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Exploiting LIBS as a spectrochemical analytical technique in diagnosis of some types of human malignancies

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ABSTRACT

In the present work we are presenting a detailed in vitro study of using laser-induced breakdown spectroscopy (LIBS) as a quick and simple method for spectrochemical analysis to identify and characterize some types of human malignancies. This has been performed via detection of the abundance of certain elements namely calcium and magnesium in malignant tissues with respect to the non-neoplastic ones. In order to improve the performance of the LIBS technique – in particular its sensitivity, reproducibility and limit of detection – the measurements have been performed under vacuum (10^{-2} Torr) and the samples were frozen down to −196 °C in a specially designed vacuum chamber. Under such experimental arrangements a pronounced enhancement has been achieved in the signal to noise (S/N) ratio of different spectral lines. Significant discriminating results have been obtained in case of breast and colorectal cancers indicating the possibility of adopting LIBS in the early detection of the malignancy as well as the identification of the severity and the grade of the disease. The present work demonstrated that future in vivo measurements are also feasible and reliable using especial endoscopic systems for delivery of laser beam and collection of the emitted plasma light.

1. Introduction

In most people's minds there is no scarier diagnosis than that of cancer. Cancer is often thought of as an untreatable, unbearably painful disease with no cure. However such popular view of cancer may be exaggerated and over-generalized. Cancer is undoubtedly a serious and potentially life-threatening illness. Specifically in Egypt, this issue is of major importance and in particular breast cancer which is the most common cause of cancer in women and accounts for 33% of all female cancers at the National Cancer Institute (NCI), Cairo University [1]. On the other hand, colorectal cancer is one of the most prevalent cancers in Egypt, as bladder and liver cancers. It was observed that age-specific rates for early-onset colorectal cancer under age 40 and premenopausal breast cancer were higher in Egypt than in the United States [2].

However, it is a misconception to think that all forms of cancer are untreatable and deadly. The truth of the matter is that there are multiple types of cancer, many of which can today be effectively treated so as to eliminate, reduce or slow the impact of the disease on patients' lives. While a diagnosis of cancer may still leave patients feeling helpless and out of control, in many cases today there is cause for hope rather than hopelessness. Cancer diagnosis and classification is extremely complicated and, for the most part, relies on subjective interpretation of biopsy material. Conventional methods are laborious and in some cases may result in different contradicting results depending on the histopathologist performing the examination. Automated, real-time diagnostic procedures would greatly facilitate cancer diagnosis and classification. Significant research efforts have been devoted, adopting different techniques, to identify malignant from non-malignant tissue cells. Although much cancer researches now focus on the fundamental molecular pathology of cancers, a critical applied clinical issue remains the early, rapid, and accurate diagnosis so that complete surgical removal of that cancer can be effective. Some diagnostic techniques distinguish different proteins, whereas others rely on identifying abnormal cellular morphology. Most recently, transcriptomics and proteomics are being developed to identify gene expression profiles diagnostic of malignancy. Complementary DNA microarrays and serial analysis of gene expression are used for transcriptomics whereas two-dimensional gel electrophoresis; matrix-assisted laser desorption ionization mass spectroscopy and surface-enhanced laser desorption ionization mass spectroscopy are used for proteomics [3]. All these techniques have the common disadvantages of being time consuming, expensive, and require relatively complicated procedures for sample preparation. Other

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Table 1
Types of breast and colorectal cancer in the obtained samples.

