Photodynamic Therapy using Laser and Fluorescence Imaging

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By

Hyun Soo Lim

Cambridge
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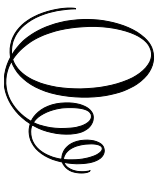

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This book first published 2025

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN: 978-1-0364-4941-4
ISBN (Ebook): 978-1-0364-4942-1

TABLE OF CONTENTS

PREFACE

The modern age is the era of convergence studies, and it is not possible to achieve the desired purpose by knowing only one field. Photodynamic therapy is a model of convergence studies, and it is a new cutting-edge study of cancer treatment that combines various disciplines and technologies. Although photodynamic therapy has been introduced for more than 100 years, it has been about 20 years more since it was approved by the FDA in the United States and applied to clinical practice, but there are still many areas where clinical engineering technology for treatment is still lacking, so systematic research through academic approach and necessary data and references are needed.

Nonetheless, references in this area are very scarce, both domestically and internationally. Fortunately, the book "Photodynamic Therapy" was published in 2007 by the Korean Society of Photodynamic Studies, which serves as a guide to photodynamic therapy, but it has not been covered in depth in terms of engineering. Photodynamic therapy must ultimately be handled by the physician's medical skills, but the optimal therapeutic effect cannot be achieved without the support of biomedical engineering, which is basically a cutting-edge technology. Only when medical technology and cutting-edge biomedical engineering technology develop side by side can the optimal effect be achieved.

Therefore, it was published for the first time in Korea as a book written using engineering measurement theory, computational control methods, and mathematical models necessary for photodynamic therapy, and it was intended to help researchers who need systematic research, including engineering students who are interested in photodynamic therapy. In order to increase the effectiveness of cancer treatment, advanced technology and a lot of efforts are needed in each field. In order to develop next-generation medicines, advanced technology of therapeutic devices, and advance clinical engineering technology, it is necessary to conduct research with the participation of clinicians, many majors in pharmaceuticals, chemistry, and biomedical engineering (electronics, computers, physics, optics, laser engineering, etc.) in order to enhance the effectiveness of actual treatments.

Based on these findings, this book focuses on research and development conducted by Chungnam National University in Korea and Sakaria University of Applied Sciences in Turkey, and is aimed at graduate students, doctors, and cancer treatment experts majoring in biomedical engineering. In addition, the concept of photodynamic therapy is explained in an easy way, and pictures of the treatment are posted to broaden the understanding of the general public and cancer patients.

This book explains the mechanism of photodynamic treatment, the efficiency of treatment using artificial intelligence, the use of clinical data, and the principles of fluorescence imaging diagnosis for cancer diagnosis, and consists of clinical application cases to support it. The Fundamentals section of Chapters 1 through 4 describes the basic concepts of photodynamic therapy and describes the optical theory of living tissues that underpins it, helping you understand the mechanisms of photodynamic therapy. The theoretical aspects are cited using references to facilitate understanding.

Chapter 5 contains the basic design and development of laser systems to help engineers in the field of science and engineering to develop lasers. It also included technical data on the development of lasers, demonstrating the functions and capabilities of lasers.

Chapter 6 is an introduction to PDT using artificial intelligence (AI), demonstrating accuracy, efficiency, and personalized treatment, and improving the effectiveness of treatment. Especially in the field of diagnostic and therapeutic devices, AI has revolutionized the field of medicine. AI-based technology has been integrated into a variety of medical devices, including imaging systems, robotic surgical instruments, and wearable health monitors. These advances have been achieved through the development of sophisticated algorithms, machine learning (ML), and deep learning (DL) models that can analyze vast amounts of data and identify patterns that are imperceptible to the human eye.

Chapter 7 is the Artificial Intelligence PDT Planning System, The provided flow chart illustrates an AI expert system designed to optimize photodynamic therapy (PDT) for cancer treatment. This system integrates patient examination data, advanced image analysis, and therapeutic simulation to create a personalized and effective treatment plan. Below is a step-by-step explanation of the treatment plan process based on the flow chart.

Chapter 8 describes the simulation of the Monte Carlo process. The Monte Carlo technique is a flexible method for simulating light propagation within tissues. The simulation is based on the random gait that photons make as they pass through tissue, which is selected by statistically sampling the probability distribution for step size and angle bias per scattering event. After propagating many photons, the net distribution of all photon paths yields an exact approximation of reality. One of the most important aspects of PDT is the accurate delivery of light to the target tumor cells. Light propagation in living tissues is highly complex due to scattering and absorption, which vary depending on the tissue

type and structure. All of them. Chapter 9 discusses the basic design concepts of AI device systems. Describe early symptoms and primary care consultations, specialist referrals, advanced diagnostics and conventional therapies, especially for patients, as considerations for photodynamic therapy (PDT) Describe a baseline design that includes pre-treatment preparations, PDT treatment processes, and concepts for post-treatment monitoring and follow-up. Chapter 10 dealt with the basic principles of optical fibers. Optical fibers are fine threads made of glass. Optical fibers are widely used in the medical field along with lasers. In particular, endoscopes, which use optical fibers to look at the stomach and organs of a person, and high-speed communication using lasers and optical fibers are widely used.

Chapter 11. Describe the mathematical considerations of laser power calculations. If you look at the beam profile of the laser, you can see that more photons are concentrated in the core of the laser flux, and the strength of the bond decreases towards the edges.

Chapter 12 describes the safety management of laser use in medicine. In the medical field, many types of lasers are used, from He-Ne lasers with an output of several mW to CO_2 lasers with a power of more than 100 W, so the safety of healthcare workers must be fully considered. Let's consider how safe it is to use laser technology based on the highest safety standards in the United States.

Chapter 13 discusses fluorescence imaging for cancer diagnosis. In order to increase the survival rate and cure rate, early detection of cancer is becoming an important factor in determining the success or failure of treatment. There are many ways to diagnose cancer, but the most popular and accurate is a biopsy. However, biopsy has many limitations in collecting, analyzing, and processing actual tumor tissue. Since the 1990s, it has led to the emergence of new diagnostic and therapeutic methods, such as photodynamic diagnostics and photodynamic therapy.

Chapter 14. The current laparoscopic system cannot diagnose according to the degree of development of cancer and intractable diseases at the time of surgery in terms of resolution or function, and it cannot distinguish the boundary between malignant tumor tissue and normal tissue, causing damage to normal tissue during surgery, resulting in functional paralysis, side effects, and increase in re-incidence rate of the human body. and this has increased the pain and medical expenses caused by the patient's revision surgery, and in clinical practice, an innovative laparoscopic system with super-high resolution and fluorescence image guidance is required. In this regard, the digital STED (Stimulated Emission Depletion technique) nano laparoscopic system, which is based on MEMS/NEMS, can diagnose the occurrence and progression of cancer from early stage to late stage cancer by imaging nano-sized structural shapes and biomolecules in ultra-high resolution,

Chapter 15 introduces laser irradiation technology for photodynamic cancer therapy. Describe the effects of treatment using laser radiation, CW, Pulse, and Burst Pulse.

Chapter 16 shows the effect of photodynamic therapy on various cancers by disease. It shows the process and results of photodynamic treatment for each disease at a university hospital in Korea. Biliary tract cancer, esophageal cancer, cervical cancer, lung cancer, neck and head cancer, and benign tracheal tumor are photodynamic cancer treatment reports.

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February 15, 2025

CHAPTER 1

BASIC IDEA OF PHOTODYNAMIC THERAPY

1.1 Introduction

Recently, cancer has been treated with photodynamic therapy (PDT), which causes a photochemical reaction in tissues. Conventional cancer therapies like chemotherapy, surgery, or radiotherapy can have side effects like lowered immunity, hair loss, pain, or mutations. These side effects are not present with this approach. Furthermore, PDT offers the benefit of selectively targeting cancerous areas while maintaining the integrity of healthy organs and tissues. The effects of photodynamic cancer treatment are dependent on the density of photosensitizers (PS) within a tumor, the stimulated photometric amounts supplied into the tissue, and the molecular oxygen content of the organic tissue. When applying these three characteristics to cancer treatment, they need to be optimally regulated. Clinical trials can be used to identify the ideal injection dose based on the agent's density. A crucial component of cancer treatment is the laser light source. When the following criteria are met, the PDT laser system operates at its best. The optical wavelength should first be adjusted to the PS's maximum absorption point. Secondly, the laser's wavelength ought to remain constant, irrespective of the treatment's time and temperature. Third, the organic tissue should have deep optical permeability. Fourth, the laser's output needs to be accurate. Fifth, the laser's optical radiation shouldn't cause the tissues surrounding the tumor to sustain irreparable thermal damage. Lastly, the oxygen shortage brought on by photodynamic reactions ought to be avoided by the PDT laser system. By applying nonthermal laser light to cancerous tissue using a fiber optic probe, photodynamic therapy effectively treats lung cancer by activating a previously injected photosensitizer and introducing a new less invasive approach. The ability to readily transmit light to the appropriate tissue using an optical fiber with a very tiny diameter and varied specialized geometries depending on the shape of the organ being treated is one of the main benefits of employing lasers in PDT. Another benefit is that almost all of the laser energy can be transferred to the

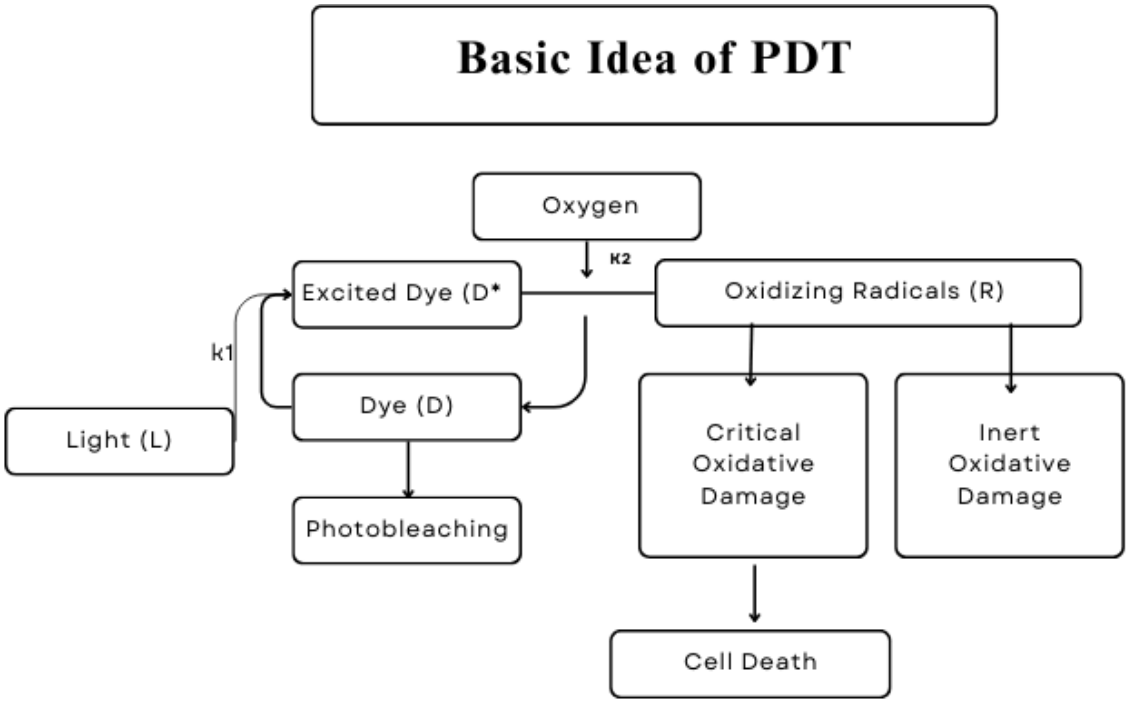

FIGURE 1.1 Basic Idea of Photodynamic Therapy (PDT)

