EVALUATION OF THE DOSIMETRIC PARAMETERS OF THE ORGAN AT RISK USING HDR INTERSTITIAL LIVER BRACHYTHERAPY TREATMENT

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by

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cm^3	centimeter cubic
Gy	Gray

LIST OF ABBREVIATIONS

AFP	Alpha-fetoprotein
BT	Brachytherapy
CLS	Central liver structure
CT	Computed tomography
CTV	Clinical Tumour Volume
CW	Chest wall
DNA	Deoxyribonucleic acid
DVH	Dose Volume Histogram
EBRT	External Beam Radiotherapy
GTV	Gross Tumour Volume
HDR	High Dose Rate
HDR IBT	High Dose Rate Interstitial Brachytherapy
LAT	Locally ablative treatment
MR	Magnetic resonance
OAR	Organ at risk
PTV	Planning Tumour Volume
RCW	Right chest wall
RD	Right diaphragm
RT	Radiotherapy; Radiation therapy; Radiation technique
SBRT	Stereotactic Body Radiotherapy
SPSS	Statistical Package for Social Sciences
TNM	Tumour Nodes Metastases
TPS	Treatment Planning System
US	Ultrasound
USM	Universiti Sains Malaysia

LIST OF SYMBOLS

$D_{0.2cc}$	Dose received by 0.2 cm^3 of OAR volume
$D_{50\%}$	Dose received by 50% of OAR volume
Ir-192	Iridium-192

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PENILAIAN PARAMETER DOSIMETRI BAGI ORGAN BERISIKO MELALUI RAWATAN BRAKITERAPI HDR INTERSTISIAL HATI

ABSTRAK

High dose rate interstitial brachytherapy (HDR IBT) merupakan teknik kerap digunakan dan termaju untuk merawat tumor hati dengan memaksimumkan dos preskripsi pada tumor dan menyelamatkan organ berisiko (OAR) daripada sinaran dos yang tidak diingini. Objektif utama kajian retrospektif ini adalah untuk menilai parameter dosimetri OAR terutamanya struktur hati pusat (CLS), dinding dada kanan (RCW) dan diafragma kanan (RD), melalui HDR IBT dan sumber radioaktif Iridium-192 (Ir-192). Kajian ini menggunakan tomografi berkomputer (CT) daripada sistem perancangan rawatan (TPS) Oncentra untuk menganalisa secara retrospektif pengedaran dos OAR pada 55 pesakit yang menjalani 89 rawatan HDR IBT. Data yang dikumpul telah digunakan untuk menganalisa hubungan statistik antara dosimetrik OAR melalui satu dan lebih daripada satu pecahan dan dos preskripsi dari 15 - 25 Gy melalui HDR IBT. Dalam kajian ini, analisis dosimetri pada OAR adalah berdasarkan RTOG 0438 dan jurnal lain yang diterbitkan. Oleh itu, kami telah mencadangkan $D_{50\%}$ CLS $\leq$ 10.11 Gy, $\leq$ 15.38 Gy dan $\leq$ 61.25 Gy dan $D_{0.2cc}$ CLS $\leq$ 27.31 Gy, $\leq$ 60.93 Gy dan $\leq$ 150.84 Gy, $D_{50\%}$ RCW $\leq$ 4.27 Gy, $\leq$ 9.47 Gy dan $\leq$ 11.46 Gy dan $D_{0.2cc}$ RCW $\leq$ 31.54 Gy, $\leq$ 41.34 Gy dan $\leq$ 163.01 Gy dan akhirnya, $D_{50\%}$ RD $\leq$ 8.04 Gy, $\leq$ 17.63 Gy dan $\leq$ 26.30 Gy dan $D_{0.2cc}$ RD $\leq$ 72.19 Gy, $\leq$ 102.01 Gy dan $\leq$ 297.14 Gy untuk satu, dua dan lebih daripada dua pecahan rawatan pada 15 – 25 Gy dos preskripsi. Secara ringkasnya, kenaikan dos OAR melalui teknik HDR IBT, adalah disebabkan lokasi tumor dan rawatan yang melibatkan lebih daripada satu pecahan dalam kes tertentu dan bukan disebabkan saiz GTV dan dos preskripsi yang diberikan.

EVALUATION OF THE DOSIMETRIC PARAMETERS OF THE ORGAN AT RISK USING HDR INTERSTITIAL LIVER BRACHYTHERAPY TREATMENT

ABSTRACT

High dose rate interstitial brachytherapy (HDR IBT) is a widely used and advanced technique to treat liver tumours by maximising the prescribed dose and sparing the adjacent organ at risk (OAR) from unwanted radiation. The main objective of this retrospective study was to evaluate the dosimetry parameters of the OAR especially central liver structure (CLS), right chest wall (RCW) and right diaphragm (RD) using HDR IBT and Iridium-192 (Ir-192) source. This study used computed tomography (CT) data from the Oncentra treatment planning system (TPS) to retrospectively analyse the dose distribution in 89 HDR IBT treatment cases of 55 patients. These data were used to statistically analyse the relationship between the dosimetric variables of OAR doses through single and multiple HDR IBT fractionations at prescribed dose of 15 Gy, 20 Gy and 25 Gy. Dosimetry analysis on OAR of this study were based on RTOG 0438 and other published journals. Therefore, have suggested $D_{50\%}$ of the CLS $\leq$ 10.11 Gy, $\leq$ 15.38 Gy and $\leq$ 61.25 Gy and $D_{0.2cc}$ of CLS $\leq$ 27.31 Gy, $\leq$ 60.93 Gy and $\leq$ 150.84 Gy, $D_{50\%}$ of the RCW $\leq$ 4.27 Gy, $\leq$ 9.47 Gy and $\leq$ 11.46 Gy and $D_{0.2cc}$ of RCW $\leq$ 31.54 Gy, $\leq$ 41.34 Gy and $\leq$ 163.01 Gy and finally, $D_{50\%}$ of the RD $\leq$ 8.04 Gy, $\leq$ 17.63 Gy and $\leq$ 26.30 Gy and $D_{0.2cc}$ of RD $\leq$ 72.19 Gy, $\leq$ 102.01 Gy and $\leq$ 297.14 Gy for single, two and more than two fractions treatment respectively across 15 to 25 Gy prescribed dose. In a nutshell, dose increment to OAR through HDR IBT, is due to location of the tumour and multiple fractionations, instead of tumour size and prescribed dose.

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND OF THE STUDY

Liver cancer is the sixth most life threatening cancers in Malaysia with expected figure around 2149, or 4.4 % of the Malaysian population and third highest mortality rate of 2,050 or 6.9% of Malaysian population in 2020 (Malaysia - International Agency for Research on Cancer, 2020). Liver malignancy can be classified into primary cancer or metasised from other primary cancers (Park & Kim, 2020). Therefore, early detection of liver tumors help to improve the prognosis of this disease due to advancement in available treatment options (Raihan et al., 2018) (Walter et al., 2021).