Type	No. of cases	Pathological Diagnosis
Breast	7	Grade 2 duct carcinoma with negative metastasis to lymph nodes. (G2 D −ve)
can-	7	Grade 2 lobular carcinoma with positive metastasis to lymph nodes. (G2 L +ve)
cer	8	Grade 2 duct carcinoma with positive metastasis to lymph nodes. (G2 D +ve)
	8	Grade 3 mixed duct and lobular carcinoma with positive metastasis to lymph nodes. (G3M +ve)
	11	Grade 2 lobular carcinoma with negative metastasis to lymph nodes. (G2 L −ve)
Colorectal	15	Grade 2 Adenocarcinoma with positive metastasis to lymph nodes. (G2 adenoma carcinoma)
can-	11	Grade 2 Mucinous carcinoma with positive metastasis to lymph nodes. (G2 mucinous carcinoma)
cer	6	Grade 3 Mucoid carcinoma with positive metastasis to lymph nodes. (G3 mucoid carcinoma)

techniques, such as X-ray fluorescence and proton-induced X-ray fluorescence, monitor the concentrations of nutrient metal ions, which are different in malignant and non-malignant cells [4]. However, X-ray fluorescence is a technique used for elemental analysis for the elements with atomic numbers above 8. It cannot readily detect the common elemental constituents of organic materials such as carbon, hydrogen, oxygen, and nitrogen. Laser-induced breakdown spectroscopy (LIBS) technique is a developing and promising technology that has the advantages of simplicity and robustness and the possibility of detecting both low and high atomic number elements [5]. In LIBS, laser pulses from a Q-switched laser source are focused via a suitable focusing lens onto the surface of the sample. Adopting laser pulses of few tens milli-Joules and pulse duration of few nanosecond leads to an irradiance in the order of some mega Watts. Putting such huge amount of laser power in a tiny volume, results in the evaporation, dissociation, atomization and ionization of some nanograms to micrograms of the sample surface material. At the end of the laser pulse we are left with the so-called plasma plume which consists of a collection of positive ions and swirling electrons at very high temperature in the range 6000–10,000 K. As the plasma cools down recombination and de-excitation of ions and atoms take place in the form of emission of light which is collected and fed to a suitable spectrometer to obtain the LIBS spectrum [6]. Qualitatively the spectral lines are the finger print of the atomic species in the plasma and consequently in the target material. Quantitatively there is a direct proportionality between the intensity of the spectral lines and the concentration of the relevant elements in the target material. However, in the analysis of LIBS spectra we have to take care of self-absorption of the spectral lines by colder atoms. This may results in misleading spectral lines' intensities that affect the whole calculations of the relevant element concentration. Self-absorption dominates in case of high concentration elements and for resonant lines, i.e. transition lines with the ground state as their lower energy level.

Studies about the possible correlation between some elements and disease are often among the medicine experts' and biologists' interesting. Samek and coworkers [7] performed quantitative LIBS analysis for trace element concentration in calcified tissue. They demonstrated that LIBS analysis could be implemented and used in dental drilling using lasers. Moreover, Fang et al. [8] concluded that LIBS technique has the potential for routine clinic applications in urological disorder diagnosis. Biological tissue classification via LIBS has been also dealt with recently [9]. The analysis of microscopic particles and cells has received increased interest in recent years, especially bio-aerosols (bacteria, fungi, viruses, and pollen) [10,11] have attracted wide attention because they are found nearly everywhere and are related to the threats of biological warfare and epidemic spreads. LIBS was found to be the most convenient technique for in situ and real-time measurement of metal species in the gaseous and aerosol phases, thus it is suitable for analysis and characterization of biological aerosols. Stéphane et al. [12] used time-resolved laser-induced breakdown spectroscopy (TRE-LIBS) for detecting and sorting different species.

LIBS can be used to monitor the relative concentration of calcium and magnesium elements in malignant tissues. Although the tissue samples include many other elements rather than these two elements, but calcium and magnesium have been chosen because of their physiological importance and vitality especially in case of malignancy. The ratio of calcium to magnesium is critical for cell membranes and the blood brain barrier. Mild degrees of magnesium depletion significantly decrease the serum calcium concentration. Anyway, when it comes to magnesium and calcium neither can be separated from the other.

