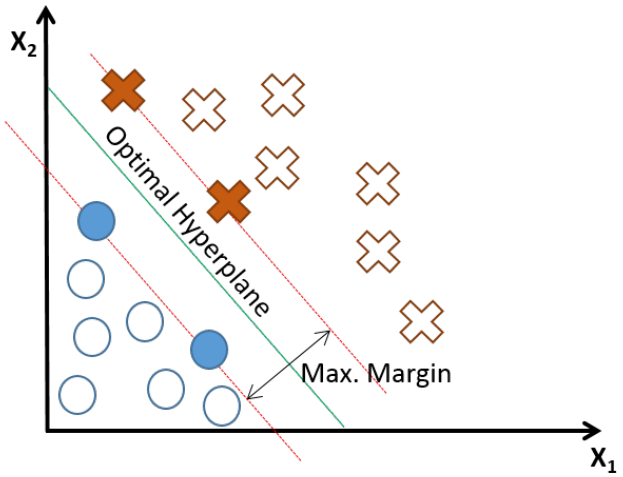


Figure 6.6: The illustration of hyperplane. There are two groups of data marked in circle and cross. The filled circles and cross is support vectors.

Every image have some background region that have another pixel information, for that reason, a third group called background is selected. Usually SVM is used for two group cases, in this project a third group case is found, therefore multi-class SVM is used. There are two types of multi-class SVM: (i) One-vs-All and (ii) One-vs-One. The One-vs-All method constructs k classifier where k is the number of classes used. Samples from one class are used to train and the samples from the other classes are used to classify whether the samples are belong to the trained-class or not. Same procedure is repeated k times and each time a new class is used, [17].
The One-vs-One method constructs $\frac{k(k-1)}{2}$ classifiers. That means there are classifier for each pair of the classes. This method is more faster and accurate than One-vs-All, [17]. In this project, the One-vs-One SVM model is selected.
MATLAB Software have an application called Classification Learner, this application have been used for SVM classification. Using the application a trained-classifier is created. Finally using the trained-classifier the tumor tissues from new images can be segmented.

Chapter 7

Materials and Validation Methods

This chapter will include a description of the used dataset for the development of the framework followed by validation of the developed framework.

7.1 Materials

For the development of the framework, therapy CT scanning images from 11 head and neck cancer patient are used. The CT scanning images are from Aalborg University Hospital and are produced by CT scanner. These CT scanning images include the manual delineation of the target volume created by physician from the department of oncology.
As mentioned in section 5.1 only four CT scanning image slides from each patient are used. In order to find those images with cancer cell, manually delineated images by physician are used. The first image slide out of the four image slides is randomly selected. The remaining three image slides are the three images found after the first image slides in the sequence. In total 88 images are used during development of the framework.
Images are divided in small image blocks and to characterize the head and neck cancer, texture information from the different images blocks are used. Using this texture information the developed framework classifies the different image blocks in three classes. These three classes are: cancer, normal and background. The texture information from the manually delineated region by physicians is defined as the class cancer. The class normal is the texture information from outside of the manually delineated region. The class background is the texture information found in the black regions that are in the background of the head and neck cancer CT images. The texture information similar to the manually delineated but found outside of the delineated region are removed from the dataset. The main reason of this that, these regions were not verified by the physicians as cancer. This means that, only the texture information from the manually delineated regions are used as the class

cancer.
As mentioned in section 4.2 several studies uses texture information energy, contrast, homogeneity, entropy and sum average to define the cancer tissue. In addition, to above-mentioned texture information the sum average, sum variance, and sum entropy are used in this project. However, the texture information from these features are not clear in the clinical aspect to define cancer tissues, [1].
The developed framework is cross-validated by using k-fold validation methods and a trained-classifier is created. The trained-classifier will be used to test new set of data from two new subjects. For that reason, four image slides from each subjects are selected using the same procedure as before. It is important to stress out that the class normal in this test differ from the normal class used in the cross-validation. The difference is that in this test all the texture information from images are included. This means that, as normal class all the texture information that are found outside of the manually delineated regions are used.

