RESEARCH ARTICLE

Depth estimation of tumor invasion in early gastric cancer using scattering of circularly polarized light: Monte Carlo Simulation study

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Abstract
Quantitative depth estimation of tumor invasion in early gastric cancer by scattering of circularly polarized light is computationally investigated using the Monte Carlo method. Using the optical parameters of the human stomach wall and its carcinoma, the intensity and circular polarization of light scattered from pseudo-healthy and cancerous tissues were calculated over a wide spectral range. Large differences in the circular polarization with opposite signs, together with the large intensity, are obtained at wavelengths 600 nm and 950 nm. At these two wavelengths, the sampling depth of the biological tissues can be modulated by tuning the detection angle. In bi-layered pseudo-tissues with a cancerous layer on a healthy layer and vice versa, the degree of circular polarization of scattered light shows systematic changes depending on the thickness and depth of the cancerous layer, which indicates the feasibility of in vivo quantitative estimation of cancer progression in early gastric cancer.

KEYWORDS
Cancer detection, circularly polarized light, early-stage stomach cancer, multiple scattering, optical biopsy

1 INTRODUCTION

Recent developments in diagnostics and treatments are one of the major causes for the gradual reduction in mortality rate due to gastric cancer in the past few decades [1]. Nevertheless, gastric cancer remains a serious health issue, especially in East Asian countries. Above all, for Japanese males, the age-standardized incidence rate of stomach cancer per 100,000 is extremely high, which is probably because of the high infection rate of chronic Helicobacter pylori and large intake of salted foods.

Early detection of cancer is the most crucial strategy for increasing the chance of effective treatment and reducing mortality due to cancer. Accurate diagnostic
results regarding the tissue types, locations, distributions and progress degrees of the cancer are required for the appropriate treatment. Gastric cancers have been classified according to the TNM staging system, where the three key parameters are T (size or direct extent of the primary tumor), N (degree of spread to regional lymph nodes) and M (presence of distant metastasis). Early-stage cancers have been identified almost only with T stage classification (Figure 1) [2–4]. The cancers categorized in the Tis and T1 stages rarely spread to a lymph node. It can be removed without sacrificing the entire organ by using endoscopic surgical procedures, such as endoscopic submucosal dissection (ESD) [5–7]. Approximately 20% to 30% of cancers in T2 stages spread to lymph nodes, which have been treated by surgical treatment with lymph node dissections. Therefore, accurate tumor invasion depth in gastric cancer is of primary importance in determining the therapeutic approach. Recently, image-enhanced endoscopy (IEE), represented by narrow-band imaging (NBI) [8], which is used for the diagnosis of tissue types and degree of spread in cancer has drastically improved the quantitative and qualitative diagnosis of gastrointestinal cancers. Magnifying endoscopy with NBI (ME-NBI) has been used for determining the invasion depth by observing the intrapapillary capillary loops for esophageal tumors and pit patterns for colon tumors [9]. For these tumors, ME-NBI has obtained a high diagnosis rate. In contrast, for the depth estimation of tumor invasion for gastric cancers, magnifying endoscopy with indigo carmine dye contrast or endoscopic ultrasonography (EUS) has been used. The correlation between the invasion depth and abnormal blood vessels or mesh patterns has been reported in recent years [10, 11]. However, only a few cases were analyzed for these studies. Methods to determine the invasion depth in gastric cancer have not yet been established, necessitating a breakthrough from a different technological viewpoint.

One of the techniques is the optical biological observation using light polarization [12]. Scattering of incident linear polarized light (LPL) provides structural information of biological tissues. This is carried out by analyzing the degree of birefringence and depolarization from the supplying images that reflect the anisotropy of the tissues [13–17]. However, in a turbid medium like biological tissues, LPL is readily lost by multiple scattering, therefore, it provides poor information from deep regions of tissues. In contrast, circularly polarized light (CPL) has comparatively more endurance against multiple scattering than LPL [18, 19]; its polarization survives even after a large number of scattering events in biological tissues with a thickness of several millimeters. Utilizing this characteristic of CPL, Meglinski et al. [20] pioneered the application of CPL for optical cancer detection by mapping the polarization-dependent optical properties of tissues on the Poincaré sphere. They verified the use of the Stokes vector of backscattered light from tissues for noninvasive optical tissue biopsy. Kunnen et al. [21] reported that when CPL impinges on a human lung tissue, the polarization states of the scattered light show clear differences between normal and tumor tissues. These findings were interpreted as follows: the CPL beams impingement on a biological tissue are scattered multiple times by cell nuclei and gradually depolarized. In the Mie regime, where the scatterers (cell nuclei) are larger than the wavelength, the depolarization sensitively depends on the size of the scatterers [22]. Therefore, the resultant degree of circular polarization (DOCP) of the scattered light provides structural characteristics, such as the size, anisotropy, distribution and density of the cell nucleus. In cancerous tissue, the cell nuclei are enlarged due to the abnormal growth of cancer, which can be detected by the difference in the DOCP of the normal and tumor tissues. Following these reports, the polarimetry technique for tissue observation using the polarization of light, including CPL, has been extensively studied [23–30]. Recently, the polarimetry technique has been applied for grading colon cancer [31], Alzheimer’s disease [32] and early-stage breast cancer [33].