At present, treatment options that are available to cure liver cancer, either via resection (surgery and liver transplant) or non-resection options, such as radiofrequency ablation, microwave ablation, radiation ablation, transarterial-chemoembolisation (TACE) and chemotherapy (Vogel et al., 2018) (Yamashita & Kaneko, 2016) (Liu, Chen & Chen, 2015). Radiotherapy (RT) procedures for liver malignancy treatment commonly performed in Pusat Perubatan USM are stereotactic body radiation therapy (SBRT) and high dose rate interstitial brachytherapy (HDR IBT).

The main RT objectives are to deliver a maximum radiation dose to the tumor, while sparing the surrounding healthy organs and tissue, known as organs at risk (OAR) (IAEA, 2022). Therefore, accurate dose constrains for OAR during treatment planning is required in avoiding unwanted radiation exposure to the OAR. This retrospective study was focused more on ideal dose constraints to the OAR via HDR IBT for liver cancer.

This is due to less investigated and less works on dose constrains to OAR via HDR IBT treatment (Sharma et al., 2013).

HDR IBT is a treatment, where sealed radioactive sources like Iridium 192 (Ir-192), are implanted near or within the tumour (Chargari et al., 2019) (Bretschneider et al., 2016) (Shirin et al., 2014). Hence, very high radiation dose to tumour region were delivered while maintaining low dose to surrounding healthy liver tissue and OAR (Walter et al., 2021) (Chargari et al., 2019) (Bretschneider et al., 2016) (Shirin et al., 2014). Single fraction of HDR IBT with prescribed dose of 15 to 25 Gy is considered to be highly effective in treating the liver tumour. This is due to conformal coverage of large and irregular shaped tumours, hence eliminating the tumor and sparing the adjacent OAR (Walter et al., 2021). Besides that, being a minimally invasive technique, it is safe to perform on centrally located liver tumors, which contains numerous great blood vessels. This is in contrast with resection treatment options (Venkat et al., 2017).

To achieve an optimal dose delivery to both tumor and OAR via HDR IBT, well experienced healthcare staffs and complete HDR IBT liver protocol are required (Raihan et al., 2018). Common documented OAR dose constrains for liver cases are stomach, oesophagus, spinal canal, liver hilum, small intestine and colon. However, there are no dose constraints for OAR like central liver structure (CLS), when it is located within the liver, right chest wall (RCW) and right diaphragm (RD), when these OAR are located superiorly to the liver (Michel et al., 2017). Hence, dose constrains to these OAR are required to avoid unwanted radiation exposure during treatment that leads to adverse side effects in future (IAEA, 2022). The purpose of this study was to evaluate dosimetric parameters of the selected OAR via HDR IBT for liver cancer.

1.2 PROBLEM STATEMENT

HDR IBT treatment is the safest and effective technique in curing liver tumors. However, limited works on this technique was observed from inadequate references on dose constraints of nearby OAR, such as CLS, RCW and RD. Therefore, this makes the treatment more difficult to be performed and exposes the tumour to underdose, which leads to loss of tumour size control due to restricting the OAR dose.

Based on human anatomy, RCW and RD located right above the liver and CLS is within the liver close to hilum and bifurcation, hence may have higher tendency in receiving unwanted radiation dose. There are limited works on standard dose constrains for these OAR through HDR IBT liver procedure. However, there are several SBRT studies that can used as reference to set up new dose constrains for these OAR in HDR IBT procedure. This includes RTOG 0438 that suggested the maximum ribs dose ($\leq$ 54 Gy). Whereas, Woody et al., 2011 and Stephans et al., 2011 suggested that overall dose to chest wall $\leq$ 30 Gy via SBRT. Therefore, in this project the reference dose constrains for CLS, RCW and RD using HDR IBT were suggested for a better dose delivery to tumour cell and maintain the functionality OAR after exposure.

1.3 RESEARCH OBJECTIVES

GENERAL OBJECTIVE

The main objective of this study is to evaluate the dosimetry parameters for the nearby OAR via HDR IBT for liver cancer cases using Ir-192 source.

SPECIFIC OBJECTIVES

1. To analyse the effect of tumour size on the dose delivered to the selected OAR (CLS, RCW and RD).

2. To evaluate dose to the selected OAR based on prescribed dose of 15 Gy, 20 Gy and 25 Gy.
3. To analyse single and multiple fractionations effect on the dose delivered to the selected OAR.
4. To propose and update the range of dose constrains for OAR as a guideline for HDR IBT for liver cancer.

1.4 SIGNIFICANT OF RESEARCH

Findings obtained from this retrospective study will be beneficial in practicing HDR IBT for liver cancer. We have analysed the radiation dose received by the selected OAR (CLS, RCW and RD) and compared with available published journals. Therefore, this study suggest and update the dose constrains for these OAR. Lack of published works and clinical experience on this technique restricts the healthcare staffs to perform this technique in curing liver tumors. With our suggested dose constrains to OAR, this will help the oncologists and medical physicists to plan an optimal treatment delivery to liver tumors diagnosed patients. Besides healthcare staffs, this study is also beneficial to researchers. Findings from this study provide a baseline for future works, such as establishing more detailed dosimetric protocols of HDR IBT for liver cancer.

1.5 RESEARCH SCOPE

The scope of this research project consists of:

1. Retrospective data from 2018 till 2023 on liver HDR IBT treatment.
2. Liver malignancy studied in this research that consist of primary and metastases liver tumors.

3. Reviewed and studied maximum and mean dose constraints for the nearest OAR, specifically CLS, RCW and RD.
4. Proposed dose constraints for selected OAR mainly for single and multiple HDR IBT fractions at prescribed dose to liver tumour of 15 Gy, 20 Gy and 25 Gy.

1.6 THESIS OUTLINE

This thesis is divided into five major chapters, starting with chapter 1, which covers background of this study, problem statements, objectives, significance, scope, and outline of this research work.

Chapter 2 provides an overview of the liver cancer, along with information on its diagnosis, stages and available treatment options. Next, detailed discussion on current RT techniques in treating liver tumours follows. Besides that, dose constraints for the nearest OAR, that have been proposed by other researchers are reviewed and discussed.

Chapter 3 describes methodology of this research project, which begins with patients' selection criteria. The process of collecting retrospective data using Oncentra Brachy software is then explained. Next, statistical analysis to assess the dose constraints for the selected OAR using SPSS software is discussed.

In chapter 4, relationships between the acquired OAR doses are analysed and discussed in various parameters like tumour volume, prescribed dose to tumour and number of treatment fractions. The obtained OAR doses are summarised and compared with published journals, to propose a new set of OAR dose constraints.

Finally, the overall research results are provided in chapter 5. Additionally highlighted on study's limitations and recommendations for future works on this project.