7.2 Validation Methods

In order to validate the classifier described in section 6.4 and to protect against overfitting the fold cross-validation technique is selected. The fold cross-validation function have the following steps:

- Divide the dataset into k random dis-joints folds
- For each k folds
  - K-1 training data
  - A single data as validation

These steps are repeated k times. The k results from the folds used to calculate the average test error over all the folds. Number of the fold in this project is selected to be five, which is the default option from the MATLAB Software.

7.3 Validation of Classification Results

In this section, the statistical measurement parameters that are used to validation of the proposed framework is described. These parameters are: sensitivity, specificity, and accuracy. Following section will include these notations TP,TN,FP and FN. The definition of these notationa are as follows:

- True positive TP is when cancer tissue image block classified as cancer.
- True negative TN is when normal tissue image block classified as normal.
- False positive FP is when cancer tissue image block classified as normal.
- False negative FN is when normal tissue image block classified as cancer.

Sensitivity

The sensitivity can be calculated based on the following expression [30]:

$$Sensitivity = \frac{TP}{TP + FN}, \tag{7.1}$$

where TP is true positive and FN is false negative. Sensitivity is a measure for the probability of the test results being positive when disease is presented. In this project the sensitivity is the probability of the framework is capable of classifying the results as positive when tumor is presented.

Specificity

The specificity can be calculated based on the following expression:

$$Specificity = \frac{TN}{FP + TN}, \tag{7.2}$$

where TN is true negative and FP is false positive. Specificity is a measure for the probability of the test results being negative when disease is absent. In this project the specificity is the probability of the framework is classified as negative results when normal is presented.

Accuracy

The accuracy (ACC) can be calculated based on the following expression:

$$Accuracy = \frac{TP + TN}{TP + FP + FN + TN}, \tag{7.3}$$

where TP is true positive, FP is false positive, FN is false negative and TN is true negative. Accuracy is a measure for the overall test performance. It includes results of both tumor and normal.

Chapter 8

Results

In this chapter, the results that are obtained from the developed framework is presented. The results are divided in two sections. First, the cross-validated classification results and the segmented images are presented. In the second section, the results from test on new subjects using the trained-classifier and the segmented images are presented.

8.1 Cross-validated Classification

In order to carry out statistical analyze, as described in section 7.3, the raw data from the cross-validated classification is presented in table 8.1. The total samples are 77673 image blocks. From that the cancer class include 2677 samples, the normal class include 35297 samples and finally the background samples are 39699.
From the 2677 true cancer class samples, the classifier have identified 2275 as cancer, 398 as normal, and 4 as background. From the 35297 true normal class samples, the classifier have identified 34155 as normal and 1142 as cancer. All the samples from the true background samples have been correctly identified as background by the classifier.
As mentioned in the section 7.1 only the texture information from the manually delineated regions are used as the class cancer. This means that the texture information similar to the manually delineated regions, which are found outside of the manually delineated are removed from the dataset.

	Classified Class		
True Class	**Cancer**	**Normal**	**Background**
Cancer	2275	398	4
Normal	1142	34155	0
Background	0	0	39699

Table 8.1: The cross-validated classification of image blocks are presented in this table. The image blocks are divided in three classes or groups (cancer, normal and background). True class represent the real class where the image blocks are from. The classified class is where the developed framework have classified the image blocks belongs to.

These raw data have been counted in to different categories. These categories are: true positive (TP), false positive (FP), false negative (FN), and true negative (TN), see table 8.2. True positive is when cancer tissue image block classified as cancer. True negative is when normal tissue image block classified as normal. False positive is when cancer tissue image block classified as normal and false negative is when normal tissue image block classified as cancer. Background class is not interest in further calculation.

TP	**FP**	**FN**	**TN**
2275/85%	398/14.9%	1142/3.2%	34155/96.8%

Table 8.2: The raw data from cross-validation used to calculate the sensitivity, specificity, accuracy and area under curve. Where, TP denotes True positive, FP false positive, FN False negative, and TN true negative.

Table 8.3 shows the results of sensitivity, specificity and accuracy using the equation presented in chapter 7.

Sensitivity%	Specificity%	ACC%
66.58	98.85	95.94

Table 8.3: Cross-validated classification results, where ACC denotes accuracy.

The figure 8.1 show the original image and the image with outlined cancer tissue location. This image will be used as one example of the developed classification based segmentation framework.