Following these studies, we also have investigated the scattering phenomena of incident CPL in biotissues for cancer detection. Before then, we have studied CPL-emitting diodes, also called spin-LEDs, and we have achieved fully polarized CPL emission at room temperature [34, 35], electrical switching of CPL helicity at high speed [36] and detection of CPL at room temperature [37, 38]. Based on these achievements, we proposed CPL scattering technique for in vivo diagnosis of gastrointestinal

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**FIGURE 1** Clinical stages of gastric cancer. Tis (carcinoma in situ; intraepithelial tumor without invasion of the lamina propria), T1 (tumor invades the lamina propria or muscularis mucosae (T1a), and submucosa (T1b)), T2 (tumor invades the muscularis propria), T3 (tumor penetrates the subserosal connective tissue) and T4 (tumor invades the serosa (T4a) or adjacent structures (T4b)) [2–4].
cancer by combining the cancer detection technique with CPL scattering which Meglinski et al. developed and spin-LEDs which we have developed. CPL cannot be transferred through a tortuous optical fiber, while maintaining its polarization. However, the spin-LED can directly emit, control and detect CPL even at spatially restricted places. The spin-LEDs integrated at the tip of an endoscope allow in vivo cancer detection using the CPL scattering technique. This technique does not require any staining, fluorescent materials, invasive ablation and waste of time. We have studied the CPL scattering technique from both aspects of experimental and computational studies to implement this proposal. To date, we experimentally demonstrated the identification of cancerous parts in sliced biological tissues using the CPL scattering technique with various optical configurations [39]. The line-scanning experiments along a region incorporating normal and cancerous parts show steep changes in the DOCP value depending on the state of the tissue, which indicates the feasibility of this technique in identifying the carcinoma concealed in healthy tissues. Meanwhile, we conducted theoretical and computational analyses using Monte Carlo (MC) simulation methods for the scattering process of CPL with cell nuclei in pseudo-tissues [40]. The single scattering of CPL against particles with diameters corresponding to cell nuclei in healthy and cancerous tissues was investigated first. Then, we introduced them into multiple scattering systems in pseudo-healthy and cancerous tissues to clarify the contribution of optical and structural conditions to the resultant polarization of scattered light. These studies revealed three major points—the resultant DOCP values of the scattered light showed obvious differences between pseudo-healthy and cancerous tissues irrespective of the scattering angles, the intensity of scattered light obtained from healthy and cancerous tissues are approximately the same and the scattering volume (depth) can be controlled by changing the scattering angle. The third deduction suggests that the depth profile of the tissue can be obtained by analyzing the scattering-angle dependences in the DOCP of the scattered CPL.

In this study, we computationally investigated the quantitative measurement of tumor invasion depth in layered structures that consists of cancerous and healthy tissues. In the preliminary stage, the wavelengths were optimized for detecting cancer and estimating distributions in terms of the polarimetric response for biological tissues and the intensity of scattered light. Subsequently, the changes in the DOCP values were analyzed using the optimized wavelengths for various structure of biological tissues; a cancerous layer lying on the surface [41], and a cancerous layer hiding under the healthy tissue.

2 | EXPERIMENTAL

The polarization state of light is expressed by the Stokes vector \( S \), given by the equation \( S = (S_0, S_1, S_2, S_3)^T \), where \( S_0, S_1, S_2 \) and \( S_3 \) are the Stokes polarization parameters [42]. The first Stokes parameter, \( S_0 \), describes the total intensity of the light beam; the second parameter, \( S_1 \), describes the preponderance of horizontal LPL over vertical LPL; the third parameter, \( S_2 \), describes the preponderance of \(+45^\circ\) LPL over \(-45^\circ\) LPL; \( S_3 \) describes the preponderance of right-handed CPL over left-handed CPL. The DOCP value, defined by the equation \( \text{DOCP} = S_3/S_0 \), is used to indicate the state of tissues in the CPL scattering technique.