The aim of the present work is to study in vitro possibilities and the effectiveness of introducing an efficient optical spectroscopic technique such as LIBS for the identification of two types of human cancer, namely breast and colorectal cancer as well as determining the disease grade and severity. In order to improve the signal to noise ratio in the LIBS spectra, frozen tissue samples have been measured in vacuum in a specially designed chamber.

2. Materials and methods

2.1. Tissue samples

Throughout the present work, samples from 41 patients with breast cancer and 32 patients with colorectal cancer who were registered in the NCI, Cairo University have been examined in vitro. These cases have been diagnosed, grouped and classified by a pathological expert as in Table 1. Samples of non-neoplastic and adjacent non-neoplastic appearing tissue measuring approximately 1 cm^3 were collected from the mastectomy or colostomy specimens. These epithelial cells from non-neoplastic breast and colorectal glandular tissues were used for comparison with tumorous breast and colorectal tissues from each patient respectively. The excision of non-neoplastic tissues was made at $\geq$1 cm away from the grossly visible tumor margin to minimize the potential of measuring adjacent carcinoma in situ. The samples have been saved in a cryostat at −80 °C till investigations.

2.2. Methodology

The experimental set up of the equipments used throughout the present work for LIBS measurements is shown in Fig. 1. A Q-switched Nd: YAG laser (BRIO, Quantel, France) has been used. The optimized laser pulse energy adopted throughout the present measurements was 100 mJ $pulse^{-1}$ of 5 ns pulse duration at the laser second harmonic wavelength (λ = 532 nm). The laser-induced plasma was produced by focusing the laser beam by 100 mm focal length plano convex lens and the emission from the plasma plume was collected by a fiber optic and fed to an echelle spectrometer (Mechelle 7500, multichannel, Sweden) coupled to a computer controlled ICCD camera, (DiCAM-PRO, PCO-computer optics Germany) with its relevant software. Each LIBS spectrum is the average of 50 spectra taken as 10 spectra at 5 different positions on each tissue sample. The obtained spectra have been displayed on a PC for further processing and spectroscopic analysis adopting $LIBS^{++}$

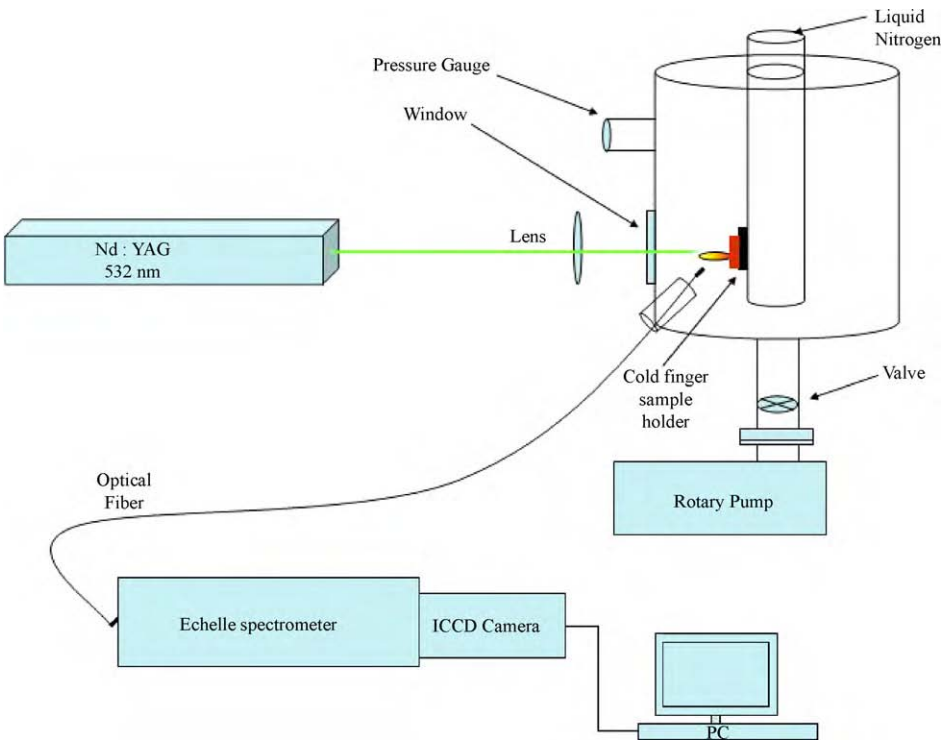

Fig. 1. LIBS experimental setup.