tissue at the wavelength that corresponds to the photosensitizer (PS) absorption peak since the light emitted by lasers is practically monochromatic. Compared to vapor dye lasers, diode lasers are more portable, making their use more convenient. The two biggest problems with PDT, however, are poor penetration depth into the tissue and thermal injury to the irradiated tissue. The optical characteristics of the tissue, which are represented by the absorption coefficient, scattering coefficient, and anisotropy factor, determine the penetration depth. Wavelength also affects the scattering and absorption coefficients. The photon energy absorbed by tissue varies depending on optical qualities indicated by the absorption coefficient, scattering coefficient, anisotropy factor, and refractive index. These optical characteristics are

also influenced by the species, density, size, and form of the tissue's constituent cells and organelles, as well as by proteins, enzymes, water, oxy, and deoxyhemoglobin molecules, and the roughness of the tissue's surfaces. Furthermore, the way light propagates through tissues is influenced by the polarization states of the incident light. Following laser irradiation, the tissue absorbs the laser energy and transforms it into thermal energy, which raises the tissue's temperature. Tissue mass density (ρ), blood mass density (ρb), the specific heat of tissue (c), the specific heat of blood (cb), the temperature of tissue (T) and blood (Tb), tissue thermal conductivity (k), blood perfusion rate (wb), and metabolic heat generation (Qm) all affect heat transfer in tissues exposed to laser light. Both progressive and selective thermal damage can happen, depending on the heating level. Different effects, such as coagulation, vaporization, carbonization, and melting, can happen depending on the length of time and peak temperature of the tissue temperature reached. At 42–45 ḌC, hyperthermia sets in, causing collagen to shrink and undergo structural changes. The enzymatic activity also declines at this temperature. At 60 ḌC, denaturation of proteins, collagen coagulation, and membrane permeabilization are evident. Temperatures rise to at least 60 ḌC during the coagulation phase, at which point the coagulated tissue turns necrotic. The denaturation of collagen begins at 65 ḌC. At atmospheric pressure, tissue water boils at 100 degrees Celsius. Blackening occurs when the tissue begins to carbonize at temperatures higher than about 100 ḌC. The PS's absorption peak is taken into consideration when selecting the laser wavelength. Based on the power density, the laser irradiation period, also known as the exposure time, regulates the fluence value in the tissue. For a fixed fluence, several power densities and irradiation durations can be employed. For instance, a certain fluence would be produced by a high-power density and a brief irradiation duration, but a low-power density would necessitate a lengthy irradiation time to accomplish the same fluence. Stated differently, varying power densities at the same irradiation time will result in varying fluence values. We can employ PDT as a tumor-selective cancer therapy since it only damages the malignant tissue and normal tissue regeneration happens swiftly. Three key components make up a PDT treatment regimen for cancer: (1) PS delivery to the body, (2) PS uptake into cancer cells, and (3) light exposure to the treated tissue area. In addition to the right amounts of light and PS, ideal oxygen content in the tissue is also necessary for effective photodynamic therapy (PDT), even though oxygen itself produces singlet oxygen, which is cytotoxic. When singlet oxygen (1O2) is present, PS sites experience the majority of the damage caused by PDT to cancer cells. The primary subcellular targets of PDT are the mitochondria, endoplasmic reticulum, cell cytoskeleton, and plasma membrane.

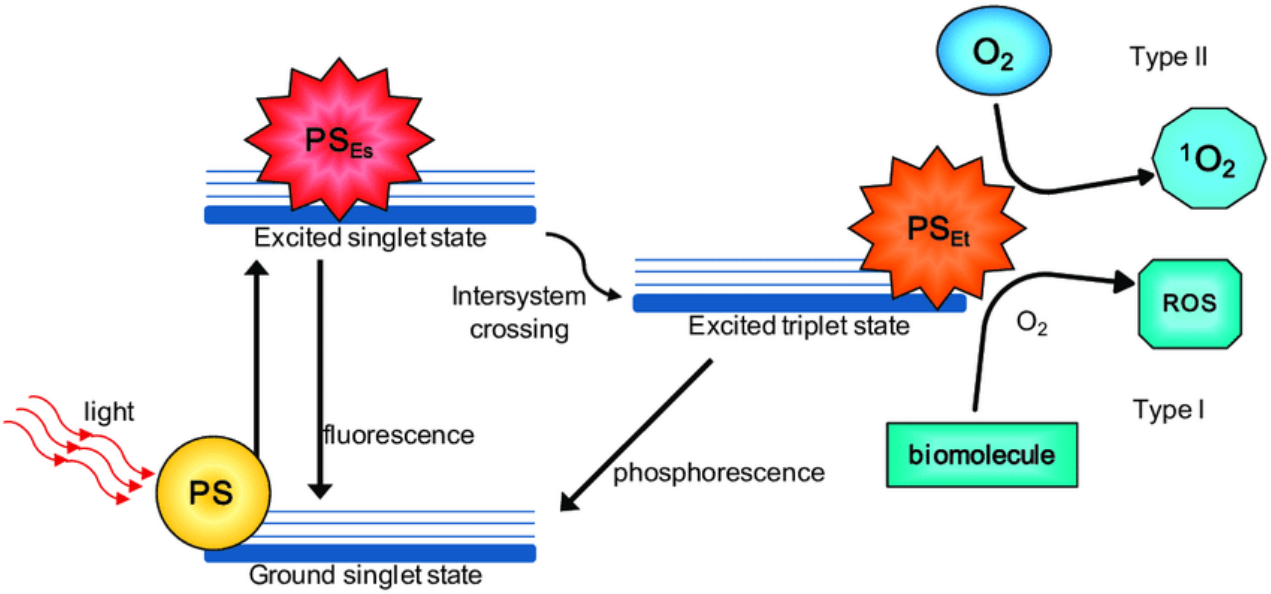

FIGURE 1.2 Mechanism of the Singlet Oxygen

1.2 Background and Trends

The technology of diagnosing and treating cancer using photodynamic reactions is recognized as a breakthrough in cancer treatment and a new and rapidly emerging optical technology. It has become a subject of interest in the medical community, having evolved from palliative treatment to a radical therapy for cancers in various organs (such as the stomach, esophagus, colon, endobronchial lung, bladder, uterus, skin, eye, etc.). "Since 2003, photodynamic cancer diagnosis and treatment technology has gained wider recognition both domestically and internationally, with more clinical applications found abroad than in Korea. In particular, international conferences such as Photonic West in San Jose, USA, Photonic Asia in Asia, and Photonics East in Europe have separate sections where intensive research is conducted, research results are presented, and speakers who present papers consistently emphasize the importance of the role of photodynamic cancer treatment. Photodynamic technology is recognized as an essential treatment as a third method in the treatment of cancer. Currently, photodynamic diagnosis and treatment technology is performed using photosensitizers (Porfimer sodium, PhotofrinḢ) and optical instruments approved by the US FDA. In addition, research

related to the development of various photosensitizers and PDD (photodinamic diagnosis) and PDT (photodinamic therapy) using optical instruments in the multiwavelength range has been conducted by NIH & NCI(USA), Lithuanian Oncology Kenter (Lithunian), Tokyo Medical College (Tokyo, Japan), Royal Collge of London (London, Uk), Roswell Park Cancer Institute (Buffalo, USA), Laser Cancer Center (Tennessee, USA), Herzen Oncology Center (Moscow, Russia), Moscow Academy of Medical College (Moscow, Russia) and other universities and research institutes around the world. The purpose of this book is to solve problems in engineering and cutting-edge technology through systematic research on this topic, and to understand the system of next-generation advanced engineering. Until now, photodynamic diagnosis and treatment have primarily relied on the development of photosensitizers, with existing technology being maintained and extended in the engineering and technical fields, without significant advancements. The photodynamic diagnosis and treatment system that is being performed in clinical practice today is not advanced in the introduction of laser light sources and the configuration of related systems, and it is only a primitive system in which the system changes according to the characteristics of the photosensitizer. Photodynamic technology in cancer treatment can achieve its intended outcomes only through the coordination of various experts, including clinicians, pharmaceutical chemists, and medical optics specialists. The research results hold the potential for significant advancements in the medical field, medical device industry, and pharmaceutical sector, greatly contributing to the improvement of cancer patients' quality of life and public health. Therefore, this article proposes innovative approaches to overcoming the clinical engineering limitations and advancing from the second to the third generation, leveraging the cutting-edge technology of artificial intelligence, which continues to evolve. The limitations and problems currently raised in clinical trials in photodynamic diagnosis/treatment technology, and the technical demands based on engineering are as follows.

Limitations of the Application of Photodynamic Therapy

Conventional photodynamic therapy has been mainly applied to superficial cancers, internal organs, and lining of cavities due to limitations in the depth of light transmission of the tissue, absorption and discharge of photosensitizers, and optical transmission and access methods. Therefore, its application has been limited in the treatment of solid tumors or inaccessible cancers such as liver and hematologic tumors. However, as interstitial photodynamic therapy (PDT) has become known, some procedures are performed in the breast and liver using needles and catheters, but there is a need to develop optical fibers capable of increasing tissue penetration depth and enabling targeted light irradiation in specific areas. Additionally, developing a light source device capable of longer wavelengths and photosensitive drugs is essential to address this issue. Recently, solutions through Multi-Photon PDT are being explored.

Thermal Damage to Normal Tissues and Limitations of Oxygen in Tissues

To enhance the effect of photodynamic therapy, it is crucial to select a wavelength band that can effectively penetrate the tumor's longitudinal distribution and mutated tissues, and to deliver light with sufficient intensity to the tissue and to inject light output of sufficient light intensity into the tissues. In this case, clinical trials have raised the issue of thermal degeneration of tissues and irreversible cell destruction. In the treatment of bronchial cancer, perforation by thermal destruction is a very important problem, and it is important to pay extreme attention to the decrease in tissue regeneration due to thermal degeneration or irreversible cell destruction, as it can cause other diseases or problems after cancer treatment.

Additionally, the oxygen supply is often insufficient during treatment due to the consumption of blood oxygen, which reduces the treatment's effectiveness. A solution is needed to address this issue. "Current solutions to this problem include introducing non-thermal lasers, conducting PDT with sufficient tissue oxygen, developing oxygen-independent photosensitizers, and generating oxygen in the treatment area using radiation-based pulse patterns. In order to solve this problem, we will describe the photo-infusion method, radiation pattern, and collimation method that can minimize the thermal destruction of tissues and overcome the limitations of oxygen in living tissues while maintaining sufficient intensity of light output.

The Need for More Quantitative Diagnosis

Currently, photodynamic therapy is mainly performed on the lining of internal organs or cavities, and access and procedure are carried out through an endoscope, and therapeutic light is transmitted through optical fibers. The problem here is that it is difficult to quantify and error and distortion in determining the incidence area, angle of incidence, distance between the light emission and the tissue surface, and power density of the injected light based on the images obtained through the existing endoscope-based system. In addition, the saturation problem of the response of the image detector due to the high intensity of the therapeutic light source during treatment is a problem that makes it difficult to observe with the naked eye even after laser radiation. This hinders the identification of problems in the treatment process caused by disturbances

Extraction of Objective Treatment Parameters and Application of the System

In photodynamic procedures, the most important factors to enhance the effectiveness of treatment are the concentration of photosensitizer accumulated in tumor tissue, the supply of oxygen, the sufficient amount of photo incubation, and the

characteristics of the injected light. Studies that evaluate the tumor accumulation of injected photosensitizers or measure their concentration have been dealt with in the clinical and drug properties domains. If the concentration of photosensitizer accumulated in tumor tissue is low, no matter how much light is injected, it will only cause irreversible and thermal destruction, and it will not guarantee the therapeutic effect. This issue is not just a question of the characteristics of the photosensitizer or the adsorption efficiency of the drug before the procedure, but it is an issue that requires continuous monitoring throughout the treatment process. In addition, in the absence of the aforementioned limitation of oxygen in living tissues, it is difficult to expect a high therapeutic effect with unilateral light injection alone.