In this study, we used the polarization-light MC algorithm developed by Ramella-Raman et al. [43], also known as “meridian plane MC algorithm,” to investigate the intensity, polarization and passage distribution of scattered light. In the polarization-light MC algorithm, light beams are traced using absorption and scattering accompanied by depolarization in a medium. A light beam propagates for a random length associated with the mean free pass in the medium, \((\mu_a + \mu_s)^{-1}\), where \(\mu_a\) and \(\mu_s\) are the absorption and scattering coefficients of the medium, respectively. The propagation length \(\Delta s\) is determined by a random number \(\zeta(0 < \zeta \leq 1)\), \(\Delta s = -\ln(\zeta)/(\mu_a + \mu_s)\). After a traveling in the medium for a distance \(\Delta s\), the light beam runs into a scatterer and is subjected to a scattering event. In each scattering process, a random direction and a particular axis are chosen by the rejection method depending on the single scattering phase function in the Mie scattering process [44]. Accordingly, the polarization state after the scattering event is rewritten by the Stokes vector \( S \) with respect to the meridian planes, which is determined by the new direction and axis. Simultaneously, a light beam is absorbed at a certain ratio, \(\text{albedo} = \mu_a/(\mu_a + \mu_s)\). All Stokes parameters are multiplied by albedo to denote a decrease in intensity due to absorption. Subsequently, the light beam travels in a new direction. After this series of processes, the beam going outwards the medium are collectively detected, and the beam whose intensity is less than a certain value falls out as they are fully absorbed. Because of the refraction at the interface to the air, the light beams having an angle less than the critical angle, \(\sin^{-1}(1.00/1.33) \approx 48.75^\circ\), can emit an outward air and can be detected, whereas the beams with angles larger than the critical angle are totally reflected and returned to the scattering process loops. These totally reflected light beams scarcely arrive at the surface again, emit outward and are detected, therefore they are ignored in this study. By repeating these processes from injection to outgoing or full absorption, we analyzed the detected beam.
for every angle of emergence, hereafter called “detection angle.”

Polarized MC simulations were carried out for pseudo-biological tissues with a bilayered structure: a cancerous layer on a healthy layer and vice versa. The pseudo-cancerous and healthy tissues comprise aqueous dispersions of particles with diameters of 5.9 and 11.0 μm, respectively. These diameters correspond to the typical nuclear size \[21, 45\] and the average values that we experimentally measured in biological specimens in a previous study \[39\]. The refractive indices of the particle \(n_s\) and matrix \(n_b\) were chosen to be 1.59 and 1.33, respectively. The refractive index ratio \(m = n_s/n_b\) is 1.195. The first layered structure, in which a cancerous layer with various thicknesses \(t\) is located on a healthy layer, corresponds to cancer that is progressing from the surface to the interior of the tissues. In contrast, the second layered structure, where a cancerous layer lies deep with a depth \(d\), corresponds to a buried cancer without exposure to the surface.

3 | RESULTS AND DISCUSSION

3.1 | Optical parameters

The optical parameters, scattering and absorption coefficients, were obtained using semiempirical formulae and experimental measurements obtained from the stomach wall and its carcinoma.
The approximate scattering coefficient \( \mu_s \) as a function of the wavelength is given by Equation (1) [46, 47].

\[
\mu_s(\lambda) = a \times \lambda^{-b} \text{ (mm}^{-1})
\]  

In this equation, \( a \) and \( b \) are constants specified by the tissue type. For a stomach wall, \( a = 792 \) (mm\(^{-1}\)) and \( b = 0.97 \) (no units) [48].