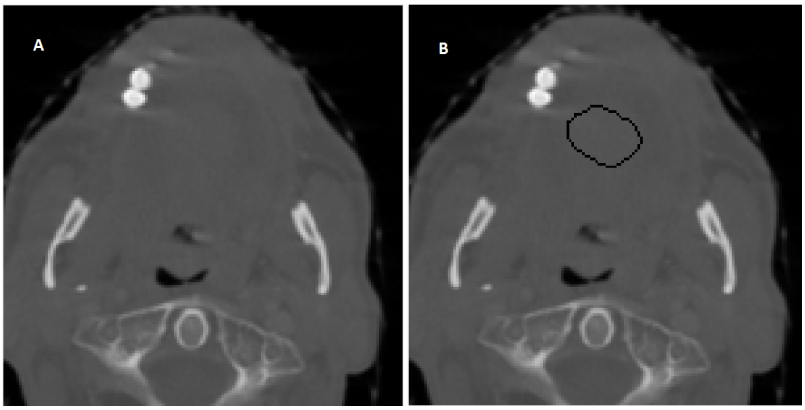


Figure 8.1: (A) the original image and (B) the manually delineated location of cancer tissue is outlined with color black.

As mentioned earlier, the images are divided in small blocks and each block is classified in three different classes. These classified classes are then used for segmentation. The segmentation results from the cross-validated classification are shown in figure 8.2 and 8.3. Those different image blocks which belong to the different classes are marked with colored squares on the original images. The true manually delineated region is marked with purple color.

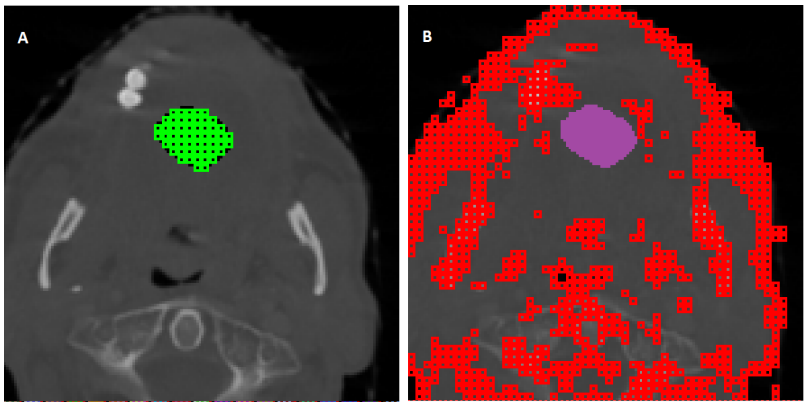


Figure 8.2: (A) the cross-validated classification result classified the region marked with green color squares as the cancer class. (B) the classified normal class, where the manually delineated location of cancer tissue is marked with purple color.

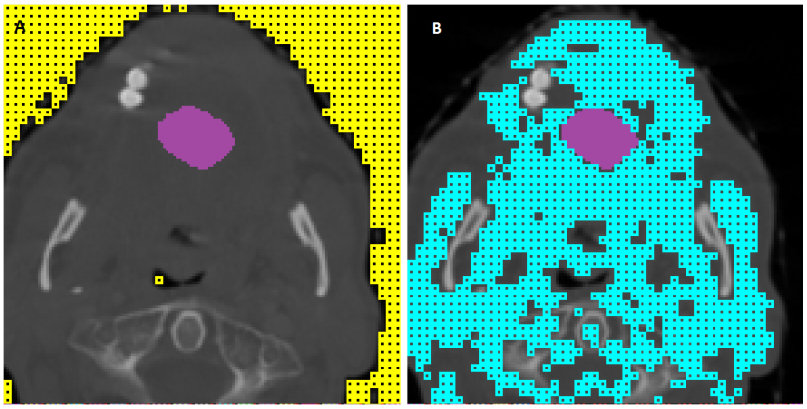


Figure 8.3: (A) the cross-validated classification result classified the region marked with yellow color squares as the background class. The manually delineated location of cancer tissue is marked with purple color (B) The image blocks similar to the manually delineated regions, which were not included in the cross-validated classification are marked with blue color square. The purple color define the manually delineated location of cancer tissue.