Currently, companies like Bio-Optics in Korea and Modlight, Biolitc, which supply PDT systems, set the laser light output, radiation time, and emission methods passively, relying on information from the system supplier or the practitioner's judgment. Since the only data required for the procedure was visual identification through endoscopes and inferential calculations based on this, problems such as errors that can occur by relying entirely on the judgment of the practitioner and verification of the accuracy of the light output are raised.

Real-time Monitoring of Photodynamic Therapy

Conventional photodynamic procedures are mostly performed in the form of open-circuit control, except in cases where the patient's movement or other unexpected situations that occur during the procedure are visible, and there is no reference in the operation process of the PDT system regarding the actual output or the invisible effect caused by light injection for a certain period of time. The condition of the lesion according to treatment or the rate of necrosis of the actual tumor tissue are not actively reflected, and there is a problem in clarifying the actual location and intensity of light injection inferred from the images obtained by endoscopy. As the error in the actual output caused by disturbances (temperature, wavelength shift, electrical interference) is ignored, the reliability of the actual light output and the efficiency of treatment are constantly raised.

Emergence of Photodynamic Complex Systems with Integrated Diagnostic and Therapeutic Functions

Research on photodynamic diagnosis and treatment has been conducted in Korea and abroad, and developed devices have been used in clinical practice, but there have been no examples of linkage between the two devices, as the diagnostic and therapeutic devices are operated independently. In order to increase the effectiveness of photodynamic treatment and promote the convenience of patients, it will be a perfect system if diagnosis and treatment are carried out at the same time. Since the same drug and laser are used for diagnosis and treatment, it will be possible to create a complex system that integrates the two functions, and it will be possible to create a complex system that can synchronized real-time diagnosis and real-time treatment. The problems and technical requirements described above are organically related to each other. In other words, each system can satisfy the technical demands and requirements, but it can be expected to have better performance and therapeutic effects through a comprehensive photodynamic system that integrates them.

Establishment of a Specific Treatment Plan and Training of Practitioners before Treatment

In order to reduce the patient's suffering and improve the effectiveness of treatment, it is convenient for clinicians and safe for patients to make a treatment plan for cancer patients in advance. By identifying the condition, location, and size of the cancer required for the treatment plan, accurately calculating the amount of light, and selecting the light wavelength and output. If the treatment plan is thoroughly prepared in advance, such as calculating the energy and selecting the optical fiber required for energy transfer and then administered to the patient after training through simulation, it will be possible to increase the effectiveness of the treatment, reduce the patient's safety, and reduce the time of pain associated with the procedure. Due to the nature of the treatment, the perfect combination of treatment materials, devices, and practitioners is essential. After establishing a treatment plan to increase the effect of photodynamic procedures, it is developed so that a simulation can be performed in advance. The development of a systematic and realistic virtual simulation program for the training and proficiency of clinicians is expected to play a major role in eliminating clinical limitations in cancer treatment.

It is necessary to develop the following theories and cutting-edge technologies on the principles of complex photodynamic systems, which will solve the limitations and problems of photodynamic diagnosis and treatment and become the core technology of the next generation of optical medical technology.

Optical Interactions, Thermal Response, and Optical Properties in Biological Tissues

Light dose measurement and thermal monitoring
Tissue diagnosis technology using laser
Extraction and quantification of treatment parameters using fluorescence imaging
Real-time PDT monitoring techniques
Photodynamic therapy techniques through photodynamic response modeling and light distribution simulation
Development of more advanced photodynamic diagnostics
Development of intelligent photodynamic therapy device
Development of artificial intelligence treatment plan and expert system

1.3 Excellence in Photodynamic Therapy

Photodynamic reactions are photochemical reactions caused by photosensitive materials and light. Photosensitizers, which are photosensitizing substances injected into living organisms, have the property of selectively accumulating in tumors and mutated tissues, and at the same time, they are sensitive to certain wavelengths of light and have the property of excitation. The interaction between the photosensitizer and the excitation light causes fluorescence with a shorter wavelength than the excitation light, and by imaging it, it is possible to obtain a contrasting light image due to the difference between the wavelength bands, so that the distribution of tumors and mutated tissues can be visualized, and the excited energy transmits energy to adjacent oxygen molecules in living tissues to change the spin state of oxygen electrons, causing radical oxygen in the blood, necrosis of tumors and mutated tissues(apoptosis). Therefore, it is possible to identify and remove accumulated tumor and mutated tissues by the energy interaction of photosensitizers and excitation light, which have a high accumulation on tumor and mutated tissues in living bodies, and the technologies used for diagnosis and treatment respectively are photodynamic diagnosis and photodynamic treatment technologies. This is a very powerful medical technology that can provide minimally invasive diagnosis and treatment of malignant neoplasms (cancer) in the human body while protecting normal tissues and maintaining the function of lesion organs as much as possible because selective necrosis of tumor and mutated tissues is possible.

CHAPTER 2

THE PRINCIPLE AND MECHANISM OF PHOTODYNAMIC THERAPY (PDT)

2.1 PDT Treatment Method

Photodynamic therapy (PDT) is a method in which a photosensitizing substance that collects into the tumor is injected into the body and then activated with light with a special wavelength. This treatment is a method of necrosis of cancer cells by causing irreversible photo-damage to cancer cells through photo-chemical and photo-biological actions. Photodynamic therapy has been proven to be useful in the treatment of various types of cancer based on the results of various clinical studies for 40 years worldwide, and since 1993, hematoporphyrin derivative compound (Photofrin) has been used in a wide range of treatments, including lung cancer, digestive cancer, esophageal cancer, skin cancer, cervical cancer, etc., and has been recognized in Korea, Canada, Netherlands, France, Germany, Japan, Russia, United States, etc.

In photochemotherapy for cancer, photodynamic reactions should only be used for photochemical reactions that consume oxygen. Photodynamic reactions produce singlet oxygen, a toxicity caused by energy transfer, from photo-excitation photosensitizers (PS) injected into biological tissues, which have an extremely short lifetime (<0.04 microseconds) and a short radius of action (<0.02 μm). In other words, photodynamic therapy uses the photoactive action of molecules that act as photosensitizers. Photoactive action refers to the process of changing or destroying biological molecules and biological systems under conditions that can be oxidized by absorbing light from a substance. Therefore, photodynamic therapy is performed using singlet oxygen generated from the photoactivation reaction. When PS is injected intravenously, it goes out of the body by metabolism in normal tissues and is adsorbed only in tumor cell tissues, and oxygen and light energy supplied by the body are activated. The oxygen molecule then has three states, the lowest of which can be divided into ground states, singlet states (^{1}S), and triplet states (^{3}S). Therefore, by electron transference, PS receives light energy and produces singlet oxygen, which has a cytotoxic effect that destroys tumor cells. If we look at the mechanism of the generation of singlet oxygen, it is as follows:

$$
\begin{aligned}
&S + \textit{light energy } (h\nu) \quad \Rightarrow \quad {}^1S \\
&{}^1S \quad \Rightarrow \quad {}^3S \\
&{}^3S + {}^3O_2 + S \\
&{}^1S_2 + \textit{strate} \quad \Rightarrow \textit{ oxidation}
\end{aligned}
\tag{2.1}
$$

The energy level in biological tissues has two types of excitation states. During laser irradiation, the PS in the basal state is converted to a singlet excitation state ^{1}S, which has a very short lifetime. In the photosensitizer, the excited single-term state changes to another excitation energy state, the triplet state ^{3}S. This condition has a much longer lifespan. Therefore, either type I by electron transfer or type II by energy transfer has any type of chemical reaction as shown in Table 2.1.1

Table 2.1 Photoactivation Mechanism of Photosensitizer

Excitation ○ Singlet state absorption	$^1S + h\nu \Rightarrow {}^1S^*$
Decays ○ Radiative singlet decay ○ Non-radiative singlet decay ○ Intersystem crossing ○ Radiative triplet decay ○ Non-radiative triplet decay	$^1S^* \Rightarrow {}^1S + h\nu'$ (fluorescence) $^1S^* \Rightarrow {}^1S$ $^1S^* \Rightarrow {}^3S^*$ $^3S^* \Rightarrow {}^1S + h\nu''$ (phosphorescence) $^3S^* \Rightarrow {}^1S$

Type I reactions ○ Hydrogen transfer ○ Election transfer ○ Formation of hydrogen dioxide ○ Formation of superoxide anion	$^3S^* + RH \Rightarrow SH^* + R^*$ $^3S^* + RH \Rightarrow S^* + RH^*$ $SH^* + {}^3O_2 \Rightarrow {}^1S + HO^*_2$ $S^* + {}^3O_2 \Rightarrow {}^1S + O^*_2$
Type II reactions ○ Interamolecular exchange ○ Cellular oxidation	$^3S^* + {}^3O_2 \Rightarrow {}^1S + {}^1O^*2$ $^1S^* + Cell \Rightarrow Cell_{ox}$
Carotenoid protection Singlet oxygen extinction ○ Deactivation	$^1O^*2 + {}^1CAR \Rightarrow {}^3O_2 + {}^3CAR^*$ $^3CAR^* \Rightarrow {}^1CAR + heat$

S: photosensitizer, RH: substrate with H-bond, CAR: carotenoid

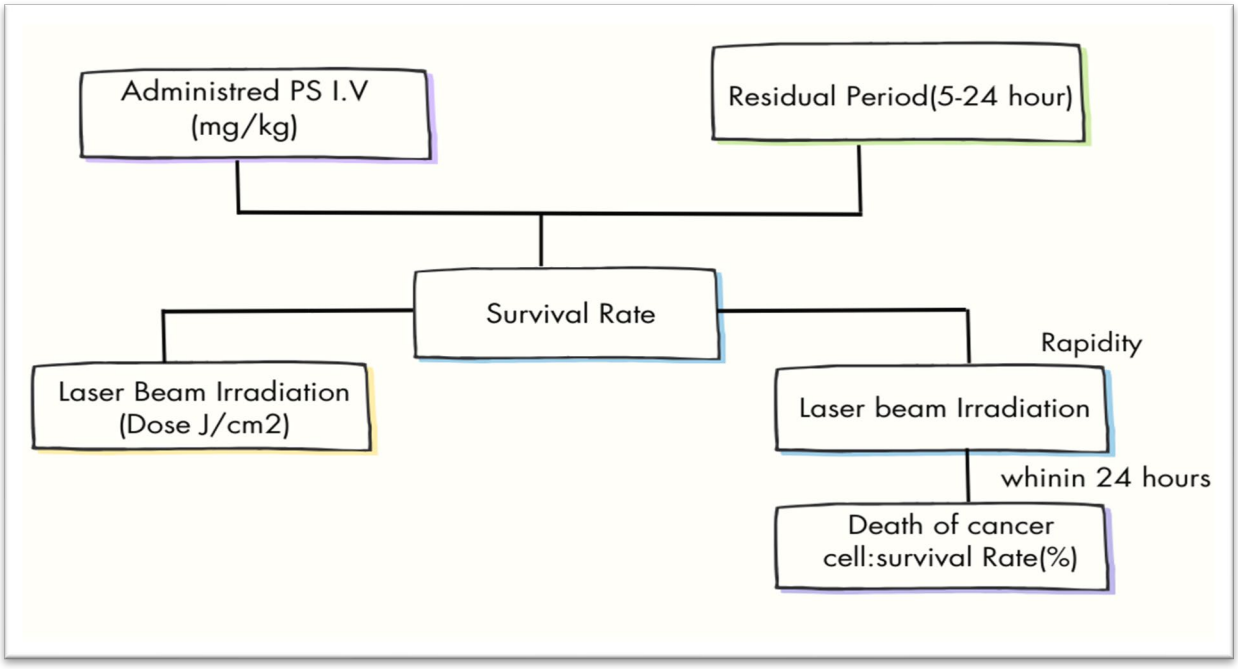

FIGURE 2.1 In this treatment, the photosensitizer (PS) is first administered intravenously (I.V) and then concentrated in the cancer tissue with a retention period of 5 to 24 hours. Subsequently, when the cancer tissue is irradiated with light rays, PS is activated and combines with oxygen in the cell tissue to generate singlet oxygen, which causes necrosis of the cancer cells.