CHAPTER 2

LITERATURE REVIEW

This chapter discussed a brief overview on liver cancer, which is further detailed on diagnosis, stages and available treatment options to cure liver cancer. Apart from that, also explained in detail on radiotherapy in treating liver tumors. Finally, reviewed on available dose constrains for the nearest OAR.

2.1 LIVER MALIGNANCY

The second largest organ in human body is the liver, which lies in right upper quadrant of the abdomen region, superior to the stomach and inferior to the diaphragm, overall liver is protected by the ribs (Ozougwu, 2017). Liver is a crucial organ in human body because it can perform numerous duties such as synthesising proteins, distributing biochemicals or hormones for growth and digestion and eliminating waste from the body ("Liver: Anatomy and Functions", 2022).

In Malaysia, liver malignancy is the sixth most deadliest cancer and third highest mortality rate in 2020 (Malaysia - International Agency for Research on Cancer, 2020). Common factors inducing liver malignancy include hepatitis B and C virus infections, which results in cirrhosis, practicing sedentary lifestyles and unhealthy diet like over consumption of alcohol and smoking, that leads to chronic diseases like diabetes and obesity (Anwanwan et al., 2020) (Park & Kim, 2020) (Raihan et al., 2018).

Liver malignancy can be classified into primary and secondary liver cancer (Park & Kim, 2020). Primary liver cancer originates either within liver as hepatocellular carcinoma (HCC) or within bile ducts as intrahepatic cholangiocarcinoma (ICC) (Cong et al., 2016). Whereas, secondary liver cancers are metastasised liver tumours that originates from various types of histology malignancies such as colorectal cancer (CRC), neuroendocrine cancer, pancreatic cancer, breast cancer, lung cancer, nasopharynx cancer and gastric cancer (Tsilimigras et al., 2021) (Park & Kim, 2020). Liver is one of the common sites of metastases due to having numerous blood and lymphatic supply, which increases the risk of cancer spreading to the liver (Park & Kim, 2020).

2.1.1 DIAGNOSIS FOR LIVER MALIGNANCY

The main reason for liver cancer in being the third highest mortality rate is due to delay in patient diagnosis at early stage, when patient experiences symptoms like right side abdominal pain, fever, sudden loss in weight, jaundice, fatigue, joint pain and prolonged cough (Raihan et al., 2018) (Kaur & Khamparia, 2015). This will result in restriction to perform curative treatment procedures to liver tumours due to disease progression and subside liver function, hence early detection of disease is always recommended (Raihan et al., 2018).

Patients who have experienced the previously mentioned symptoms and patients who are at risk should undergo screening test like alpha-fetoprotein (AFP) blood test (Vogel et al., 2018) (De Lope et al., 2012). AFP blood test will be conducted to patients every 6 months to measure the protein or AFP levels in their body using AFP tumour marker (Lee, 2022). When AFP level is high, the patient might be diagnosed with cirrhosis, hepatitis or liver cancer. However, AFP blood test alone does not conclude everything, hence other diagnosis process should be performed as well (Lee, 2022).

Diagnosis of liver cancer can be performed via non-invasively using imaging device such as computed tomography (CT), magnetic resonance (MR) imaging and ultrasound (US) (Orcutt & Anaya, 2018) (Kaur & Khamparia, 2015). However, in some cases, diagnosing small liver tumours (< 2 cm) using imaging device will be very challenging (Orcutt & Anaya, 2018). Therefore, biopsy of tissue is always recommended as it examines the histopathological of the tumour present and also on tumour progression, resulting in accurate tumour conformation (Park & Kim, 2020). Figure 2.1 illustrates the overall diagnosis of the liver cancer.

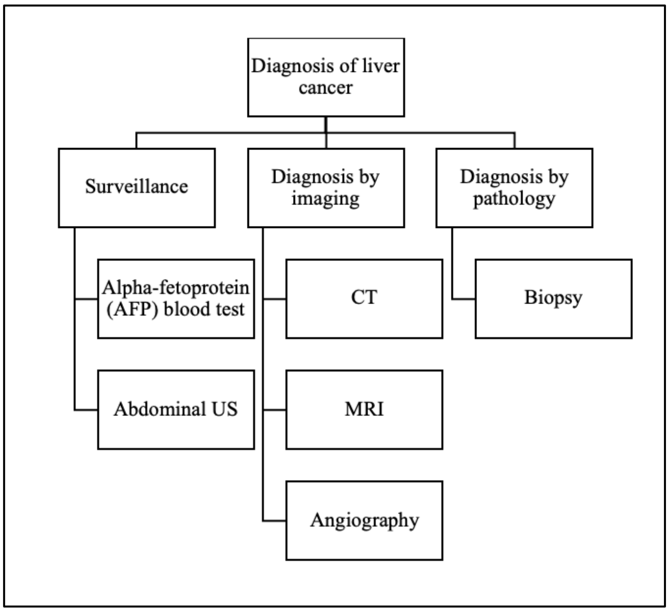

Figure 2.1: Overview of the diagnosis of liver malignancy.

2.1.2 STAGES OF LIVER MALIGNANCY

Following the diagnosis, doctors in charge will conduct tumour staging or scoring procedure, based on tumour's condition. According to the American Cancer Society (2022), staging is a critical procedure that doctors will carry out to determine a patient's life expectancy and to decide the best course of treatment in curing tumours ("Cancer Staging", 2022). There are several parameters considered during staging like size of the tumour, degree of seriousness of the underlying tumour, tumour spreading extent to neighbouring organs and tumour metastases (Liu et al., 2015).

At present, widely used staging systems for the prognosis of liver malignancies, are American Joint Committee on Cancer (AJCC) tumour-node metastasis (TNM) system, Barcelona Clinic Liver Cancer (BCLC) system and Okuda system, along with more recent schemes like Cancer of the Liver Italian Program (CLIP) score, Groupe d'Etude du Treatment du Carcinome H'epatocellulaire (GRETCH), Chinese University Prognostic System (CUPI) and Japan Integrated Staging (JIS) system.

Variations in patient's demographic background, leads to variability in patient's anatomy and liver malignancies, hence causing variances in published staging systems (Liu et al., 2015). The selection of the optimal staging system requires careful consideration of all crucial data collected by doctors during patient diagnosis for accurate tumor staging ("Cancer Staging", 2022).

2.1.3 TREATMENT OPTIONS FOR LIVER MALIGNANCY

Once the diagnosis and staging process are done performed by oncologist to the patient, the ideal treatment to liver tumours will be suggested based on patient's current disease stage, patient's liver function and patient's performance status. From that, the best treatment options will be administered to the diagnosed patient (Orcutt & Anaya, 2018). Fortunately, there are various treatment options available to treat liver tumours such as via tumor resection (surgery and liver transplant), local ablative treatments (LAT) (radiofrequency LAT, microwave LAT and radiation based LAT), transarterial chemoembolisation (TACE) and chemotherapy, as shown in Figure 2.2 (Vogel et al., 2018) (Yamashita & Kaneko, 2016) (Liu et al., 2015).