Light absorption in a tissue mostly occurs by oxyhemoglobin (HbO\(_2\)), deoxyhemoglobin (Hb) and water (W). The wavelength dependence of the absorption coefficients \( \mu_a \) is assumed to be approximated by a weighted sum of the spectral absorption coefficients \( \mu_{a,HbO_2}(\lambda) \), \( \mu_{a,Hb}(\lambda) \) and \( \mu_{a,W}(\lambda) \) [46], as given in Equation (2).

\[
\mu_a(\lambda) = S_B \{ x \times \mu_{a,Hb}(\lambda) + (1-x) \times \mu_{a,HbO_2}(\lambda) \} + S_W \mu_{a,W}(\lambda)
\]  

In this equation, \( x \) is the oxidation degree of hemoglobin, \( x = \frac{\text{HbO}_2}{(\text{HbO}_2 + \text{Hb})} \), and \( S_B \) and \( S_W \) are heuristic scaling factors adjusted to match the absorption data currently available for each tissue. In ref. [48], the values of these parameters for a normal stomach wall were \( x = 0.7 \), \( S_B = 0.01 \) and \( S_W = 0.8 \). The absorption spectra of these three constituents, \( \mu_{a,HbO_2}(\lambda) \), \( \mu_{a,Hb}(\lambda) \) and \( \mu_{a,W}(\lambda) \), were reported and summarized by Prahl et al. [49].

The obtained spectra of the optical parameters were adjusted by the experimental values for stomach wall tissue and stomach tumor tissue. The experimental data were obtained by an integrating sphere and semiconductor lasers of wavelengths 532, 820 and 914 nm. Figure 2 shows the spectra of the optical parameters of healthy stomach wall (red) and gastric cancer (blue), together with the experimental values (black squares with error bars). The experimentally obtained optical parameter values for the healthy tissues were approximately the same as the semiempirical values obtained from Equations (1) and (2) for each wavelength. Therefore, we adopted the semiempirical spectra of the optical parameters as those for healthy tissues in this study. The difference in scattering coefficients between the healthy stomach wall and tumor tissue was negligible. As for the absorption coefficient, each experimental value for tumor tissue at three wavelengths was smaller (−2.7 to −3.4%) than the values for normal tissues. The average rate of decrease was approximately 3.0%. Therefore, the spectra obtained by multiplying 0.97 to the spectra obtained by Equation (2) were employed as \( \mu_a(\lambda) \) spectra for the tumor. These values were then introduced into the algorithms of Monte Carlo simulations to investigate the possibility of cancer detection using the proposed method.

### 3.2 Wavelength optimization for cancer detection

The intensity and polarization of light scattered from pseudo-healthy and cancerous tissues were calculated using the meridian plane MC algorithm. The optical geometry for the calculations is shown in Figure 3A. The CPL beams whose polarization is \( S_3 = +1 \) are irradiated into pseudo-biological tissues with an incident angle.
The light beams that reflected directly from the surface and the light beams that underwent a few scattering events did not contain important information on the tissue. To exclude these light beams from consideration, the detection region is laid 1 mm from the point of incidence with a width of 1 mm, as shown using the thick red line on the pseudo tissue horizontally 1 to 2 mm in Figure 3A; only the light beams emitted from this region are detected by CPL detectors faced this region with a detection angle $\varphi$, and included in the calculations. Under this optical configuration, the intensity and DOCP of the light beams detected at the CPL detector were calculated for every detection angle $\varphi$. The $\varphi$ dependences of DOCP and intensity of light at three representative incident wavelengths, 600 nm (red), 750 nm (green) and 950 nm (blue), are shown in Figure 3B,C, respectively. The solid and dashed lines represent the values for healthy and cancerous tissues, respectively. At all wavelengths, the DOCP values of scattered light show a similar (almost parallel) gradual uptrend behavior with respect to $\varphi$. However, the magnitude of DOCP values shows significant differences between healthy and cancerous tissues, as well as among three wavelengths. At 600 nm, the difference in the DOCP of light scattered from healthy and cancerous tissues (hereafter, this is defined as $\Delta P = P(\text{healthy}) - P(\text{cancer})$) is negatively large, $\Delta P \approx -0.33$ in wide angular range. In contrast, $\Delta P$ at 950 nm is positively large; that is, the DOCP values obtained from healthy tissue are larger than those from cancerous tissues, which is $\Delta P \approx +0.30$. The intermediate wavelength, 750 nm, shows a small $\Delta P$, $\Delta P \approx +0.01$. The intensities of the scattered light show almost the same angular distribution, with a peak at around 30º. Only the data from healthy tissue at 600 nm showed a slightly small peak, which was derived from the largest absorption coefficient $\mu_a$. To compare $\Delta P$ values among different wavelengths, we employed the average values $\Delta P$ within the positive angular range of $\varphi$ (0-60º) while the sum of intensity $I$ in the same angular range was used for comparison.