Photodynamic therapy irradiates the local photo-sensitizer to the cancer cells that have already been injected with an appropriate amount of laser energy density (J/cm^2) to necrosis the cancer tissue as shown in Figure 2.1.1.

Measurement of light dose between light dose (J/cm^2, PS dose (mg/kg), volume of cancer cells, and accumulation time (hr) of photosensitizer (PS) has been empirically measured, and the calculation of laser dose takes into account the size, shape, total power density, and irradiation time of cancer cells. Therefore, in order to clarify the understanding of photodynamic therapy, an in-depth examination of the following topics is required, and the photodynamic parameters are shown in Figure 2.2.

(1) Model of malignant tumor
(2) Laser system
(3) Photosensitizer
(4) Photodynamic response and therapeutic effect of malignant tumor

In order to effectively perform photodynamic therapy, it is important to choose the wavelength of the laser system and the dose of energy density. The criteria for selecting the wavelength band are that the higher the relative absorption with

PS, the better the photoactivation, and the closer it is to the depth of light transmission of biological tissues. The international unit of wavelength is meter, and energy refers to the ability to do work. The unit of work and energy is Joule(J), and the unit less than J is the erg, which is 1 erg = 10^{-7}J. The amount of energy in a light beam is inversely proportional to the wavelength, and the shorter the wavelength, the greater it becomes. Light intensity is expressed as the amount of energy per unit area (cm^2). This can be expressed as irradiation energy density (dose: J/cm^2). It is known that light rays do practical work on the human body, and it is a photobiological unit that irradiates light energy to an area of light. The irradiation intensity can be expressed as the intensity of the rays per unit area (W/cm^2), which is a physical unit that indicates how many rays are irradiated in an area (cm^2). In other words, it can be obtained by multiplying the irradiation intensity (W/cm^2) by the irradiation time. The dose is again expressed as the intensity of the light rays in a certain area for several hours (unit: second).

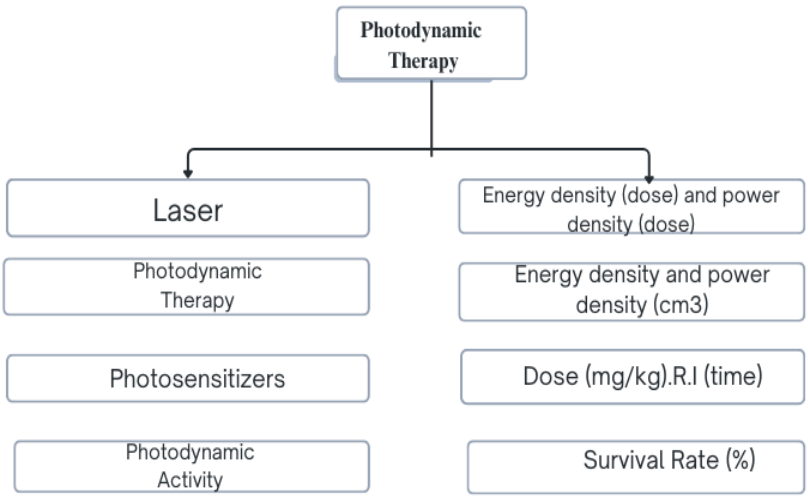

FIGURE 2.2 Measurement Parameters for Photodynamic Therapies

2.2. Tumor Destruction Mechanisms of Photodynamic Therapy

The mechanism of tumor destruction for photodynamic therapy is shown in Figure 2.3. Tumor destruction has been reported as a mechanism of damage to blood vessels, destruction of internal organs, and destruction of immunity.

2.2.1 Accumulation of photosensitizing substances

Mitochondria, lysosoms, plasma membranes, nucleus and tumor vasculature of tumor cells are known to be possible targets for photodynamic therapy. Vascular occlusion is clearly an important aspect of photodynamic therapy, but since blood vessels and tumors are made up of individual cells, recognizing the appropriate subcellular targets is a problem. Most photosensitizers are fluorescent substances, so the place where the photosensitizers collect can be seen under a fluorescence microscope. Since free radicals, which are cytotoxic substances, can move at a rate of less than 0.02 μm after they are formed, the places where phototoxicity occurs are places where photosensitizers are concentrated. Despite being heterogeneous components of porphyrins, mitochondria have been found to be targets of phototoxicity. When hemoglobin, which carries oxygen in the blood, loses the iron ions in the center, it loses its oxygen-carrying function and instead becomes a substance that can easily absorb light and effectively transmit the absorbed energy to oxygen molecules. Oxygen molecules change from a triplet state ($^3O_2$) with a pair of unmated electrons in the ground state to a single-term state ($^1O_2$) when energy is transferred, and oxygen in this single-term state is highly reactive and causes fatal damage to proteins, lipids, and nucleic acids in the cell, causing the cell to die. In other words, just as plants use a molecule called chlorophyll to produce sugar through light, porphyrins produce active oxygen through light. Due to the small distance movement from the place where free radicals are generated, the initial cell and tissue damage caused by photodynamic therapy is closely related to the place where the photosensitizer is concentrated. The most selected photosensitizers currently known are lysyl chlorin P6 in ribosomes, monocation porphyrin in cell membranes, porphycene monoers in mitochondria, and porphycene in cell membranes. Because photosensitizers that are not selected by intracellular targets are extremely ineffective, and most photosensitizers used in photodynamic therapy do not aggregate in the cell nucleus, photodynamic therapy generally has the advantage of less frequent occurrence of DNA damage, muation, and carcinogesis. Photofrin is a photosensitizer that focuses on mitochondria and appears to cause apoptosis, while photosensitizer confined to plasma membrane seems to cause necrosis when irradiated with light.

Apoptosis in Vitro

Photodynamic therapy can rapidly induce cell death in vivo. Mechanisms of apoptosis after photodynamic therapy have been linked to a link between mitochondrial photodamage and apoptoic response in recent studies, suggesting that accompanying cell membrane photodamage can delay apoptosis.

Selective Tumor Aggregation Mechanism of Photosensitizers

The dispensation mechanism of selective photosensitizers in tumors has not yet been fully elucidated. The characteristics of tumor tissue contribute to such selective distribution. Characteristics of tumor cells include an increase in the number of low-densisty protein receptors, the presence of macrophages, and a decrease in pH levels. The non-fixed structures of tumor stroma, characterized by large interstitial spaces, vascular leakage, impaired imp perfusion, large amounts of newly formed collagen (bound to porphyrins), and large amounts of lipids (with high affinity for lipophilic dyes), also enable selective distribution of photosensitizers.

Tumor Destruction Mechanism

The targets of photodynamic therapy are tumor cells, tumor microvasculature, normal microblood vessels and host inflammation and immune system. The effects of photodynamic therapy affect each other in their interrelationships, resulting in an overreaction. A combination of these factors is required to control long-term tumors. In vivo, exposing tumors to light can reduce tumor cell counts by direct phototoxicity. In animal experiments, direct photodynamic necrotic cells were below the 1 log. The uneven distribution of photosensitizing substances in tumors can lead to these limitations. Thus, photosensitizer aggregation and tumor cell killing decrease when they move away from the vascular distribution. Another factor that directly interferes with the necrosis of tumor cells is the availability of oxygen in tissues during photodynamic therapy. There are two mechanisms here: the photochemical consumption of oxygen during photodynamic therapy, and the other is the effect of photodynamic therapy on tissue microvessels. Vascular damage that occurs after photodynamic therapy contributes to long-term tumor suppression. Microvascular occlusion is easily observed after photodynamic therapy and this results in severe and persistent hypoxia/anoxia. The photodynamic action on blood vessels depends on the photosensitizer. Photofrin-PDT causes vasoconstriction, macromolecular vessel leakage, leukocyte adhesion, thrombus formation, and eventually platelet activation and thromboxane release.

2.3. Photobleaching and Photodynamic Therapy Necrosis Dose

As soon as the light is absorbed by the photosensitizer, the energy is transferred to the oxygen molecules, which increases the energy state of the oxygen molecules in the triplet state, creating an excited singlet state. It is thought that singlet oxygen reacts with many other cellular molecules and interacts with plasma and mitochondrial membranes to produce acidic toxicity, a photodynamic effect. The optical properties of light waves in the 600-1100 nm wavelength range to tissues are subject to scattering effects. The optical properties of light waves in the 600-1100 nm wavelength range to tissues are subject to scattering effects. Therefore, light transmission in an organization is best explained by diffusion theory using scattering coefficient (δ) and total attenuation coefficient (α). Here, the attenuation coefficient includes absorption scattering. It should be noted that δ and α are wavelength-dependent, and the absorption varies between various tissues, i.e., tissues with different chromophores. One of the notable findings of clinical review is the selective toxicity of photodynamic therapy to tumor tissue. This phenomenon can be explained by the selective retention of photosensitizers (PS) in tumors, a phenomenon called photobleaching, which also functions to efficiently increase the ability to select tumors. Photobleaching refers to the permanent photochemical loss of the chromophore used in photodynamic therapy. If the photosensitizer used in photodynamic therapy is so stable that it can continuously supply energy to oxygen molecules during the presence of light, the maximum depth at which the tumor can be necrosized without harming the normal tissue will be determined by the ratio of the drug to the tumor tissue. At this time, the maximum depth of necrosis of the tissue can be defined by the following equation:

$$\alpha Z_{\max} = \ln(\frac{C_T}{C_N}) \tag{2.2}$$

Here, C_T : Photosensitizer concentration in tumor, C_N : Photosensitizer concentration in normal tissue $_{\alpha:}$ Total attenuation coefficient, Z_{max} : Maximum Tissue Necrosis Depth. If the ratio ($\frac{C_T}{C_N}$) of the photosensitizer concentration in normal tissue and tumor tissue in Photofrin-R is about 3, then we obtain (if it were, $\alpha_{= 0.33mm}$).

$$\frac{C_T}{C_N} \square 3, \ln(3) \square 1.09 \tag{2.3}$$

$$Z\max = \frac{\ln(\frac{C_T}{C_N})}{\alpha} = \frac{1.09}{0.33} = 3.3mm \tag{2.4}$$

However, most photodynamic treatment-induced tissue necrosis exceeds 3 mm. It is speculated that this is due to the photobleaching described in the following equation. The amount of photosensitizer in the tissue is proportional to the amount of injection injected. If a certain amount of light intensity is irradiated at a point in the tissue, the photodynamic dose (D) in proportion to the amount of light irradiated is expressed as follows:

$$D = \int_0^{j\beta} C(J)dJ \tag{2.5}$$

$C(J)$: The amount of light that causes photobleaching depending on the concentration of the photosensitizer. In other words, the amount of light that causes the photodynamic effect can be obtained by the following equation:

$$C(J) = C_0 e^{-\beta J} \tag{2.6}$$

Here, J: light injection, C_0: Initial Drug Concentration, βJ: Initial Drug Concentration.

