CHAPTER 1 INTRODUCTION

1.1 Research Background

Cancer is a deadly non-communicable disease and the second leading cause of death globally, with over 9.7 million deaths and 19.9 million new cases in 2022, according to GLOBOCAN, published by the International Agency for Research on Cancer (IARC, 2022). One of the most lethal types of cancer is esophageal cancer, which is often diagnosed at an advanced stage, resulting in a very low survival rate for patients. In 2024, the Global Cancer Observatory (GCO) projected that the number of cases and deaths due to esophageal cancer would continue to increase until 2050, with a higher prevalence in men than in women. Currently, on a global scale, the incidence and mortality rates of esophageal cancer rank 11th and 7th, respectively, with a mortality risk reaching 87.15%. In Indonesia, the mortality risk of esophageal cancer ranks second about 96.27% after liver cancer (IARC, 2022).

The available therapies for esophageal cancer include surgery, chemotherapy, radiotherapy, or a combination of these methods (Kaur et al., 2024). Surgery is effective in removing localized cancer; however, it carries the risk of complications and requires a long recovery period (Antonowicz et al., 2020; Harish et al., 2020; Syamputra et al., 2020). Chemotherapy can shrink cancer cells but may also damage healthy tissues and cause side effects such as myelotoxicity (Febriani and Rahmawati, 2019) and hair loss (Urtekin and Eroglu, 2024). Immunotherapy enhances the body's immune system to combat cancer; however, it carries the risk of targeting normal cells, potentially leading to autoimmune responses (Darni et al., 2022). In advanced-stage esophageal cancer, radiotherapy is more considered as it can effectively destroy cancer cells locally without invasive procedures and has a relatively lower toxicity compared to chemotherapy and immunotherapy (Health Commission of the PRC, 2022).

Radiotherapy utilizes ionizing radiation to destroy cancer cells, as seen in conventional radiotherapy, fast neutron therapy, proton therapy, and carbon-ion therapy. However, these methods can also expose surrounding healthy tissues or

Organs at Risk (OARs) to radiation-induced damage. Considering these limitations, a more selective radiotherapy has been developed to effectively target cancer cells while minimizing damage to surrounding tissues. As a solution, Boron Neutron Capture Therapy (BNCT) is being developed as a radiotherapy method to minimize radiation effects on OARs (Kawasaki et al., 2023). The advantages of BNCT over other radiotherapy methods are cell targeted and single-session therapy (Fukuda, 2021a). Research on BNCT as a selective cancer therapy has been conducted in various cases, including head and neck cancer (Syamputra et al., 2020; Wang et al., 2016), lung cancer (Harish et al., 2020; Trivillin et al., 2019), liver cancer (Huang et al., 2022), melanoma (Hiratsuka et al., 2020; Yong et al., 2016), breast cancer (Kurosaki et al., 2024), and cervical cancer (Terada et al., 2023).

BNCT eliminates cancer cells by utilizing the stable isotope boron-10 ($^{10}_{5}B$), which captures thermal neutrons (σ_a = 3830 barn), through the nuclear reaction $^{10}_{5}B$ ($^{1}_{0}n$, $^{4}_{2}\alpha$) $^{7}_{3}Li$. This reaction produces an excited state of boron-11 ($^{11m}_{5}B$), which rapidly decays ($T_{1/2}$ = 10^{-12} s) into alpha particles and lithium-7. These particles exhibit high Linear Energy Transfer (LET), approximately 150 keV/µm and 175 keV/µm, respectively (IAEA, 2023). Their short path length of 5–9 µm, which is smaller than the diameter of cancer cells (D_{cancer} >10 µm), ensures that the radiation damage occurs only within a single boron-containing cell (cell targeted) (Skwierawska et al., 2022). To achieve selective boron accumulation in cancer cells, boron carrier agents are used, while neutron sources are typically generated from accelerators such as cyclotrons (IAEA, 2023). BNCT involves two main procedures: (1) the patient is injected with a boron-containing compound, like 4-boronophenylalanine (BPA), boron sodium borocaptate (BSH), or sodium decahydro-decaborate (GB-10), which selectively accumulates in the tumor; (2) the target tumor volume is irradiated with thermal or epithermal neutrons to induce the boron-neutron capture reaction (Matsumura et al., 2023).