Figure 4A,B shows the wavelength dependences of $\Delta P$ and $I$, respectively. The average difference in polarization $\Delta P$ shows a negative peak at around 600 nm and a positive peak in the near-infrared region from 900 to 1400 nm, together with large vibrations. The total intensity $I$ shows large values within the range of 500 nm to 1300 nm, which is because of the small $\mu_a$. To assess the ability to detect and estimate cancerous tissue depending on the wavelength, the figure of merit $F$ is defined as $F = \Delta P \times I$, and its spectral profile is shown in Figure 4C. In the spectral range less than 500 nm and longer than 1400 nm, significant performances in $\Delta P$ are lost owing to the weak intensities. Meanwhile, in the spectral region from green to near infrared, $F$ inherits $\Delta P$ behavior, with a negative large peak at around 600 nm, a monotonic increase with large vibrations and a large positive peak at around 950 nm. The spectral dependence of $F$ clearly indicates that 600 and 950 nm are the appropriate wavelengths for cancer detection, which has a significant difference in polarization with the opposite signs. The largest $F$ derived from the largest $\Delta P$ is also obtained at 1050 nm. However, there is a larger fluctuation at around 1050 nm than at 950 nm, due to which this excluded for the optimization.

In the experimental report by Kunnen et al. [21], a light source with 639 nm of wavelength was used as the incident CPL. In their experiments, DOCP values from the tumor tissue were found to be larger than that from healthy lung tissues (i.e., $\Delta P$ and $F$ were negative). By contrast, in our previous experimental report [39], cancer detection demonstrated via the CPL scattering technique using various optical geometries with a laser of wavelength 914 nm. In this experiment, DOCP values of scattered light from cancerous parts were found to be smaller than that from healthy parts (i.e., $\Delta P$ and $F$ were positive, regardless of the optical geometry). The sign reversal of $\Delta P$ and $F$ were experimentally confirmed at wavelengths of 639 nm and 914 nm.

Furthermore, the diameters of cell nuclei in the tested tissue specimens of metastasis were found to have a distribution of 3 to 7 μm with a peak at 5.9 μm in the healthy part, and that of 4 to 12 μm with a peak at 11.0 μm in the cancerous part. For healthy tissues, the calculated DOCP values of scattered light exhibited fluctuations of less than 0.1 in the distribution range of the nucleus size for both wavelengths. Conversely, for cancerous tissues with the larger nuclei, the calculated DOCP values for the cell nuclei within the diameter range of 8.8 to 11.6 μm were almost identical to that for 11.0 μm. However, the smaller cell nuclei in the cancerous tissue had negligible effect on the experimental results. It was therefore deduced that the contribution of larger cell nuclei is more significant than that of the smaller nuclei. Furthermore, fluctuations of the refractive index have previously been considered. The refractive index ratio $m = n_a/n_b$ enhances suppression of the helicity survival ability; specifically, the degree of depolarization for CPL increases with an increase in $m$ [50]. In addition, we calculated the contributions of $m$ for the cases. The calculations with fluctuations of $m$ between 1.01 and 1.25 indicate that the resultant DOCP values exhibit a decrease of less than 0.05 consistently for healthy and cancerous tissues. Therefore, the measured values of $\Delta P$ values are less significantly influenced. Moreover, because cells contain not only cell nuclei but also various organelles, their contribution should be
considered. In previous studies [50, 51], the effect of sub-micron scatterers on the polarization memory effect have been investigated for polydisperse media with various sizes of cell nuclei. Photons that undergo a small number of scattering events strongly influence the resultant signals, whereas a large number of scattering events reduces the effect of the smaller scatterers. The optical geometry in this study considered the latter case.

In conventional pulse oximeters, two wavelengths—665 and 880 nm—are used to evaluate the degree of oxygen saturation in the blood. Light at 665 nm has a larger absorbance for hemoglobin than oxyhemoglobin, whereas light at 880 nm has the opposite absorption characteristics [49]. The oxygen saturation is not evaluated by absolute values of absorption but by the ratios between two wavelengths in the pulse oximeters, which ensures the measurement accuracy. Similarly, the accuracy of cancer detection is expected to be enhanced by using the two wavelengths, 600 and 950 nm, which have opposite polarization tendencies for cancerous and healthy tissues.