Therefore, the photodynamic necrosis dose (PDT dose) of the photosensitizer can be obtained as follows:

$$D = \int_0^{J_0} C(J)dJ = \int_0^{J\beta} C_O e^{-\beta J} dJ = C_0 \left[\left(-\beta^{-1} \right) e^{-\beta J} \right]_0^{J\beta} =$$

$$= C_0(-\beta^{-1})e^{-\beta J_O} - C_0(-\beta^{-1}).1 = C_0\beta^{-1}(1-e^{-\beta J_0}), D = C_0\beta^{-1}(1-e^{-\beta J_0}) \tag{2.7}$$

If the limit is close to $\beta J_0 \ll 1$ and D.= C_0J_0, the PDT dose is determined by the mutual change between the drug and the dose of photo injection. In PS, this occurs when the amount of drug injection is high, and the amount of photogenic intake is low. At the limit of the limit close to $\beta J_0 \gg 1$, photobleaching becomes a very important factor, with $\beta e^{-\beta Jo}$ being approximately 0 and D_{max} = C./β. At this point, there is no point in adding any more, because the drug has already been photobleached.

$$\beta J \square 1 : C_0\beta^{-1}(1-e^{-(0)}) = 0 \tag{2.8}$$

$$\beta J_0 \square 1 : C_0\beta^{-1}(1-e^{-(\beta)}) \square \frac{C_0}{\beta} \tag{2.9}$$

If there is a peripheral normal tissue with 1/3 of the drug concentration and photobleaching rate compared to the tumor tissue, the maximum PDT dose should also be administered to the tumor tissue with 1/3 of the tumor tissue. If D_{max} is below the threshold for tissue necrosis in normal skin, but above the threshold value in tumor tissue, no necrosis reaction will occur in normal skin except for tumors. This is due to the clinical application of this concept by Dougherty et al in the treatment of skin cancer.

2.4. Tumor Destruction Mechanisms of Photodynamic Therapy

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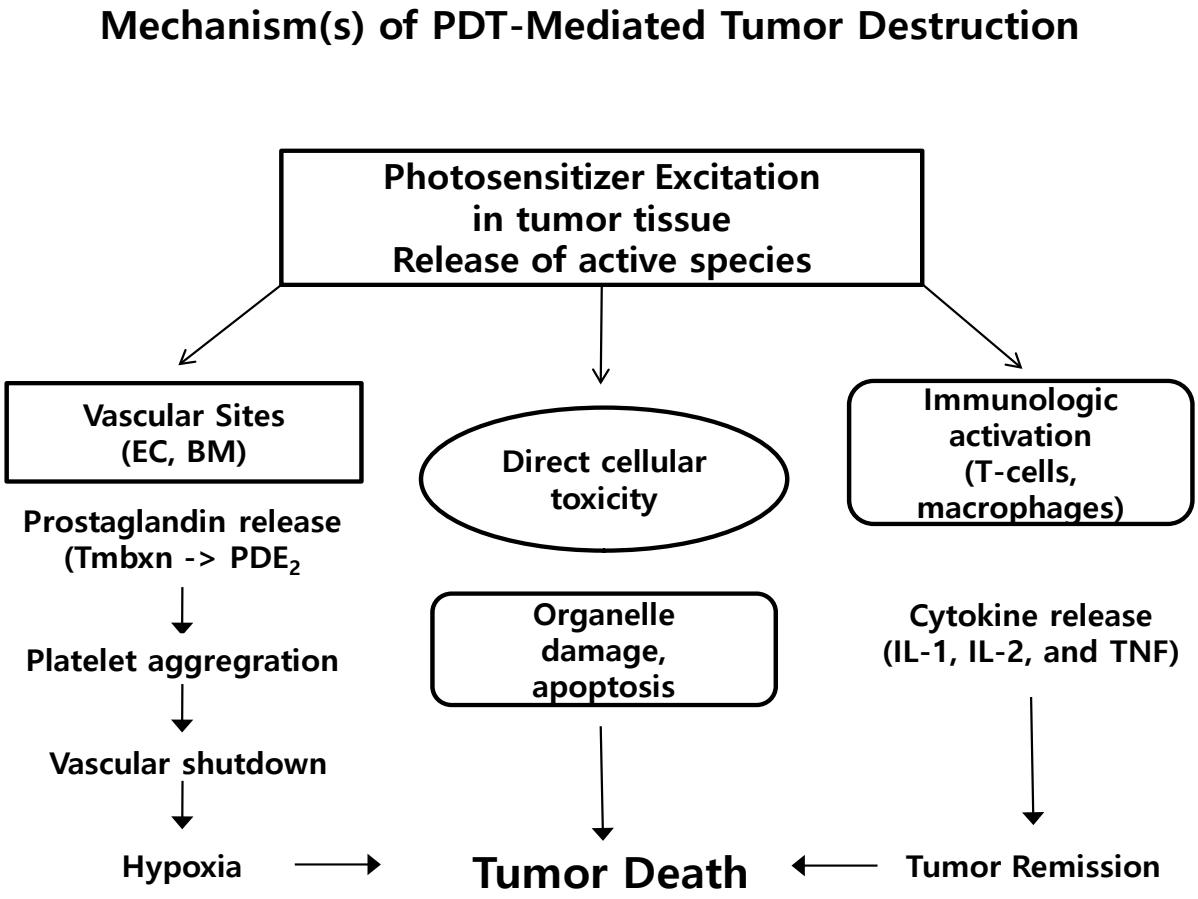

FIGURE 2.3 Tumor Necrosis Mechanism of Photodynamic Therapy

Tumor Destruction Mechanism

The targets of photodynamic therapy are tumor cells, tumor microvasculature, normal microblood vessels and host inflammation and immune system. The effects of photodynamic therapy affect each other in their interrelationships, resulting in an overreaction. A combination of these factors is required to control long-term tumors. In vivo, exposing tumors to light can reduce tumor cell counts by direct phototoxicity. In animal experiments, direct photodynamic necrotic cells were below the 1log. The uneven distribution of photosensitizing substances in tumors can lead to these limitations. Thus, photosensitizer aggregation and tumor cell killing decrease when they move away from the vascular distribution. Another factor that directly interferes with the necrosis of tumor cells is the availability of oxygen in tissues during photodynamic therapy. There are two mechanisms here: the photochemical consumption of oxygen during photodynamic therapy, and the other is the effect of photodynamic therapy on tissue microvessels. Vascular damage that occurs after photodynamic therapy contributes to long-term tumor suppression. Microvascular occlusion is easily observed after photodynamic therapy and this results in severe and persistent hypoxia/anoxia. The photodynamic action on blood vessels depends on the photosensitizer. Photofrin-PDT causes vasoconstriction, macromolecular vessel leakage, leukocyte adhesion, thrombus formation, and eventually platelet activation and thromboxane release.

CHAPTER 3

THE MATHEMATICS OF PHOTODYNAMIC THERAPY

3.1 The Amount of Light Delivered (L), Photosensitizing Drug (D), and Oxygen (O_2)

Photodynamic therapy (PDT) relies on three key factors: the amount of light delivered (L), the amount of photosensitizing drug (D), and the amount of oxygen (O_2) present. When light is absorbed by the photosensitizer, it converts the drug into an activated form (D*). This activated drug then reacts with oxygen, producing oxidizing radicals. These radicals can attack critical sites within the cell, causing oxidative damage. Membranes are particularly important targets for this oxidative damage, although other cellular sites can also be affected. The oxidative damage accumulates over time. There is a threshold damage level that leads to cell death; when the accumulated damage exceeds this threshold, cell death occurs.

In the diagram:

- L, D, D*, and R represent the concentrations of light, dye, activated dye, and oxidizing radicals, respectively.
- k_1 and k_2 are rate constants expressed per unit time.

$$L = \frac{\phi}{c}\frac{\lambda}{hc_0}\frac{1000}{6x10^{23}} \tag{3.1}$$

The light concentration L can be expressed as a concentration *[mole/L]*, $1 W/cm^2$ at $630nm$ = 1.45 X 10^8 photons/cm^3 = 2.41 X 10^{-13} [*moles/L*].

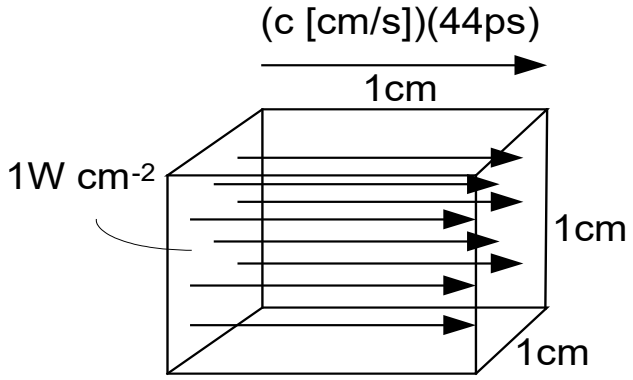

FIGURE 3.1 Fluence rate of light J/(cm2·s)J/(cm2·s)J/(cm2·s), λ/(hc): Number of photons per joule of energy ph/Jph/Jph/J, λ : Photon wavelength cm^3, c : Speed of light in tissue, $\frac{3.0x10^{10}}{1.37} = 2.26x10^{10}$[cm/s], **h** : Planck's constant, h=6.63×10−34[J·s]. There are **1000 cm^3** per liter. There are $6x10^{23}$ photons per mole of photons.

The light penetration into the tissue can be described by the expression.

$$\phi(z) = k_s E_{\exp}(-\frac{z}{\delta}) \tag{3.2}$$

Here, **E**: Irradiance at the tissue surface W/cm**ks** : The backscattering factor, which accounts for how reflected light from tissue augments delivered light (dimensionless), **z** : Depth into the tissue *cm*,**δ** : The optical penetration depth *cm.*

Conversion of drug to activated drug;

$$drug\ \ activation: \frac{dD^*}{dt} = k_1 LD \tag{3.3}$$

Here, k_1 : Rate constant for drug activation by light (moles/liter)$^{-1}$s^{-1}]; $k_{1=\mathrm{cln}(10)}$, **D**: Photosensitizing drug concentration moles/liter, **D*** : Activated drug concentration moles/liter, **ε** : Extinction coefficient of the photosensitizing drug [(cm^{-1})/(moles/liter)], t : Time duration of light exposure s. **L** : Photon concentration of light;

$$L = \frac{\left(\frac{\phi}{c}\right)\left(\frac{\lambda}{hc}\right)(1000)}{\left(6x10^{23}\right)} \tag{3.4}$$

Drug administration and accumulation; If drug dose were to distribute uniformly within the body, the initial tissue concentration D_0 would be the same value as D_{admin} expressed as [ug/ml].

$$D_0 = D_{ad\,\min} f_{tumor} \frac{10^6}{MW} 1000 \tag{3.5}$$

Here, f_{tumor} : dimensionless factor, MW: molecular Weight [g/mole] is

$$(10^{-6}\ \text{g/}\dot{z}\,\text{g})/\text{MW}.$$

During irradiation the time course of drug concentration, D(t), will often fall due to photobleaching.

$$D(t) = D_0 \exp(-\frac{\phi t}{H_{pb}}) = D_0 e^{-t/\tau}, \tau = \frac{H_{pb}}{\phi} \tag{3.6}$$

The factor H_{pb} is the dose or radiant exposure[J/cm^2] which photobleaches all but 37% of the drug. The ratio $H_{pb/\varphi}$ has units of time[s]. The D* factor is quantifiable a therefore a practical dosimetric parameter which has been called the "Photodynamic dose".

$$D^* = k_1 L D_0 \sum_0^T e^{-t/\tau} dt = k_1 L D_0 \tau (1 - e^{-T/\lambda}) = k_1 L D_0 \tau \tag{3.7}$$

If $D^* > D^*_{th}$ then cell death. For very long exposures that achieve complete photobleaching of the photosensitizing drug, the term $e^{-T/\tau}$ goes to zero. The conversion of activated drug(D*) and oxygen(O_2) into oxidizing radical (R), primarily singlet oxygen, is governed by the rate parameter k_2. The rate of reaction of D* and O_2 to yield is expressed as the change in R per unit time[(moles/liter) s^{-1}].

$$\textit{Radical Generation}: \frac{dR}{dt} = k_2 D^* O_2 \tag{3.8}$$

Where, D^* : activated drug concentration [moles/liter], O_2 : the oxygen concentration [moles/liter], k_2: the rate parameter for oxidizing radical formation [(s^{-1})/(moles/liter)].