8.2 Test on New Subjects

In this section, the results obtained from the test on new subjects using the trained-classifier are presented. The test includes eight CT images from two new subjects. Four image slides from each subject. During the Cross-validated Classification section 8.1 the texture information similar to the manually delineated found outside of the delineated region was not included. In this section, the texture information from all the image blocks are used. This means that the texture information that are not included in the section 8.1 is included in this section. The raw data from the test is shown in table 8.4. The third group (background) will not be account in further analysis.

The total samples are 19169 image blocks. From that, the cancer class include 2355 samples, the normal class include 13307 samples and finally the background samples are 3507. From the 2355 true cancer class samples, the classifier have identified 1374 as cancer, 963 as normal, and 18 as background. From the 13307 true normal class samples, the classifier have identified 8641 as normal and 4666 as cancer. All the samples from the true background samples have been correctly identified as background by the classifier.

	Classified Class		
True Class	**Cancer**	**Normal**	**Background**
Cancer	1374	963	18
Normal	4666	8641	0
Background	0	0	3507

Table 8.4: The test results of cross-validated classification of the developed framework are presented in this table. The image blocks are divided in three classes or groups (cancer, normal and background). True class represent the real class where the image blocks are from. The classified class is where the trained-classifier that is classified where the image blocks belongs to.

The raw data is used to identify the different categories: true positive (TP), false positive (FP), false negative (FN), and true negative (TN). These are shown in table 8.5.

TP	**FP**	**FN**	**TN**
1374/58.3%	963/40.9%	4666/35.1%	8641/64.9%

Table 8.5: The raw data to calculate the sensitivity, specificity, accuracy and area under curve. Where, TP denotes True positive, FP false positive, FN False negative, and TN true negative.

Table 8.6 shows the results: sensitivity, specificity, and ACC calculated by the raw data using the equation presented in chapter 7.

Sensitivity%	Specificity%	ACC%
22.8	90	64

Table 8.6: The results from test of cross-validated classification is shown in this table, where ACC denotes accuracy.

Figure 8.4 and 8.5 show the results from test of the cross-validated classification segmentation. Figure 8.4(B) represents the classification class tumor. In this class, all the image blocks where the developed framework was classified as tumor is shown. In figure 8.5(A), the image blocks where the classifier classified as normal is shown. Finally, in figure 8.5(B) the third background class is showed.

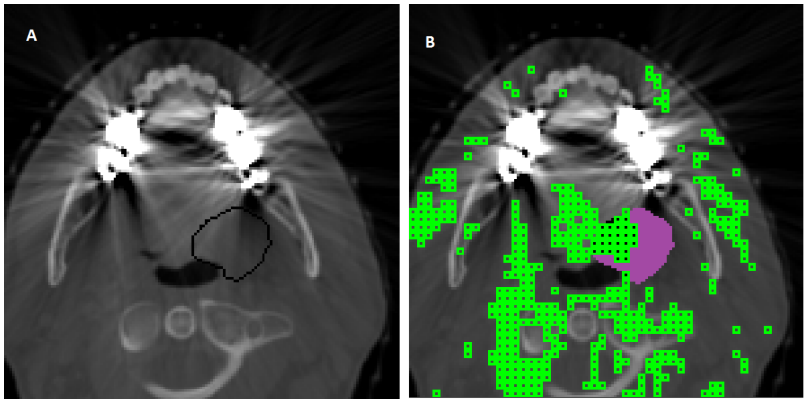


Figure 8.4: Results from test of the cross-validated classification segmentation. (A) the original where the location of cancer tissue is outlined with color black. (B) the region marked with green squares are the classified class cancer. The original cancer location is marked with the color purple.