Here, we examine the reason for the opposite sign in $\Delta P$ between the two wavelengths by considering a single scattering behavior, because the calculation results for multiple scattering as shown in Figures 3 and 4 result from repetitions and accumulations of a single scattering event. Figure 5 shows the calculated results of single scattering for wavelengths $\lambda = 600$ nm (upper row) and 950 nm (lower row). Figure 5A,D shows the scattering angle dependence of intensity $I$ as a function of scattering angles when a light beam $(S_3 = +1)$ comes with an angle of incidence 180° and impinged on a particle at the origin. The calculated intensity values are plotted on a logarithmic radial axis. B,E, $P$ as a function of scattering angles. C,F, Angle dependences of the product of $I \times P$ which are the relative expectation values of DOCP values for single scattering. The insets show the magnified graph in the small angular region (15°).

**FIGURE 5** Calculation results for single scattering against a particle with $\lambda = 600$ nm on the upper row and 900 nm on the lower row, respectively. The red and blue lines show the results for a cell nucleus $a$ in cancerous ($a = 11.0 \mu m$) and healthy tissues ($a = 5.9 \mu m$), respectively. The repetition (photon) number is 100,000. A,D, Intensity of scattered light $I$ as a function of scattering angles when a light beam $(S_3 = +1)$ comes with an angle of incidence 180° and impinged on a particle at the origin. The calculated intensity values are plotted on a logarithmic radial axis. B,E, $P$ as a function of scattering angles. C,F, Angle dependences of the product of $I \times P$ which are the relative expectation values of DOCP values for single scattering. The insets show the magnified graph in the small angular region (15°).
polarization $P$ ($S_1$ in terms of the Stokes parameters), shown in Figure 5B,E, denote complex behaviors with some oscillations, which greatly deviate from the cosine-like shape shown in the Rayleigh regime [21, 40]. To consider the contributions to the resultant polarization, the products of $I$ and $P$ for the wavelengths 600 and 950 nm are plotted in Figure 5C,F, respectively. At 0°, the contributions from the cancerous tissue are larger than those from the healthy tissue, and they are reversed at around 3° at both wavelengths (the insets in Figure 5 (c) and (f)). This indicates that the opposite signs in $\Delta P$ between the wavelengths cannot be explained by considering only the contribution within the dominant, forward angular range. The magnitude relations of $\Delta P$ between the wavelengths are not reversed until the contributions of backscattering are considered. In conclusion, the sign of $\Delta P$ shown in Figure 4 depends largely on the intensity and polarization of the backscattered light. The contributions of the backscattered light are extremely complicated and difficult to define universally. The contributions of backscattering have been considered in previous studies, for example, the so-called “memory effect of polarized light.” The contribution of backscattered light was found to drastically vary according to the scattering anisotropy and transport length, which are characterized by the size of scatterers and wavelength-dependent optical parameters of the media [52–54]. Moreover, the optical geometry including the distance between incident and detection points was also found to contribute to the helicity survival ability. To find the cause of the opposite sign in $\Delta P$, further theoretical and numerical efforts considering to these previous studies are required.

3.3 | Depth estimation of tumor invasion

The measurements of the depth profiles were verified using the two optimized wavelengths. An example of the distribution of simulated light beam paths is shown in the area of a biological tissue of Figure 3A, which is obtained under the conditions that the detection angle is $\varphi = 35 \pm 5^\circ$, the wavelength $\lambda = 950$ nm, the medium comprises spheres of diameter $a = 5.9$ μm, (a pseudo-healthy tissue) and a photon number of the incident CPL is 500 000. The simulated light beam paths under the other condition ($\lambda$ and $a$) are shown in Figures S1–S4. The distribution of light beams drastically varied with $\varphi$: changing from $-90^\circ$ to $+90^\circ$ while maintaining $\varphi = 1^\circ$. When $\varphi$ is close to zero (vertical incidence), the detected light beams contain many light beams that dive deeper. In contrast, light beams scattered in a shallow volume tend to exit from the surface with a large $\varphi$. The averaged maximum depth of the detected light beams is defined here as $L$, which can be paraphrased as a sampling depth. Figure 6 shows $L$ values as functions of $\varphi$. The value of $L$ at $\varphi$ implies that the photons emitted (detected) with an angle $\varphi$ provide information on the entire average volume between the surface to the depth $L$. The values of $L$ increase monotonically with $\varphi$ in the whole angular range irrespective of wavelengths and tissue states. The sampling depth $L$ depends only on the mean free path of photons in the tissue, which is determined by the optical parameters, $\mu'_s$ and $\mu_a$. Therefore, the relationship among the optical parameters, particularly $\mu_a$, as shown in Figure 1, is reflected in the behavior of $L$ behavior shown in Figure 6. Because these optical parameters are obtained using semiempirical and experimental methods, the effects of fluctuations in size and refractive index and the contributions of the smaller scatterers such as organelles, are included. This result indicates that the sampling depth can be modulated by tuning $\varphi$. Specifically, the depth profile can be obtained based on the detection angle dependence of the DOCP values.