Treatment zone in below. Where ρ=density of tissue [g/cm^3], about 1 g/cm^3.

$$A = fk_2 \in \phi \frac{\lambda}{hc} \frac{1000}{6x10^{23}} DO_2 T \tag{3.9}$$

$$A_{th} = fk_2 \in \phi \frac{\lambda}{hc} \frac{1000}{6x10^{23}} DO_2 TEK_S \exp(-z_{necrosis} / \delta) \tag{3.10}$$

$$Z_{necrosis} = \delta \ln\left(\frac{f \in k_2 DO_2 TEK_S}{A_{th}} \frac{1000}{hc6x10^{23}}\right) \tag{3.11}$$

$$D^* = \phi \in \ln(10) D_0 \frac{\lambda}{hc_0} \frac{1}{\rho} \tag{3.12}$$

CHAPTER 4

PHOTOSENSITIZER FOR PDT

4.1 The role of Photosensitizer

The PS is the key component among the three, together with visible light and molecular oxygen, needed to induce photodynamic cytotoxicity. PS properties such as the chemical nature of the PS including molecular weight, lipophilicity, amphiphilicity, ionic charge, and protein binding characteristics can determine its localization and effectiveness. In principle, an ideal PS should be endowed with the following properties:

- Strong absorption (with a high absorption coefficient) in the red or near-infrared (650–800 nm), where penetration in tissues is deeper.
- High quantum yield of triplet state formation (ΦT), the energy of the triplet state above ∼94 kJ/mol, long lifetime of the triplet state (τT in the long μs range), and high quantum yield of singlet oxygen formation (ΦΔ).
- Low toxicity in the dark, i.e., in the absence of light, the PS must not be harmful.
- High accumulation in the target area.
- Excellent biocompatibility securing rapid disposal by the body.

High chemical stability and low photobleaching (to allow sustained photoinduced singlet oxygen production) [32].

The first generation of PS consisted of hematoporphyrin derivatives (HpDs). In 1993, a HpD called PhotofrinḢ (porfimer sodium) was approved for clinical use, and it was used for several types of cancer despite its disadvantages:

(i) low chemical purity; (ii) intense accumulation in the skin causing a prolonged photosensitivity (even 2–3 months after administration); and (iii) the wavelengths range of its absorption, which does not allow a good penetration into tissues. Motivated by these drawbacks, an intense research activity was undertaken to develop new photosensitizing agents with defined chemical identity, improved photophysical characteristics, and enhanced tumor selectivity. Second-generation PSs have higher chemical purity, the higher quantum yield of singlet oxygen formation, and have higher tissue penetration (thanks to their absorption peaks falling in the red portion of the visible spectrum or in the near infrared). Second-generation PSs were developed following different synthetic strategies, focusing on the modification of the macrocycle or the substituents, or considering different molecular architectures. This has led to the development of several molecular families, including chlorins (FoscanḢ), metalloporphyrins (LlutrinḢ, LutexḢ), verteporphin (VisudyneḢ), pheophorbides (TookadḢ), phtalocyanines, porphycenes, protoporhyrin IX precursor (HexvixḢ, MetvixḢ, LevulanḢ), cyanines, dipyrromethenes, hypericin, phenothiazines (methylene blue, toluidine blue), purpurins (PurlytinḢ), and xanthenes (Rose Bengal), Table 1 shows some clinically approved photosensitizers and its applications.

TABLE 4.1 Photosensıtizer(PS) Informations

Photosensi-tizer	**Cancer Application**	**Country**	**Chemical Base Structure**	**Activation Wave-length(nm)**
Photofrin	Lung, gastric, bladder, cervical, esophagoal	Canada, Japan, the United States, and Europe	Hematoporphyrin	630
Foscan	Head and Neck	European Union, Norway, and Iceland	Chlorin	652
Metvix	Nonhyperkeratotic actinic keratonis and basal cell carcinoma	United Kingdom, EMEA, the United States, and Canada	Protoporphyrin IX precursor	570-670
Levulan	Actinic keratosis, HPV	EMEA, the United States, Austria, and China	Protoporphyrin IX precursor	635
Visudyne Verteporfin	Age-related macular degeneration, basal cell carcinoma	Switzerland, China, and the United States	Benzoporphyrin	690

Laserphyrin talaporfin	Early centrally located *lung* cancer and glioma	Japan	Chlorin	664
Redaporfin	Biliary tract cancer	Portugal	Bacteriochlorin	749
Tookad	Prostate	Europe, Israel, and Mexico	Bacteriochlorophyll	762

In-depth analysis of 5-ALA photosensitizer

5-ALA (5-Aminolevulinic acid) is one of the widely used photosensitizers in photodynamic therapy (PDT). 5-ALA is converted in the body to protoporphyrin IX (PpIX), which works by producing free radicals when exposed to a specific wavelength of light, which selectively destroys surrounding tumor cells.

- How 5-ALA Photosensitizer Works in biological tissues?
- 5-ALA administration: 5-ALA is primarily administered to tumor sites due to its selective accumulation in tumor cells.
- PpIX Generation: The body converts 5-ALA to PpIX.
- Light irradiation: When irradiated with light of a certain wavelength (mainly 630- 635nm), PpIX produces free radicals.
- Tumor cell destruction: The free radicals produced damage the cell membranes and DNA of tumor cells, leading to apoptosis.

Advantages of 5-ALA Photosensitizer

- High selectivity: selectively accumulates in tumor cells, minimizing normal cell damage.
- Low toxicity: It has fewer side effects compared to other anti-cancer drugs.
- Repeatable treatment: Repeated treatment is possible as needed.
- Minimally invasive: Can be treated with a simple procedure without surgery.

Clinical Utilization of 5-ALA Photosensitizers

- Skin cancer: It is used to treat various skin cancers, such as epidermal cell carcinoma and basal cell carcinoma.
- Head and neck cancer: It is used for the prevention and treatment of local recurrence of head and neck cancers such as laryngeal cancer and pharyngeal cancer.
- Bladder cancer: Used in the treatment of superficial bladder cancer.
- Brain tumors: Research is underway to treat malignant brain tumors.

Types and Forms of 5-ALA Photosensitizers

- 5-ALA is manufactured and used in a variety of forms.
- Cream: It is mainly used to treat skin cancer.
- Gel: Easy to apply to mucous membranes or wounds.
- Injections: Used to treat tumors in the deep area.

CHAPTER 5

THE BASIC DESIGN OF LASER SYSTEM

5.1 Introduction

Photodynamic therapy (PDT), which induces a photochemical reaction in tissues, has recently been used as a treatment method for cancer. This method does not have the side effects such as decreased immunity, hair loss, pain, or mutations that can accompany conventional cancer treatments such as chemother apy, surgery, or radiotherapy. In addition, PDT has the advan tage of being selective for cancer tissues, while organs and normal tissues are preserved in their original state 8–12. The den sity of photosensitizers (PS) in a tumor, the excited photometric quantities injected into the tissue, and the amount of molecular oxygen in the organic tissue are factors that affect the results of photodynamic cancer treatment. These three parameters must be optimally regulated in their application to cancer treat ment. Based on the density of the agent, the optimal injection dose can be determined through clinical experiments. In addition, the laser light source for cancer treatment is an important element. The laser system for PDT has optimal per formance when the following characteristics are satisfied. First, the optical wavelength should be set at the maximum absorption point of the PS. Second, the wavelength of the laser should be held constant, regardless of the temperature and duration of the treatment. Third, the optical permeability of the organic tissue should be deep. Fourth, the output of the laser should be precise. Fifth, irreversible thermal damage to the tissues surrounding the tumor should not occur due to the optical radiation of the laser. Finally, the PDT laser system should prevent oxygen deficiency caused by photodynamic reactions.

5.2 System Design

5.2.1 Laser Resonator Configuration

The laser system was designed to produce an effective and stable optical wavelength of 635 nm at 1.5 W using a temperature controller. Precise and stable laser output was achieved using digital-to-analog (D/A) and current-to-voltage (I-V) converters, which produced 150-level laser output resolution. The laser system was configured using a microprocessor controller that integrated and controlled the optical radiation mode control circuits. The IEC 60601-2-22 standard was applied to the control user interface designed as an LCD touch screen, which was used to carry out safety management. In figure 5.1, the laser resonator with 1.5-W optical output with maximum source biases of 4 A and 2.46 Vand a semiconductor laser diode with a 635 ḍ3 nm output wavelength were installed. In addition, a thermoelectric cooler (TEC) and thermistor were installed to cool the resonator and sense the temperature on the inside of the resonator next to the semiconductor laser chip, which radiates through the laser. The bias current had a threshold of a 2.2-A region for the forward bias. Figure5.2 presents the transfer function of the laser resonator from the 2.4-A to the 4-A region, demonstrating effective output.

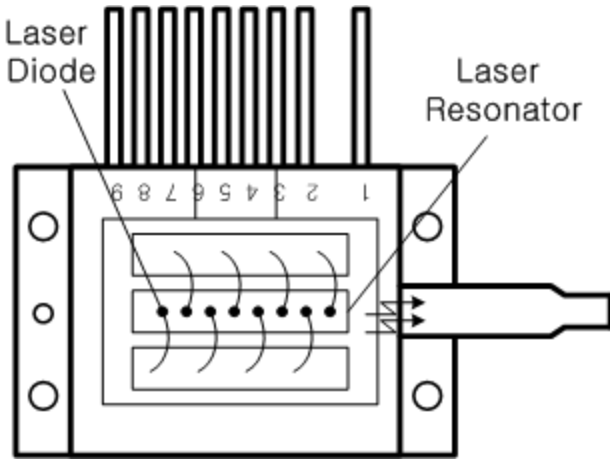

FIGURE 5.1 Laser Resonator

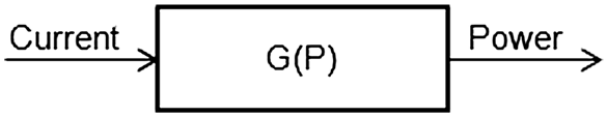

FIGURE 5.2 Transfer Characteristics of the Laser Diode.