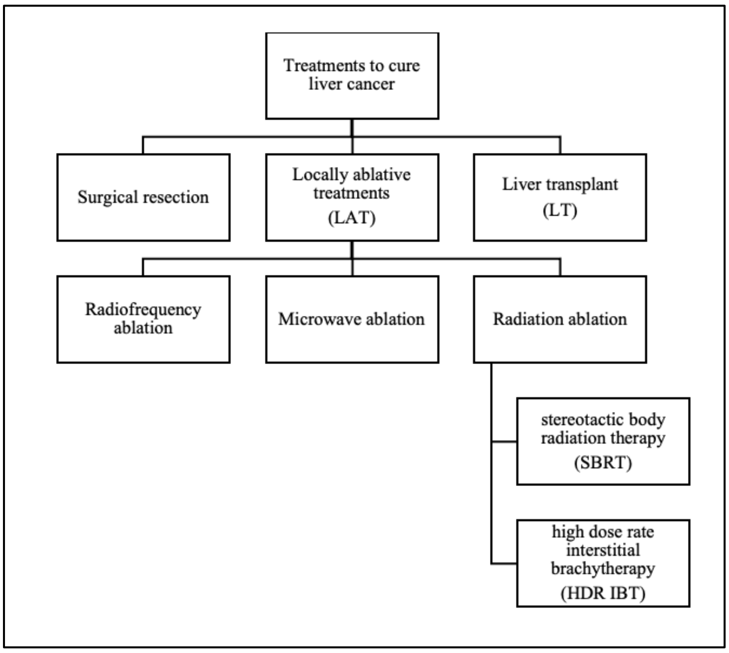

Figure 2.2: Treatments for liver malignancy.

Till today, the most effective method in treating liver tumours is surgery (Appalanaido et al., 2021). However, surgery does have some downfall that makes it more challenging to be performed, such as only ideal for nonmetastatic disease with good liver function, applicable in 20 – 30 % of the liver cancer cases considering tumor size and location and patients' age and condition (Appalanaido et al., 2021) (Orcutt & Anaya, 2018). Thermal ablation is only feasible to small sized tumours and subject to the cooling-effect of adjacent great vessels, hence quite challenging to perform this technique in centrally located lesions (Orcutt & Anaya, 2018). Consequently, suitability of choosing a treatment in treating liver tumours are solely depending on cases' scenarios and several parameters.

2.2 RADIOTHERAPY

Radiation therapy, also known as radiotherapy (RT) is a widely using treatment technique to kill tumour cells with the help of radiation exposure towards the tumour. RT can be used to treat various tumour sites such as lungs, liver, head and neck, prostate and female reproductive tract and spine (Walter et al., 2021). RT can be categorised into external beam RT (EBRT) and internal RT, also known as brachytherapy (BT) (King et al., 2017) (Bretschneider et al., 2016).

2.2.1 EXTERNAL BEAM RADIOTHERAPY AND BRACHYTHERAPY

EBRT uses radiation doses in the form of radiation beams emerging from a linear accelerator machine, outside of the patient's body, to the tumour site, as shown in Figure 2.3 (a) (King et al., 2017). Whereas, BT is a sub-specialised treatment in RT that uses radiation from the sealed radioactive sources, which are implanted either within or near the tumour cells in patient's body, as shown in Figure 2.3 (b) (Bretschneider et al., 2016) (Shirin et al., 2014). These sealed radioactive sources are responsible to deliver the planned treatment by medical physicist and oncologist, where maximum exposure administered to the tumour cell whereas the surrounding healthy tissue will be spared (Shirin et al., 2014).

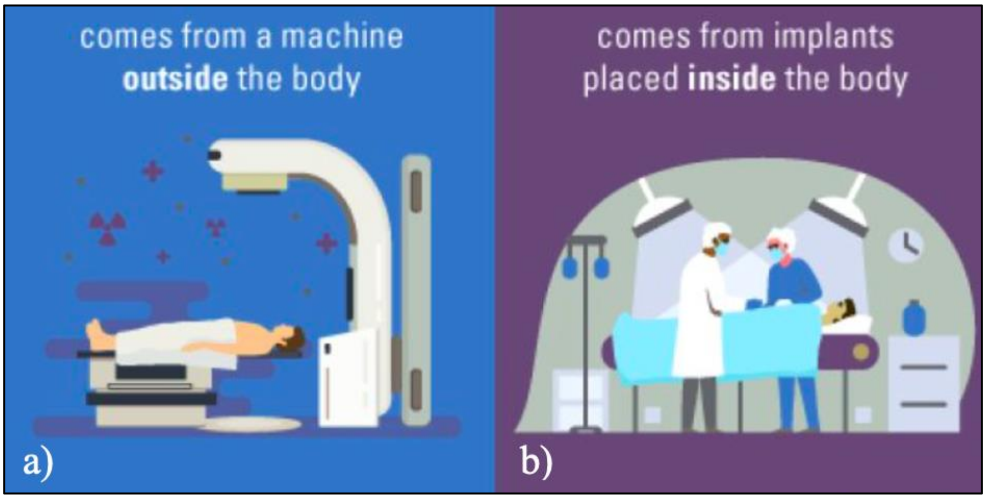

Figure 2.3: (a) external beam radiotherapy; (b) brachytherapy.

One of the advanced technique in BT is the high dose rate brachytherapy (HDR BT), which uses a remote afterloader system to deliver radioactive sources into the target.

HDR BT is beneficial to patients with primary and metastasised cancer by completely eliminating or reducing the size of the tumour. HDR BT can be performed in various tumour sites such as lungs, prostate, lymph nodes, cervix and the kidneys (Bretschneider et al., 2016). The most common radioactive sources used in HDR BT technique is the Iridium-192 (Ir-192), whereas the least common ones are Cobalt-60 (Co-60) and Cesium-192 (Cs-192). These radioactive sources delivers high specific activity, which are essential in achieving HDR simultaneously (Shirin et al., 2014).

2.2.2 RADIOTHERAPY WORKFLOW

Both EBRT and BT workflows to treat liver tumours are quite similar, which begins with patients need to undergo CT simulation to determine the exact location, shape and size of the tumour to be treated (Ricke et al., 2011). Contrast aided CT images are commonly taken for treatment planning purpose, hence accurate patient positioning during CT simulation is necessary, that can be achieved using patient immobilisation device such as vacuum pillow and abdominal compression. In certain special cases, MR images are taken for better image viewing and planning through fusion of both CT and MR images (IAEA, 2022).