By taking advantage of the tunable sampling depth, the cancer distributions along the depth direction were examined with MC simulations. The schematic representations of the optical configurations and the structure of pseudo-biotissues are shown in Figure 7A,D. As shown in Figure 7A, the pseudo-biotissues having a cancer layer with the thickness of $t$ on a healthy layer represent cancer tissues progressing deeper from the surface, which is used for measuring the tumor depth invasion in the early stages of cancer. Conversely, the buried cancer layer shown in Figure 7D corresponds to the pseudo-tissues that lies hidden beneath a healthy layer with a depth of $d$. This cancer layer is assumed to be an intraepidermal
carcinoma concealed with epithelial tissues or the tissue at the marginal region of cancer with invasive spreading into the submucosa layer. The calculated DOCP values for 600 and 950 nm as a function of structural parameters, $t$ and $d$, are shown in Figure 7B,E, respectively. (The $\varphi$ dependences of intensity and DOCP values are shown in Figures S5 and S6.) Additionally, the differences in the DOCP values between 600 nm and 950 nm ($\Delta$ DOCP) are shown in Figure 7C,F, respectively. The variation of DOCP with $t$ and $d$ show an opposite tendency between 600 and 950 nm wavelengths, which is attributed to the opposite sign in $\Delta P$ shown in Figure 4C. For superficial cancer, when $t$ increases from 0 to approximately 1.0 mm, the DOCP values increase and decrease monotonically for 600 and 950 nm, respectively, and the $\Delta$DOCP values exhibit an approximately linear variation. In this thickness region, most of the light beams reach the underlaid healthy layers. Therefore, the DOCP values change depending on the ratio of the cancerous layer volume to the entire sampling volume. When $t$ increases further, there are two types of DOCP behavior depending on the detection angle $\varphi$: the DOCP values for large $\varphi$ are saturated at 1.4 mm, while the values for small $\varphi$ continue to change up to 2.0 mm. The difference in the DOCP values between $\varphi$ becomes small at 600 nm and large in 950 nm. This difference in DOCP values between $\varphi$ is due to the fact that the scattering volume of light with large $\varphi$ is fulfilled with a cancer layer, whereas the scattering volume of light with small $\varphi$ still includes healthy tissues. A further increase in $t$ ($t \geq 2.0$ mm) induces saturation of DOCP values in the entire angular range, because the scattering volumes are fulfilled with a cancer layer. When considered together, the depth profile can be obtained by dividing two thickness regions: for a cancer layer thinner than 1.0 mm, the thickness can be estimated from the differences in the DOCP values shown in Figure 7C; for a cancer layer with thickness between 1.0 mm and approximately 2.0 mm, the comparison among DOCP values at different $\varphi$ shown in Figure 7 (b), can provide information on the thickness. Under existing conditions, the detection limit for the quantitative measurement of cancer thickness is approximately 2.0 mm, which is sufficient to diagnosis whether the cancers stay in the mucosa whose thickness is approximately 1.0 mm (Tis, T1a and T1b in Figure 1) or progress beyond the mucosa to the

FIGURE 7 Schematic of optical geometry and layered structure of the pseudo-tissues in which, A, a cancerous layer lying on the surface progresses deeper and D, a cancerous layer is under the healthy tissue. The calculated resultant DOCP values of light scattered from pseudo-tissues as a function of, B, thickness of cancer $t$ and D, depth of cancer $d$ with different detection angles $\varphi$ for $\lambda = 950$ nm (opened squares) and $\lambda = 600$ nm (closed squares). C,F, Differences in the DOCP values between 600 nm and 950 nm plotted in B,E, respectively.
underneath layers (Ts or worse in Figure 1). Due to the opposite tendencies between the two wavelengths, the difference in DOCP values between $\phi = 0^\circ$ (purple) and $60^\circ$ (red) in the thickness range $t > 1.0$ nm decreases for $\lambda = 600$ nm and increases for $\lambda = 950$ nm. Such variations can be used for a more accurate estimation of cancer thickness. Moreover, the contributions of fluctuations in size and refractive index of cell nuclei, and the existence of the smaller scatterers, such as organelles, would add a constant value to the signal, which does not introduce noise in differences in DOCP values between $\phi$ and wavelengths.