The laser output and wavelength of the diode laser resonator can be affected by the operational temperature. To produce a 635-nm optical wavelength, the inside temperature of the resonator should be maintained at 15°C. The TEC installed inside the laser resonator was a semiconductor element making use of the Seebeck–Peltier effect that can control a maximum 27.5 W of thermal load at maximum values of 5.3 A and 8.1 V. In figure 5.3, the thermistor was used to observe the temperature of the laser module and operate the cooling device. The response voltage varied with the bias voltage of the thermistor and had a 10-kΩ resistance at 25°C. Figure 5.4 presents the temperature change versus thermistor resistance. The change in the resistance of the thermistor with temperature (K) follows the Steinhart–Hart equation for temperature:

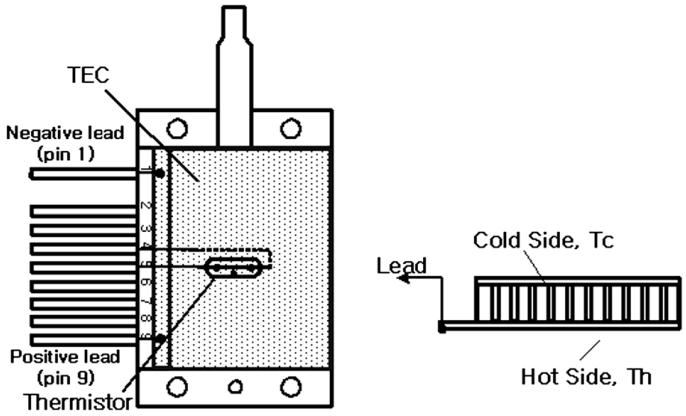

FIGURE 5.3 Thermoelectric Cooler (TEC) Module and Thermistor.

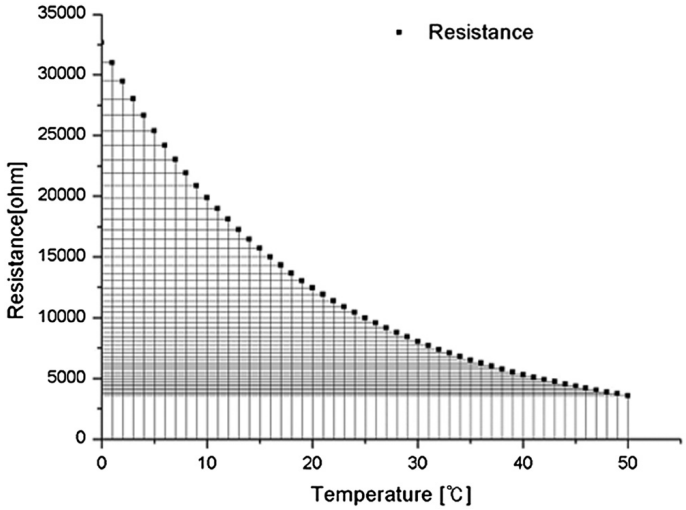

FIGURE 5.4 Resistance vs. Temperature of the Thermistor.

$$\frac{1}{T} = A + B(\ln R_T) + C(\ln R_T)^3 \tag{5.1}$$

where R_T is the resistance (Ω) at temperature *T(K)*. A, B, and C are determined through a calibration process. The thermistor constants A, B, and C were A = 1.1235E – 03, B =2.3500E −04, and C = 8.4538E – 08. This equation can be rearranged for temperature in °C as follows:

$$T_C = \frac{1}{A + B(\ln R_T) + C(\ln R_T)^3} - 2.73.15. \tag{5.2}$$

The resistance of the thermistor was configured at 15,710 Ω by setting the current input to maintain a constant temperature of 15ḌC. Figure 5.5 illustrates the configuration of the PDT laser system. The system consists of the main control section, which integrates and controls the entire laser system, the laser generation and radiation control section, the user interface section, the safety device section, and the laser output section.

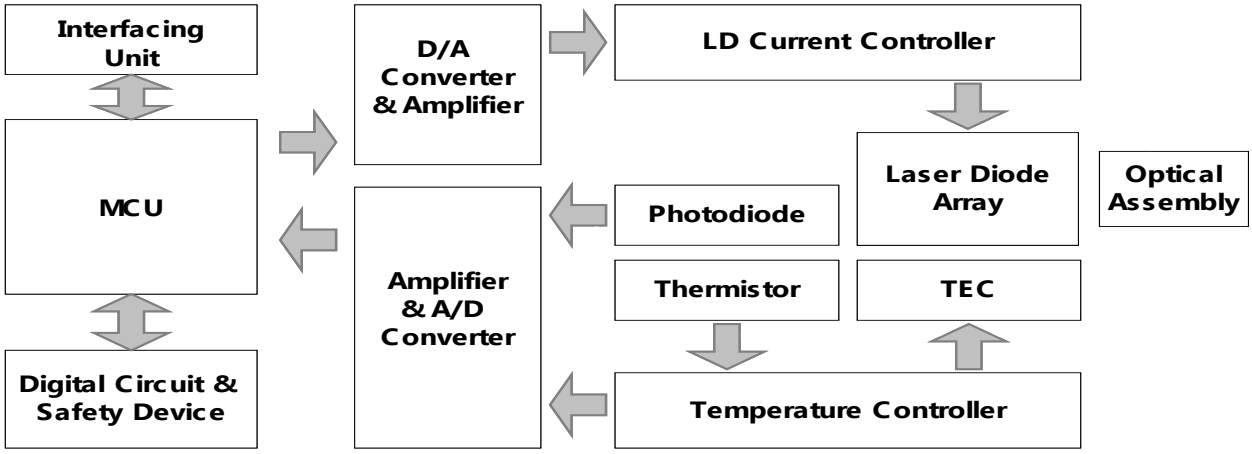

FIGURE 5.5 Block diagram of the Photodynamic Therapy (PDT) Laser System.

5.2.2 Signal Processing Control Section

This section controls the entire function of the system and consists of the main controller, a D/A converter, and an I-V converter, as shown figure 5.5. and □igure 5.6. The microcontroller unit (MCU) used in this study was the AT89C55, an element of the 8051 family. In addition, a universal asynchronous receiver/transmitter (UART) serial port was used to communicate with the touch screen, which acted as the user interface. The D/A converter transformed the 8-bit laser output data acquired from the MCU to current values. The transfer function for the maximum current output of the D/A converter is as follows:

$$I_{out} = \frac{12}{(5.1x1000)x(\frac{D_{value}}{256})} \tag{5.3}$$

where D_{value} is the input value for the D/A converter. The laser output can be precisely controlled by adjusting the D/A output using the variable resistor of the I-V converter (VR_1). The transfer function for the I-V converter is as follows:

$$Vout \approx \frac{V_{ref}}{R_{ref}}.VR_1.\frac{D_{value}}{256} \approx I_{out}VR_1 \tag{5.4}$$

In figure 5.6, this system used ~150 values of the 256-resolution 8-bit device to produce output of up to 1.5 W with a 10-mW unit. An I-V converter was used to convert the output current values. Figure 5.6 presents the outputs of the D/A and I-V converters. The final output of the I-V converter was the value obtained when the resistance of VR1 was configured at 1.7 *Kω* to produce a maximum operating current of 4 A. The control input values from the touch screen were converted to timer interrupt values through the CPU. In addition, the radiation mode was implemented according to the input control time. A photo-coupler was used to directly cut the bias to perform on/off operations for the laser module and pulse as shown figure 5.6. The photo-coupler prevents damage to the laser diode from noise by separating the laser driver, irradiation mode controller, and main control circuits from the power source.

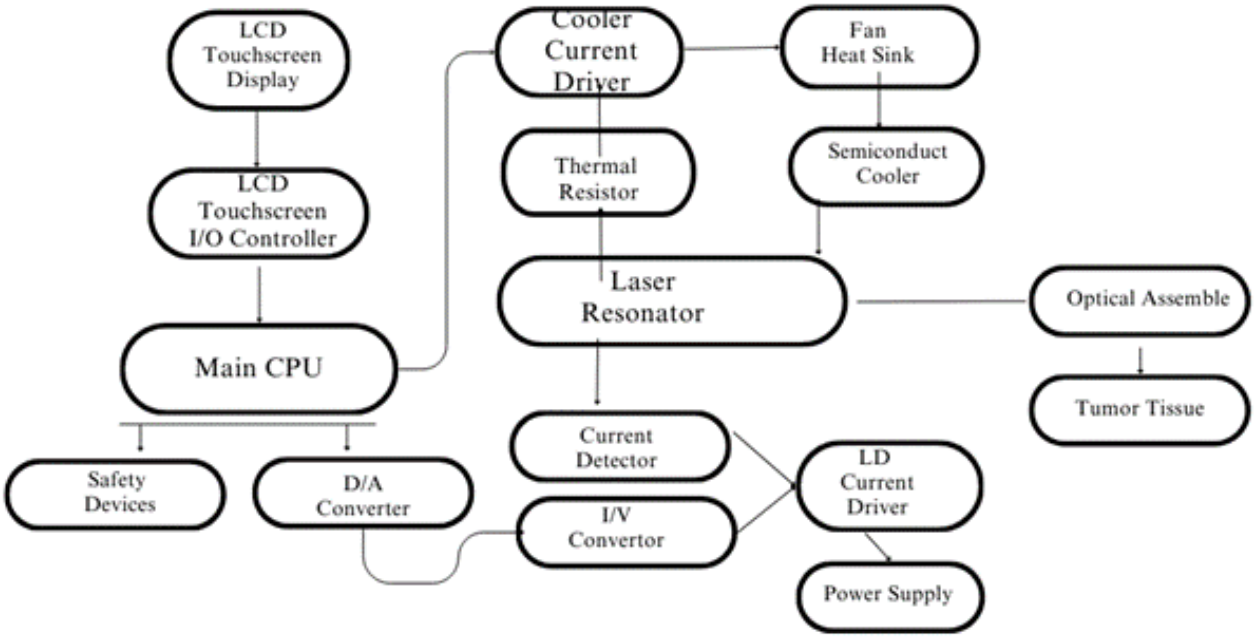

FIGURE 5.6 The Entire Laser System

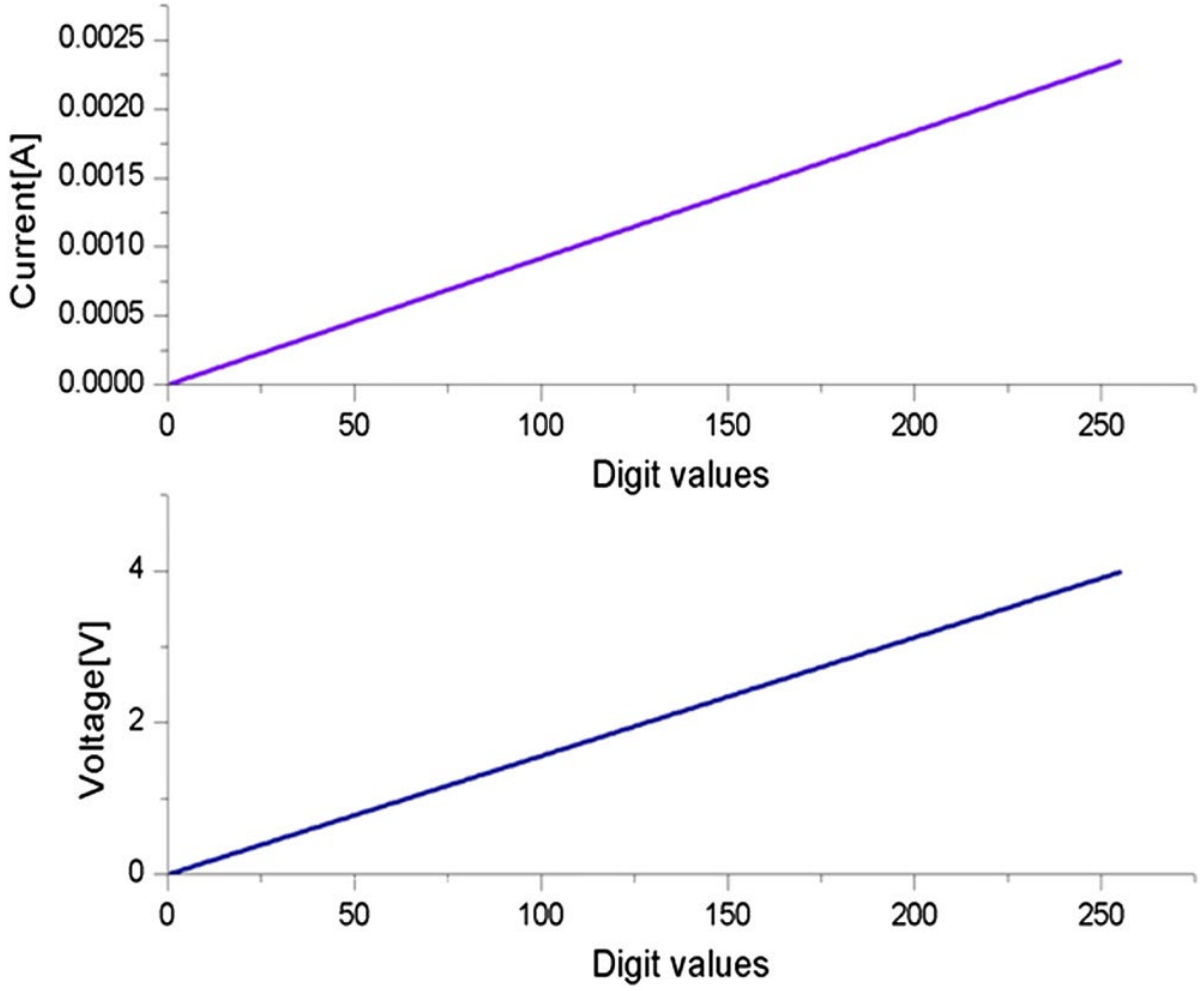

FIGURE 5.7 Digital-to-Analog (D/A) and Current-to-Voltage (I-V) Outputs.