After completion of CT simulation, treatment planning process will be performed using highly sophisticated treatment planning system (TPS) (IAEA, 2022). This computerised system will be used by the radiation oncologists and medical physicists to precisely plan the treatment with the help of advanced features in the TPS before executing to real patients (Yang et al., 2019). Main purpose of treatment planning is to maximise the radiation dose to the tumour while reducing the unwanted exposure to the surrounding healthy tissues and organs known as organ at risk (OAR) (IAEA, 2022). It is recommended that delineation of target and all OAR should be performed by the same oncologist and physicist, so that intra- and interobserver variation can be reduced (Ricke et al., 2011).

Finally, planned treatment will be delivered to actual patients. Immobilisation devices that were used during CT simulation, will also be used in actual treatment to reproduce the patient setup as planned in treatment planning system (TPS) (Ayuso et al., 2018). After completion of treatment, patient will be followed up for any adverse effects in future. General RT workflow is summarised in Figure 2.4. Currently, the main RT technique in eliminating liver tumors are either stereotactic body radiation therapy (SBRT) or high dose rate interstitial brachytherapy (HDR IBT) or using either technique as an adjunct to the surgery (Walter et al., 2021).

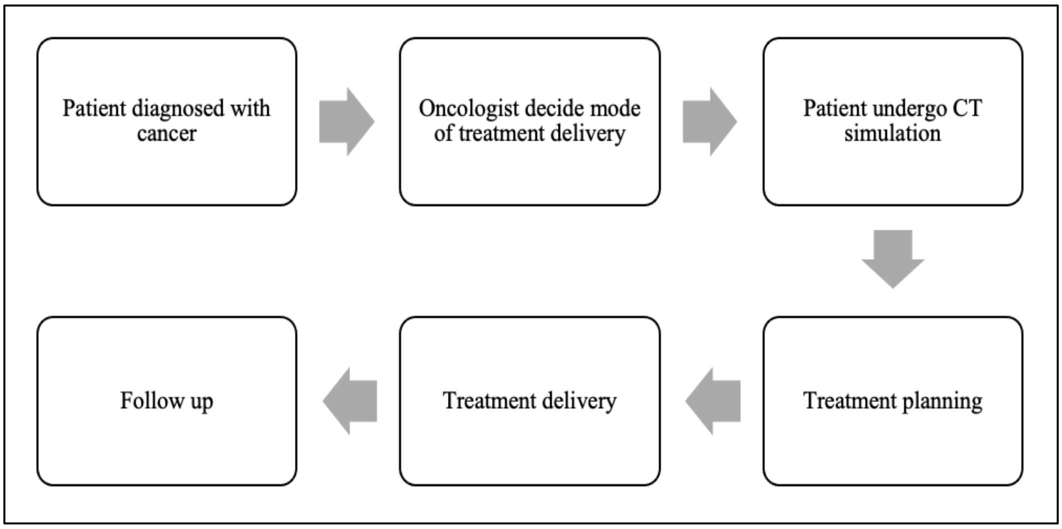

Figure 2.4: The general radiotherapy workflow.

2.3 RADIOTHERAPY FOR LIVER MALIGNANCY

SBRT is a modernised version of EBRT, that uses ultralarge radiation doses per fraction (6 to 30 Gy) in the form of hypofractionated of less than five fractions in total (Gibbons and Khan, 2020). Due to involvement of large doses per fraction, precise and focused treatment planning in creating conformal radiation beams to the liver tumours are very crucial (Gibbons and Khan, 2020). Whereas HDR IBT is an advanced type of BT, where sealed radioactive materials will be inserted within patient's body with help of remote afterloader to deliver very high radiation dose to a more specific tumour region (Walter et al., 2021).

Both SBRT and HDR IBT treatments to liver tumours produce similar tumour local control rates (Walter et al., 2021). However, HDR IBT technique is considered safe due to being minimally invasive and efficient treatment to liver tumours. Usually radiation dose of 15 Gy – 25 Gy are prescribed in single fraction to liver tumours, in contrast to SBRT technique that delivers 37 Gy – 70 Gy in 5 fractions (Walter et al., 2021) (Venkat et al., 2017). Other than that, HDR IBT for liver tumours can also cover larger and more irregular shaped targets depending on the number of catheter used for the implant (Kieszko et al., 2018).

Besides that, HDR IBT reduces unwanted radiation exposure to the adjacent healthy tissues and OAR (IAEA, 2022). This is due to its nature of rapid fall off of radiation dose within the liver that can be achieved with accurate and precise catheter implantation, hence provides maximal radiation dose to tumour (Ricke et al., 2011) (Kieszko et al., 2018) (Bretschneider et al., 2016). Therefore, creating highly conformal dose distribution towards the tumour while sparing the surrounding normal, healthy tissue, as shown in Figure 2.5 (Yang, 2018). Whereas, in SBRT, several hundred millimetres of normal liver tissue will be exposed to ≥ 40 % of the reference dose depending on the location and anatomy of the patient (Ricke et al., 2011).

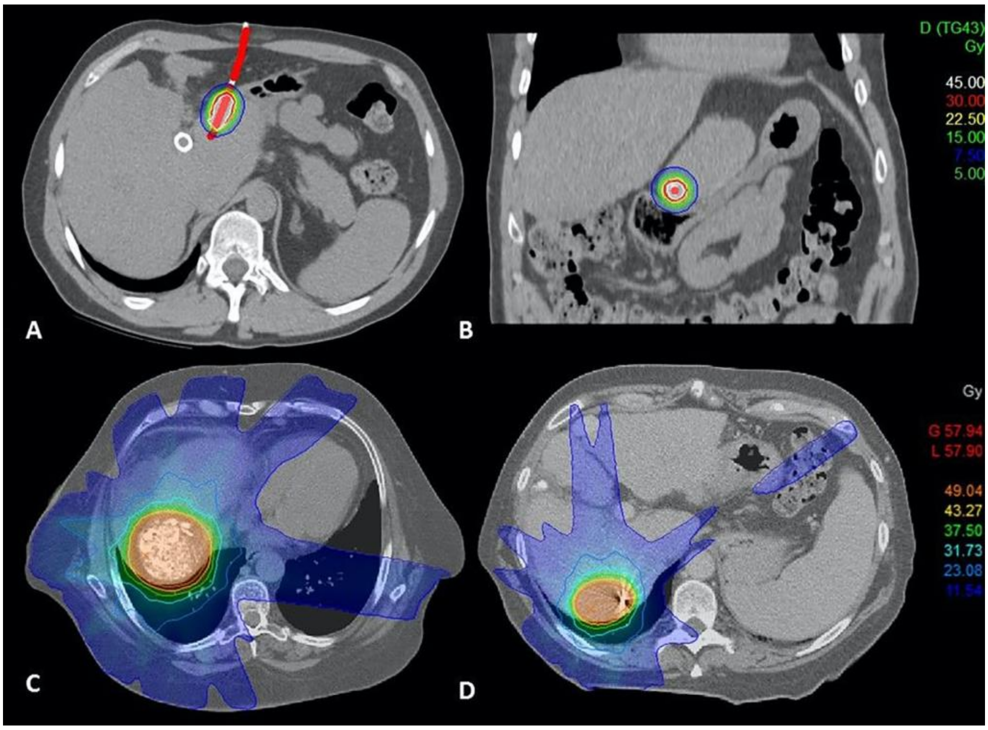

Figure 2.5: (A) and (B) shows BT dose distribution in coronal and sagittal views. (C) and (D) shows SBRT dose distribution in different CT slices (Walter et al., 2021).