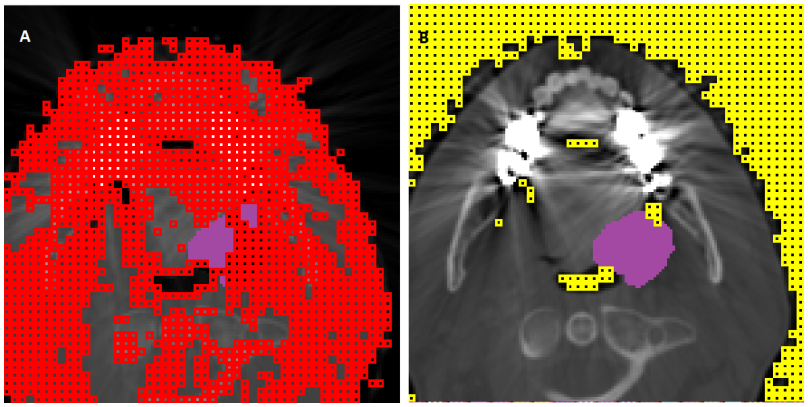


Figure 8.5: Results from test of the cross-validated classification segmentation. The original cancer location is marked with the color purple on both images. (A) the region marked with red squares are the classified class normal. (B) the region marked with yellow squares are the classified class background.

Chapter 9

Synthesis

This chapter first presents the key motivation behind this project, followed by a discussion based on the developed software framework, and finally conclusion of this report.

The head and neck cancer involves many important organs. As of this, it is important to consider these organs in the cancer treatment as the side effect of such treatment may affect the functionalities of a healthy organ. It is important to identify or validate the cancer suspicion as soon as possible such that the treatment plan can begin. The survival prognosis of the patient with head and neck cancer depends on the time. Therefore, detecting a potential cancer tumor location is one of the main task in the imaging modalities utilized during the cancer management phase. Currently in clinical practice, the target volume definition is done by manual delineation on CT and PET images by physicians. It is time-consuming and leads to intra- and inter-observer variation.

Furthermore, the used imaging modalities makes the target volume definition more complex. In case of a PET scanning, the tumor tissue location identification is considered as a simple task. However, defining the boundaries of the tumor can be difficult. One of the reason could be pointed at the low spatial resolution. When considering CT scanning, then the tumor tissue location and boundaries definition gives intra- and inter-observer variation. However, CT scanning is the de facto standard when considering imaging in head and neck cancer treatment. The CT scanning have advantages during the radiation dose calculation that requires CT electron density data. Several studies showed that by using the PET/CT image gives will lead to some promising results in target volume definition.

There are many studies working on the segmentation of the normal and tumor tissues, however, there are no one standard method found in the literature. The classification-based segmentation are used for other types of cancer, such as prostate cancer, breast cancer and pulmonary cancer.

9.1 Discussion

In following section the developed framework and the results obtained from this framework is discussed.

9.1.1 Discussion of the developed Framework

Classification based segmentation method was used for the developed framework for head and neck cancer. Texture features from different CT scanning images were used as input for this method. The GTV location was not limited to one specific organ, e.g., to include the tumor that was found in throat only. The SVM classification method have two sections, namely: training and classification sections. In the training section, different GTV locations, which were found on the different organs need to be included. If the GTV location was not used in the training section, then the classification of the input image with new GTV location, can be difficult, and negative result may occur from the test. Furthermore, other artifacts such as the image resolution, noise which also could have influenced the results.

In this project, the manual delineation was used. If not all the cancer tissues were included in the manual delineation, then the classification trainer will train the not included tumor region as normal. If this situation occurs then the developed framework gives a negative result. Furthermore, only the locations that were manually delineated was used as cancer tissues. The texture information similar to the normal tissue outside of the contoured region were removed from the dataset. The removed information could have influenced the final classification results.

Three classification classes were used in the developed framework, (i) cancer, (ii) normal and (iii) background. The regions that were identified by the manual contouring was selected as the true class cancer. The regions that were not included in the manual delineation and the texture information differ from the manual delineation were defined as true class normal. However, the class normal does not only contain one pixel intensity or one contrast level. This makes the classification task more difficult because normal tissue will include different image information. This could have contributed negatively to the segmentation result.

In general, there was a variation in the used sample size. The normal and background class were large than the cancer class. The sensitivity, specificity and accuracy results were affected by the sample size. One of the other method called precision recall could have been used in this purpose.

9.1.2 Discussion of the Results

The result from classification training was presented in table 8.3, where the sensitivity was at 66.58%, specificity at 98.85%, and accuracy at 95.94%. The sensitivity result was low in compare to these other two results. One of the reasons could be pointed at the used sample size as above-mentioned could have contributed to this low sensitivity result.