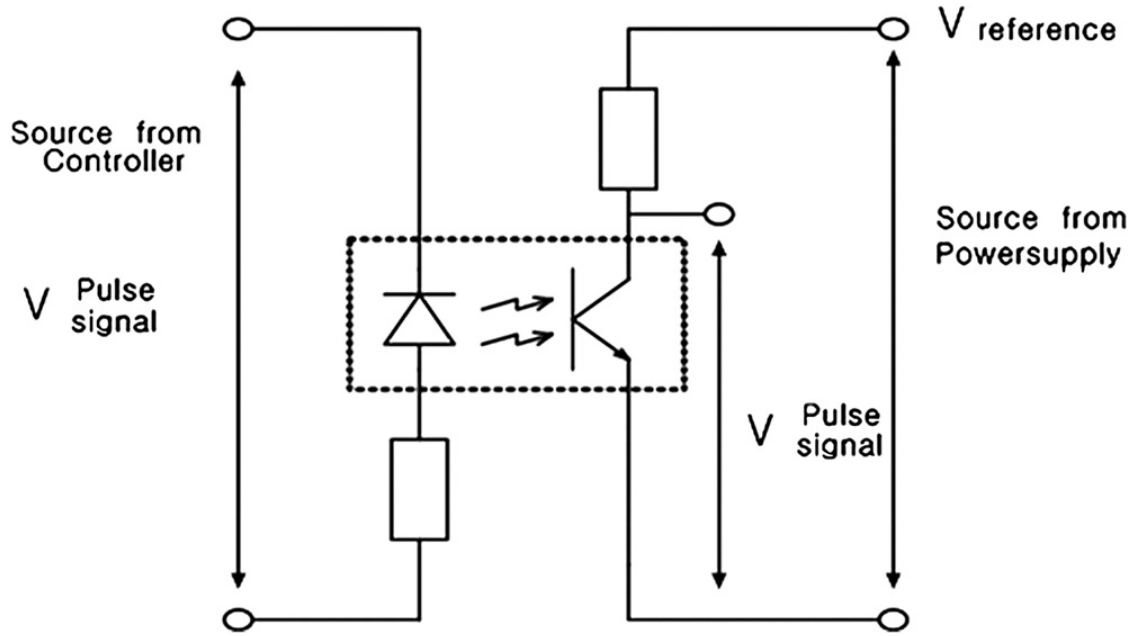

FIGURE 5.8 Laser Radiation Circuits.

The laser driver supplements the current source to the laser diode. The laser driver consists of a modulation input section, a current monitor section applied to the laser, and a current output section. In the modulation input section, the laser output and radiation mode are transferred from the main controller. The current output section applies the current to the laser resonator. The transfer characteristics of the laser driver consist of the voltage at the driver (V_{Driver}), the input current to applied to the laser diode (I_{LD}), and the current ($I_{Feedback}$) from the laser diode to the I-V converter.

$$\frac{I_{LD}}{V_{Driver}} = 1000mA/V \tag{5.5}$$

where the applied input voltage to the laser driver becomes the loaded current to the laser diode.

5.2.3 Temperature Controller Configuration

The power supply of the temperature controller is independent from that of the main controller. In addition, the temperature controller was designed to supply a forward bias current to the TEC module when the temperature increases above the selected value upon receiving data on the interior temperature of the resonator from the thermistor. The temperature can be observed using the bias voltage of the thermistor as an input element as shown figure 5.9.

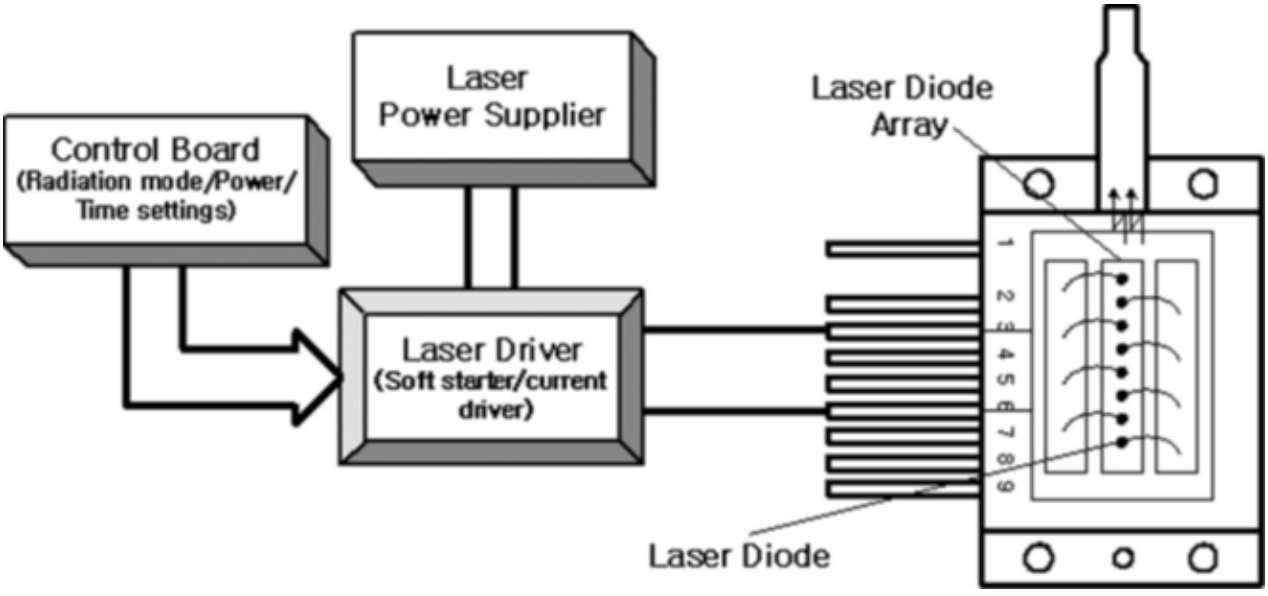

FIGURE 5.9 Laser Driver Unit

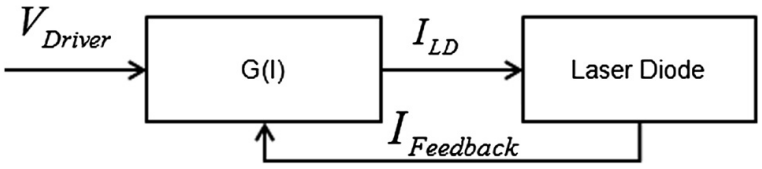

FIGURE 5.10 Transfer Characteristics of the Laser Driver.

When the temperature of the laser module is higher than the selected tem-perature, cooling is conducted by applying a forward bias; a reverse bias is applied in the opposite case as shown figure 5.11 As noted above, the temperature of the resonator is controlled by applying a semiconductor cooling method that makes use of the Seebeck–Peltier effect.

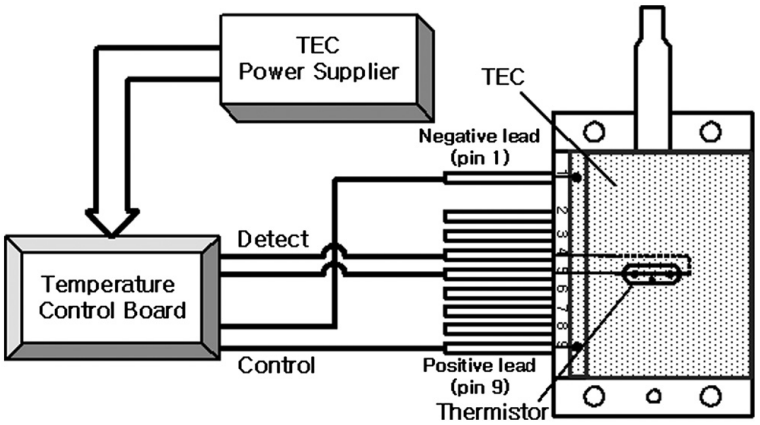

FIGURE 5.11. Temperature ControllerUunit.

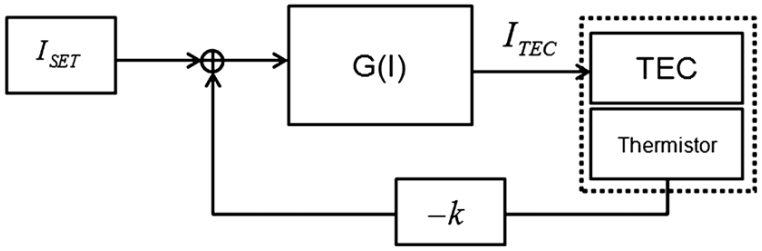

FIGURE 5.12 Transfer Characteristics of the Temperature Controller.

In figure 5.12, the transfer characteristics for this method consist of the input current (I_{SET}) for the previously selected temperature, the current (I_{TEC}) for the adjusted temperature, and the feedback value *(k)*. Based on the temperature change in the laser diode, the input current to the temperature controller TEC can be calculated as follows:

$$I_{TEC} = (I_{SET} - k)x\,G(I) \tag{5.6}$$

During instantaneous optical output or heat generation, such as when laser output or pulse mode is initiated, the temperature of the laser module increases rapidly. In addition, there is a slow response time when approaching stable state at the set temperature depending on the heat load and ΔT.

5.2.4 SyatemControl MaınProgram (CW, Pulse, and Burst-Pulse Radiation Mode)

The initial display screen once a mode is selected requires user specification of the laser radiation settings or return to the main menu to select an alternative mode. Laser radiation begins after entering the required power and radiation time through the keypad. In addition, output can be controlled by viewing information on each page. The on/off time for the pulse radiation mode is controlled using the interrupter of an 89c55 timer. In pulse mode radiation, the output time is configured after entering the required pulse on/off time. The burst pulse radiation mode stores the pulse on-time and off-time as well as the duration on-time and off-time as individual variables. These values are used as input for the timer interrupter and control the radiation output. The burst-pulse mode is based on a pulse mode, but outputs the laser as pulse flux radiation, such as radiation-start/radiation-stop. This mode was designed to prevent thermal damage due to excess accumulation of optical energy in the laser and to provide sufficient oxygen. After the input stage, laser radiation begins; the settings can be changed by the user and alternative irradiation modes can be selected during radiation.