2.4 ADJACENT OAR IN HDR IBT FOR LIVER MALIGNANCY

Till today, RT technique are broadly advancing and often practised in curing various tumor sites due to the maximum radiation dose delivery towards the tumour region while sparing the surrounding healthy tissues and OAR (IAEA, 2022). However, due to location of the tumour close to OAR, unwanted radiation exposure will be received by that adjacent OAR, hence damaging the deoxyribonucleic acid (DNA) of the OAR, which leads to OAR dysfunction (Hsieh et al., 2016).

The nearest OAR surrounding the liver tumours are liver itself (without the tumour), biliary tract, diaphragm, ribs, chest wall and stomach, duodenum, bowel whereas the less exposed OAR are heart, kidney, esophagus, spinal canal and mostly left quadrant of the human body, as shown in Figure 2.6 (Michel et al., 2017).

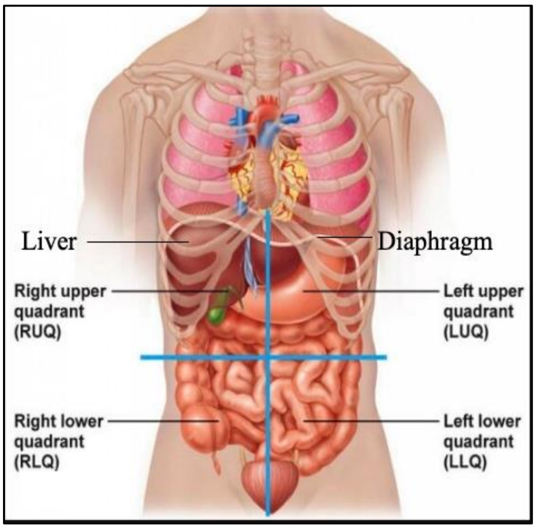

Figure 2.6: Anatomy of liver (“Right upper quadrant of the abdomen”, 2022).

Therefore, nearest OAR to the tumours must be spared from the planned RT treatment delivery (IAEA, 2022). However, there are lack of publish works on dose constrains to OAR via HDR IBT for liver cancer. Based on the literature, 3 OAR dose reference for central liver structure (CLS), right chest wall (RCW) and right diaphragm (RD) were very limited but still important due to its location from the brachytherapy source.

2.4.1 CENTRAL LIVER STRUCTURE

Central liver structure (CLS) is located adjacent to the liver hilum and bile duct bifurcation, within the liver itself (Tselis et al., 2013). This structure is very crucial compared to the surrounding liver structure due to the compact arrangement of blood vessels within CLS such as hepatic duct, portal vein, hepatic artery and inferior vena cava (Tselis et al., 2013). Therefore, resection options and RFA are not ideal to be performed within or adjacent to CLS due to may cause adverse complications like continuous blood loss (Orcutt & Anaya, 2018).

2.4.2 RIGHT CHEST WALL

Right part of chest wall (RCW) is the outer delineation of the thoracic cavity which consists of skin layer (mostly made up of subcutaneous tissues), muscle layer (consists of pectoralis major and minor) and ribs layer (consists of intercostal muscle and rib bones) (Wang et al., 2020). RCW should be spared well from unnecessary radiation due to common adverse side effects such as chest wall pain and pneumothorax (Woody et al., 2011) (Stephan et al., 2011).

2.4.3 RIGHT DIAPHRAGM

Diaphragm is a thin layer of muscular skeletal tissues covering the superior part of the liver and inferior to the lungs, hence separating both abdominal and thoracic cavities (Hsieh et al., 2016). Main function of diaphragm is during the respiratory process. As a muscle tissue, it continuously contracts and flattens during inhalation and relaxes to form the dome shape during exhalation. Skeletal muscles are quite resistant to radiation because these muscle cells are mature cell, hence unable to undergo mitosis process for renewable of the death cells due to radiation (Hsieh et al., 2016). Therefore, diaphragm dose constraints via HDR IBT for liver cancer are needed so that treatment planning can be more efficient. However, there are no documented reports on that.

Therefore, dose constrains for CLS, RCW and RD are necessary to be established especially via HDR IBT for liver cancer, which can serve as a guideline for oncologists and medical physicists. There are several publication on dose constrains for OAR toxicity following RT for liver cancer, as shown in Table 2.1. The variations in OAR dose constraints can be attributed to the different treatment plans, prescribed doses to the tumour and number of treatment fractions (Michel et al., 2017) (Venkat et al., 2017) (Bretschneider et al., 2016).

Table 2.1: List of OAR dose constraints.

Organs at risk	**Study**	**Dose tolerance**
Liver without tumour (alpha/beta 3)	Michel et al., 2017[a]	$D_{30\%} < 7Gy$ $D_{50\%} < 5Gy$
Small intestine	Michel et al., 2017[a] Bretschneider et al., 2016[b]	$D_{max} < 30$ Gy $D_{max} < 15$ Gy
Colon	Bretschneider et al., 2016[b]	$D_{max} < 15$ Gy
Stomach (alpha/beta 5)	Bretschneider et al., 2016[b]	$D_{max} < 15$ Gy
Oesophagus	Michel et al., 2017[a] Bretschneider et al., 2016[b]	$D_{max} < 14$ Gy $D_{max} < 18$ Gy
Spinal cord (alpha/beta 3)	Michel et al., 2017[a] Bretschneider et al., 2016[b]	$D_{max} < 18$ Gy
Ribs	RTOG 0438[b]	$D_{max} < 54$ Gy
Chest wall	Michel et al., 2017[a] Venkat et al., 2017[b] Woody et al., 2011[b] Stephans et al., 2011[b]	$D_{max} < 50$ Gy $D_{0.5cc} < 50$ Gy $D_{100\%} \leq 30$ Gy
Heart	Michel et al., 2017[a]	$D_{max} < 7$ Gy
Skin surface	Bretschneider et al., 2016[b]	$D_{1cc} < 10$ Gy

[a]SBRT study

[b]HDR IBT study

CHAPTER 3

MATERIALS AND METHODOLOGY

This chapter discussed two main materials used in this retrospective research work which were Oncentra Brachy software and SPSS software. This section discussed the methods used for this retrospective study, which were patients' selection criteria, brief retrospective study workflow and statistical analysis to evaluate the tolerance dose for the selected OAR in this study, using SPSS software.