The trained-classifier was tested on two new patients. The CT scanning image slides from these two patients were not included on the calculation of the classifier. The testing dataset include only 8 CT scanning image slides. From the results that was shown in table 8.6, it can be seen that the sensitivity is 22.8%, specificity is 90%, and accuracy of 64%. This results differ from the cross-validated classification. One of the reason could be that the texture information found outside the manually delineated region was not included during the cross-validated classification. The main reason for not including the texture information found outside the manually delineated region during the classification was that these were not verified by the physicians. Furthermore, the samples used in the cross-validated classification did not include all the possible cases that could occur in the head and neck cancer this could contributed negatively to the overall results.

In figure 8.1(A) and (B), the original image and the manually delineated were shown. These illustrate the difficulties of identification of the tumor tissue. Figure 3.8 showed the tumor identification from the different imaging modalities. Figure 3.8 (A) showed how difficult it was to identify the tumor tissue using the CT scanning image by three different observers. Figure 3.8 (B) showed the most agreement among these three observers. Figure 3.8(B) showed the least agreement among these three observers. Furthermore, figure 8.1(A) and (B), showed one of the original image and the manually delineated used in this project. These illustrated the image quality and the difficulties of identification of the tumor tissue using CT scanning.
The segmentation results from the cross-validated classification was shown in image 8.2(A) and (B). Figure 8.2(A), showed how good the developed framework classified the manually delineated region. Figure 8.2(B), showed the classification of the normal class. As it was illustrated in this figure, there were regions that was not classified as normal, cancer or background. These regions were illustrated in figure 8.3(B). These regions were removed from the dataset, as they were similar to the texture information found in the manually delineated region. From this, it is clear that there are texture information similar to the manually delineated region found outside this region. This makes, segmentation of tumor from images using the developed framework difficult.

There are several aspects of the developed software in this project that can be improved and optimized. One such aspect is that this project only includes CT scanning images to target volume identification. As mentioned in section 3.3.4 there are sev-

eral studies stating that the target volume identification using integrated PET/CT can decrease the observer variability and from this a more precise target volume identification can be achieved. Having tested on the integrated PET/CT could have improved the result produced by the developed framework of this project.

Furthermore, the window level and contrast level is kept constant for all the images. In every day cases the physician changes the setting to get a better view of the images. This scenarios is not taken in to account in this project. If this scenario were included in the development of the framework, then the framework could have improved the tumor segmentation results. As an effect, the tumor tissues could be clearly visible from the images.

9.2 Conclusion

The key focus of this project is to develop a framework that segment tumor tissues based on head and neck cancer CT scanning images. In order to segment the tumor tissues, this framework uses classification-based segmentation with texture information as input.
The developed framework have first been cross-validated, and from this a trained classifier have been created. Finally, the trained classifier have been tested on new images. The results from the cross-validation showed a sensitivity of 66.58%, specificity 98.85%, and accuracy of 95.94%. With a sensitivity of almost 67% the classifier can in most cases identify cancer. The results obtained from the test using the trained classifier, is as follows: sensitivity 22.8%, specificity 90%, and accuracy of 64%. The sensitivity in this test is lower than the result from the cross-validation. This means that, in most cases the classifier will classify cancer as normal. However, there are room for improvements, e.g., to improve the sensitivity, one option could be to include more samples during the cross-validation. It is important to include all the possible scenarios of cancer types to get better results, e.g., a large variation in the samples, which include different location, variation and appearance when considering head and neck cancer classification. Another option for improve the results from the developed frame work is to include other imaging modality addition to the CT .e.g., to use both PET and CT scanning images.
Overall, it can be concluded that the developed framework can with success segment the tumor tissues based on head and neck cancer CT scanning images. However, for an in-depth statistical analysis more images are needed.

9.3 Future Work

This project have some weak points that could have influenced the results attained from the developed framework. These weak points can be stated as follows, and must be accounted for in an eventual future work:

- Not include whole texture information from the head and neck cancer CT scanning image in the training section
- The samples from different classes varies in the training section
- The statistic measurement to evaluate the developed framework depends on the sample size. Other methods that are account for the varies sample size need to be used.
- Include more samples
- Include other imaging modalities such as PET integrate with CT.

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