The success of BNCT depends on two main factors: the concentration of boron in cancer cells and the direction of neutron irradiation relative to the target volume (IAEA, 2023). Optimizing these two factors is important to achieving an optimal therapeutic dose; sufficient to destroy cancer cells while ensuring that the

dose received by OARs does not exceed the tolerance threshold and minimizing irradiation time. Previous studies have primarily focused on optimizing boron concentration, such as those conducted by Fitraturrahma (2023) used boron concentration variations of 60-150 ppm to determine the optimal dose for lung cancer using software Particle and Heavy Ion Transport Code System (PHITS) V 3.30 simulations, while Agestha (2023) used variations of 80-150 ppm for cervical cancer with PHITS V 3.26. The results of both studies show that the optimal boron concentration is 150 ppm, with higher injected concentrations leading to more effective dose distribution.

In contrast, research on the optimization of neutron irradiation angles remains limited, particularly in esophageal cancer cases. Most existing studies focus only on specific angles or patient positions for other cancer types. For instance, Agestha (2023) analyzed neutron irradiation only from the left lateral direction in cervical cancer, while Pratiwi (2022) compared left lateral and prone positions in ovarian cancer therapy, finding that the prone position was more effective in dose distribution. Since the optimal neutron irradiation direction may vary depending on the cancer location and the position of OARs, further research is needed to explore various combinations of angles and patient positions to enhance the effectiveness of BNCT for esophageal cancer.

The optimal neutron irradiation direction will result in the optimal radiation dose. To achieve this, a dose calculation simulation is required to ensure that the radiation dose effectively reaches the target without exceeding the OAR tolerance limits. This simulation is performed using the Therapy Planning System (TPS), which considers various parameters such as patient geometry, neutron source flux and direction, boron concentration and distribution, and dose to the cancer and OARs. Since the dose calculation in BNCT involves various probabilistic nuclear reactions, the Monte Carlo method is used to simulate the interaction of neutrons with body tissues. In this study, PHITS V 3.34.1 was chosen over other Monte Carlo software such as Fluctuierende Kaskade (FLUKA), Geometry and Tracking version 4 (GEANT4), and Monte Carlo N-Particle (MCNP), due to its advantage in calculating a wide energy range (10^{-4} eV - 1 TeV), which provides higher accuracy

and shorter simulation time (Kumada et al., 2020). As the latest version, PHITS V 3.34.1 offers improved particle transport, updated nuclear models, and faster parallel processing compared to previous versions. Therefore, this study aims to optimize the combination of angles and patient positions to achieve the optimal radiation dose for the selected esophageal cancer case. The optimization is carried out by exploring various irradiation angles (0°, 30°, 45°, 60°, and 90°) and different patient position models, including supine, prone, right lateral, and left lateral, with a fixed boron concentration of 150 ppm.

1.2 Research Purposes

1. Determine the shortest irradiation time for esophageal cancer therapy according to the optimal neutron irradiation direction.
2. Determine the equivalent and effective dose values received for esophageal cancer and OARs according to the optimal irradiation direction.
3. Determine the optimal neutron irradiation direction to the target volume and safe for OARs.

1.3 Research Benefits

This research is expected to provide benefits in:

1. For scientific advancement

   It is expected to make a scientific contribution in optimizing the direction of irradiation and patient position to improve the effectiveness of BNCT therapy.
2. For medical practitioners

   The findings of this study can serve as a reference for oncologists and medical physicists in planning BNCT therapy more effectively.
3. For policymakers

   These findings are expected to be used as a reference in evaluating and advancing cancer therapy modalities.

1.4 Research Scope and Limitations

The scope and limitations of this study are as follows:

1. The type of cancer studied is esophageal cancer located in the middle thoracic region.

2. The phantom characteristics follow the Oak Ridge National Laboratory (ORNL), and its composition refers to International Commission on Radiological Protection (ICRP) Publication 145 (IAEA, 2023; ICRP, 2020).
3. The neutron source is a 30 MeV cyclotron accelerator with a 1 mA current.
4. The boron compound concentration is 150 ppm.
5. The irradiation angle variations are 0°, 30°, 45°, 60°, and 90°, with patient models position in supine, prone, right lateral, and left lateral.
6. The prescription dose is based on clinical guidelines, such as 60 Gy.Eq (Health Commission of the PRC, 2022).
7. The simulation uses software PHITS Version 3.34.1, which is the latest available version. This version was selected to ensure the most up-to-date physics models, improved accuracy, and enhanced features for neutron and particle transport simulations.