3.1 ONCENTRA BRACHY

TPS for HDR IBT treatment used in our institute is the Oncentra Brachy (V.4.5.4) (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden) as shown in Figure 3.1. This is an advanced software with various features to plan the treatment before performing the real treatment to the patients in a shorter period of time. Precise dose delivery planning to the target can be conducted by medical physicist and oncologist using this software. The Oncentra TPS can be used in all BT techniques and various tumour sites, such as interstitial, superficial and intracavitary technique and in skin, gynaecologic, breast, prostate, and many other applications respectively (Yang, 2018).

To plan a treatment, there are several steps that have to be fulfilled which begins with contouring the GTV and OAR, reconstructing the catheter in the CT images, activating the necessary catheters in each slices, setting a normalisation point, where dose will be delivered, setting the prescribed dose and number of fractions and finally optimise the plan. Once these steps are fulfilled, a rapid calculation will be conducted by the system based on the planning that have been made. Results of the calculations will be shown as overall dose distribution and dose volume histogram (DVH) of the GTV and OAR. Once the plan was optimised by the radiation oncologist and medical physicist, then the treatment plan will be transferred to the treatment system for an actual treatment delivery to the patient. In a nutshell, Oncentra Brachy helps to produce an accurate and highly conformal treatment plan with minimal workload and time to treat cancer cells. (Elekta, 2017).

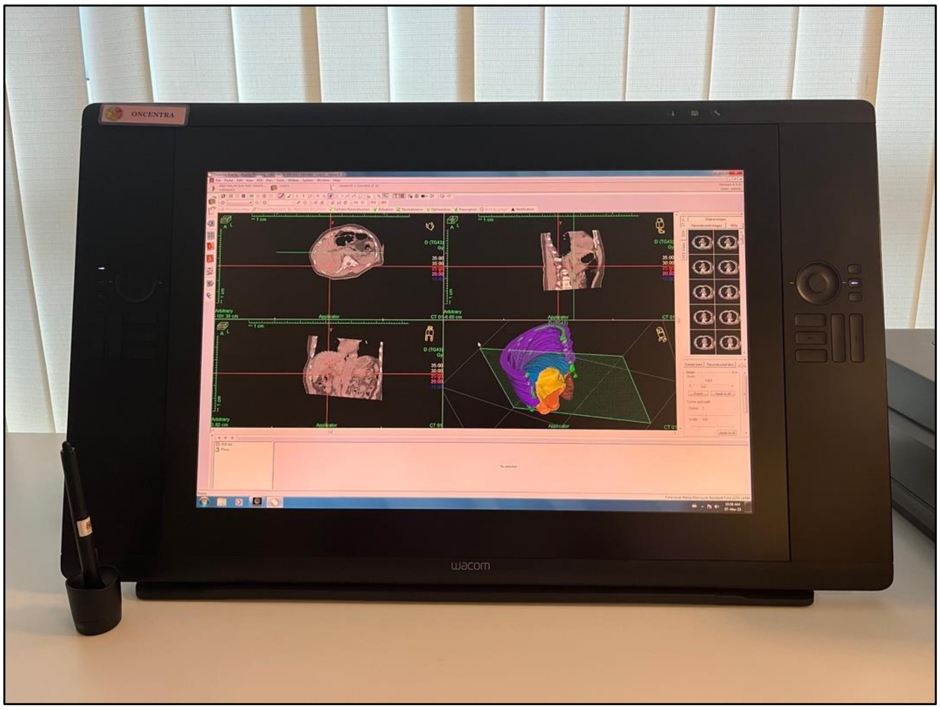

Figure 3.1: Oncentra Brachy system in Oncology Unit, Pusat Perubatan USM.

3.2 STATISTICAL PACKAGE FOR THE SOCIAL SCIENCES (SPSS)

After collecting data from the Oncentra Brachy, a statistical analysis will be conducted using a software called Statistical Package for the Social Sciences (SPSS) version 25 (IBM Corporation, Armonk, New York), which was installed in MacBook Air with 8 GB RAM (macOS Big Sur version 11.2.3), as shown in Figure 3.2. This software helps to analyse the data that have been collected for this retrospective study and report them in a ways that is more accurate and easy to understand. Therefore, it helps to provide a very good quality of statistical analysis (SPSS Statistics, 2022).

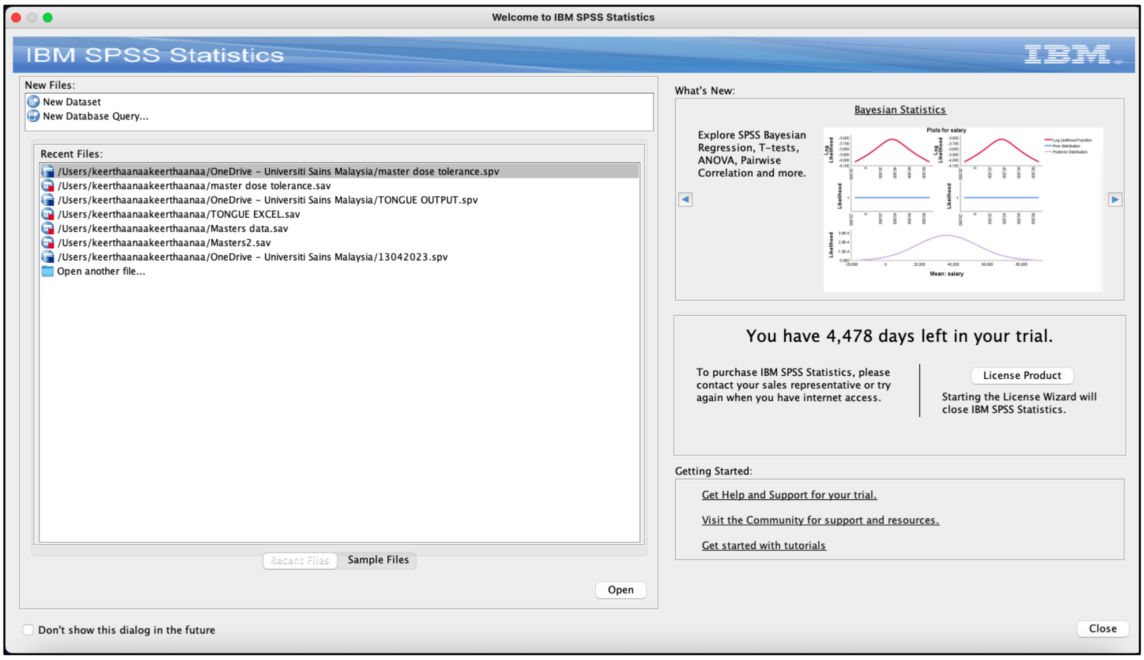

Figure 3.2: The SPSS software use interface.