On the other hand, the calculation results for a buried cancerous layer beneath a healthy layer shows the opposite behavior to the results for the superficial cancer at 600 and 950 nm (Figure 7E). However, similar to the superficial cancer, the differences in the DOCP values between wavelengths (Figure 7F) provide the cancer depth for a cancerous layer lying in a shallow place, while the depth of cancer laminating in the deeper can be evaluated from the difference in DOCP values between different $\phi$. For 600 nm, the differences in the DOCP values between different $\phi$ are small within the depth range, $0 < d < 1.0$ mm. This characteristic of 600 nm light can be used for a more accurate depth estimation of cancer tissues buried shallower than 1.0 mm. In contrast, the depth measurement with CPL at 900 nm is possible in the wider $d$ range, $0 < d < 1.6$, because the DOCP values continuously change to the deeper region. The depth detection limit is approximately 1.6 mm for this method. Two wavelengths exhibiting the opposite responses from healthy and cancerous tissues enable us to distinguish between the cancer on the surface and buried in the depth, as well as to extract the valid signals from noise to increase the reliability.

4 | CONCLUSION

We conducted a computational analysis of the quantitative depth estimation of tumor invasion in early gastric cancer using the CPL scattering technique. First, the optical parameters, the scattering and absorption coefficients, of the human stomach wall and its carcinoma were obtained by semiempirical and experimental methods. By introducing the obtained parameters into MC algorithms, the differences in circular polarization, $\Delta P$ and intensity, $I$, of the resultant scattered light were calculated for a wide range of wavelength: from visible to near-infrared light. The wavelength dependence of the figure of merit, $F = \Delta P \times I$, indicates that 600 and 950 nm have considerable differences in circular polarization with the opposite signs and large intensity, indicating their appropriateness for cancer detection. The opposite signs of $F$ at 600 and 950 nm emerge from the contribution of the back-scattered light. At the two optimized wavelengths, the sampling depth in the biological tissues can substantially depends on the detection angles, indicating that the depth profile can be detected by tuning the detection angle. The calculated results for the pseudo-biological tissues of the bilayered structure containing a cancerous and healthy layer indicate the successive changes in the DOCP values depending on the thickness or the depth of cancerous layer. The structure consisting of a cancerous layer on a healthy layer corresponds to an early-stage cancer, in which cancer progresses deeper from the surface. The cancer thickness in this structure can be evaluated by comparing the DOCP values in a completely healthy tissue and a progressing cancer tissue for thin cancer. For the further progressed cancer (thicker cancer), the difference in DOCP values between the different $\phi$ allowed us to determine the thickness. In the cancerous layer crept under the healthy layer, the cancer depth can be estimated from the same comparisons. The two wavelengths exhibiting the opposite tendency against the thickness and depth of the cancerous layer can not only increase the accuracy of estimation but also facilitate noise elimination from the detected polarization signal, that is, offsets with the same tendency between two wavelengths in the detected signals can be inferred to be signals from unintended factors and can be eliminated as noise. The identification limit of the thickness and the depth of the estimated cancer are approximately 2.0 mm and 1.6 mm, respectively. The thickness resolution notably depends on the detection resolution of the DOCP values in the CPL detectors. At least 0.1 or less resolution of DOCP values is sufficient to discriminate cancer remaining in the mucosa (Tis or T1) from the cancer progressed deeper than the submucosa (T2 or the further), which will provide quantitative information effective for diagnosis concerning the therapeutic approach, endoscopic treatment or surgical procedure with dissections. The simultaneous detection of DOCP values with different detection angles is possible with an endoscopic probe consisting of a CPL emitter, some CPL detectors, and a parabolic mirror attached to the tip of an endoscope, which we proposed in Ref. [40]. However, the tip of the endoscope is crowded because of the recent multi-functionalization of endoscopes. Alternatively, we propose to attach the endoscopic probe to the sidewall of an endoscope, which we obtained from the intravascular optical coherence tomography [55, 56]. The smaller spatial restrictions will enable the longer semi-latus rectum of a parabolic mirror to detect light with a detection angle within a large angular range. To estimate the depth of invasion tumors in
gastric cancer using the CPL scattering technique, experimental demonstrations using cancerous biological specimens at various stages of early gastric cancer are required. Moreover, further developments are needed in the CPL emitter and detector based on spin-LEDs used for this technique.

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CONFLICTS OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Please see Supporting Information online.

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