3.3 PATIENTS SELECTION

This is a retrospective study, where existing CT data of HDR IBT for liver cancer cases from year 2018 till 2022 in Pusat Perubatan USM were collected directly from the Oncentra Brachy. A total of 55 patients, were diagnosed with liver cancer and underwent 89 HDR IBT treatment in our institute were randomly chosen. Administered prescribed dose to the GTV ranging between 15 Gy and 25 Gy, either in single or multiple fractionations to the patients.

Patients' who underwent HDR IBT for liver cancer, aged 18 years and above are chosen. The JePEM ethical committee members have reviewed and approved this study in the protocol code of [USM/JEPeM/22010028], shown in appendix A. The list of patients' inclusion and exclusion criteria are provided as follows.

Inclusion criteria

1. Adults' liver patients (> 18 years old).
2. Patient with primary and/or secondary liver malignancies.

Exclusion criteria

1. Patients with prescribed dose to tumour of < 15 Gy and > 25 Gy.

3.4 BRIEF STUDY WORKFLOW

As this is a retrospective study, CT numerical data of 55 patients with 89 cases were collected from Oncentra Brachy TPS (V.4.3) (Nucletron, an Elekta company, Elekta AB, Stockholm, Sweden). This software helps to plan and generate the treatment before executing to real patients using HDR modality (Yang, 2018). The selected OAR were contoured, as shown in Figure 3.3, in all CT data using the TPS, based on oncologist advice from Pusat Perubatan USM and published journals (Wang et al., 2020) (Tselis et al., 2013). For RD contouring, 0.2 cm was outlined using the "pearl" tool in Oncentra Brachy between the liver and thoracic cavity on sagittal CT images. Whereas the RCW was delineated at least 1.5 cm, using the same "pearl" tool to include the muscles like intercostal muscles, pectoralis major and minor and the ribs, on coronal CT images (Wang et al., 2020). Finally, the CLS was outlined based on liver hilum and bile bifurcation (Tselis et al., 2013).

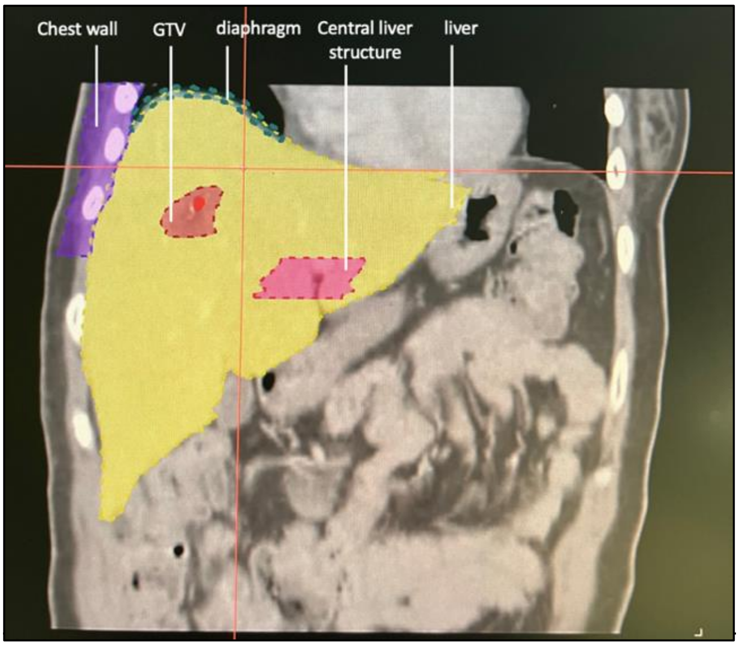

Figure 3.3: GTV and OAR delineation in sagittal view.

Then, data of the contoured OAR such as dose received by 0.2cc and 50% of its volume ($D_{0.2cc}$ and $D_{50\%}$) respectively, were collected so that statistical analyses can be performed using SPSS for all 89 treatment case (single and multiple fractionations). Figure 3.4 shows the overall study workflow of the patients that underwent the HDR IBT treatment for liver cancer treatment.

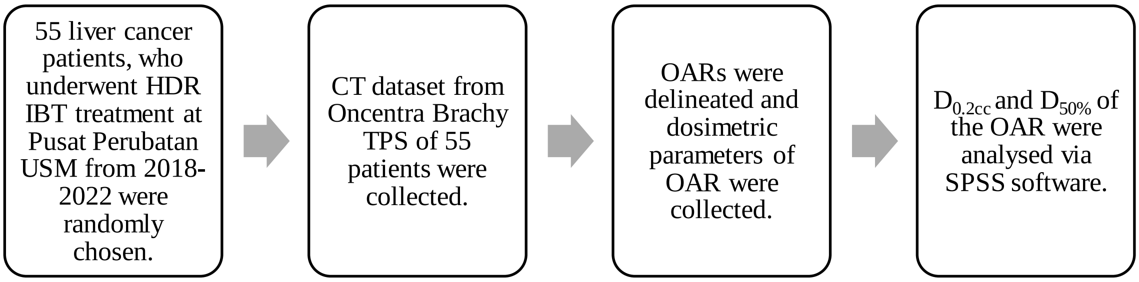

Figure 3.4: Summary of the retrospective study workflow.

3.5 STATISTICAL ANALYSIS

Statistical analysis were conducted to analyse this retrospective study that emphasis on evaluation of the tolerance dose for the selected OAR (CLS, RCW and RD) using SPSS and Microsoft Excel Spreadsheet Software for a total of 55 patients who underwent 89 treatment case. 3 groups of patients were categorised based on prescribed dose administered to GTV of 15 Gy, 20 Gy and 25 Gy. Several data analysis tests were conducted based on the results from the Shapiro-Wilk test (to evaluate the normality distribution of the data set) by comparing the significant value of 0.05, as shown in Appendix B, C and D. Those data were analysed among tumor volume and dose received by three OAR, followed by analysis between three groups of prescribed dose and dose received by OAR and finally, analysis on OAR dose in single and multiple fractions.

3.5.1 ANALYSIS BETWEEN TUMOR VOLUME AND DOSE TO OAR

A Spearman's correlation analysis was conducted between tumor or GTV volume and OAR dose at $D_{50\%}$ and $D_{0.2cc}$ to analyse the dose received by OAR based on GTV volume. Total of 89 cases were analysed and results from this analysis were recorded and evaluated based on Table 3.1. If the obtained p-value from this analysis was within 0.05, relationship between GTV volume and OAR dose was present. The analysis on the strength of these relationship based on Table 3.1 was to analyse the variation in GTV size, contributes dose to the OAR. However, if the p-value exceeded 0.05, there was no relationship between these two variables.