software and relevant data base. To avoid any experimental fluctuations, all the measured spectra have been normalized against the intensity of carbon I spectral line at 247.8 nm. The choice of this carbon line is mainly because it is a well resolved spectral line of an element which is not relevant to the malignancy status of the tissues.

LIBS spectra obtained from biological soft tissues as shown in Fig. 2 can in principal discriminate between malignant and non-neoplastic breast and colorectal tissues samples, for future in vivo measurements, despite of being with lower quality concerning signal to noise ratio compared with solidified freeze tissues as demonstrated in Table 2. Thus, it has been suggested that solidification of tissue samples may improve the S/N ratio in the obtained emission spectra and facilitate the differentiation procedure. This has been verified adopting the specially designed vacuum chamber shown in Fig. 1, in which liquid nitrogen has been used to cool down the target holder to −196 °C. The sample holder cold finger was made of copper that has very good thermal conductivity. After fixing the sample, the chamber is evacuated by means of a rotary pump to 10^{-2} Torr, while pressure is regulated with a throttle valve and measured with a capacitive MKS baratron.

2.3. Optimization of the experimental conditions

It is well known that at the early stages of the plasma evolution, the continuum emission is overwhelming, masking many spectral lines and deteriorating the signal to noise ratio for the others. Time resolved measurements are important to get rid of the high background continuum by delaying the trigger of the detector with respect to the firing of the laser [13]. As the delay time increases, the continuum drops strongly with a pronounced improvement of the S/N ratio. A systematic optimization of the delay time and the gate width has been performed to obtain the best experimental conditions leading to high quality LIBS spectra with very good S/N ratio. The LIBS experiment was performed on both types of investigated tissue samples including non-neoplastic and tumorous samples with different delay times starting from 200 ns to 1200 ns corresponding to a constant gate time which is 2500 ns, after that the gate time has been changed starting from 1300 ns to 3200 ns corresponding to a constant delay time which is 800 ns. An optimum delay time of 800 ns and gate width of 2500 ns were adopted in the present study to provide continuum-free spectra with reasonably improved values for the S/N ratio.

The optimized experimental parameters, namely laser energy, delay time, gate width, number of accumulated single shot spectra, and geometrical arrangements are fixed for all experimental data acquisition procedures.

3. Results and discussion

To follow up the relative concentration of calcium and magnesium in the samples under investigation, the intensity of two spectral lines for each element has been systematically studied. For calcium the emission lines at 373.6 nm and 422.6 nm have been chosen, while the lines at 280.2 nm and 285.2 nm were chosen for magnesium. Despite the presence of other spectral lines for calcium and magnesium with higher intensities, in the obtained LIBS spectra, but the chosen lines have been selected because they are well resolved, free of interference with other spectral lines and suffer very little from self-absorption [14].

Calcium and magnesium spectral lines have been identified in all obtained LIBS spectra of the investigated tissue samples. A remarkable spectral lines intensity difference for both Ca and Mg is pronounced between non-neoplastic and tumorous tissue samples. It was found that there is a significant increase in the intensity of the chosen calcium and magnesium lines in all malignant tissue samples of all types of both breast and colorectal cancer compared to the intensity of the same lines in non-neoplastic tissue samples as shown in Figs. 3 and 4. The intensity of both calcium and magnesium lines are clearly higher in case of tumorous tissues than in non-neoplastic one in both types of malignancy. Figs 5 and 6 depict the intensity of the spectral lines of Ca II and Mg I at 373.6 nm and

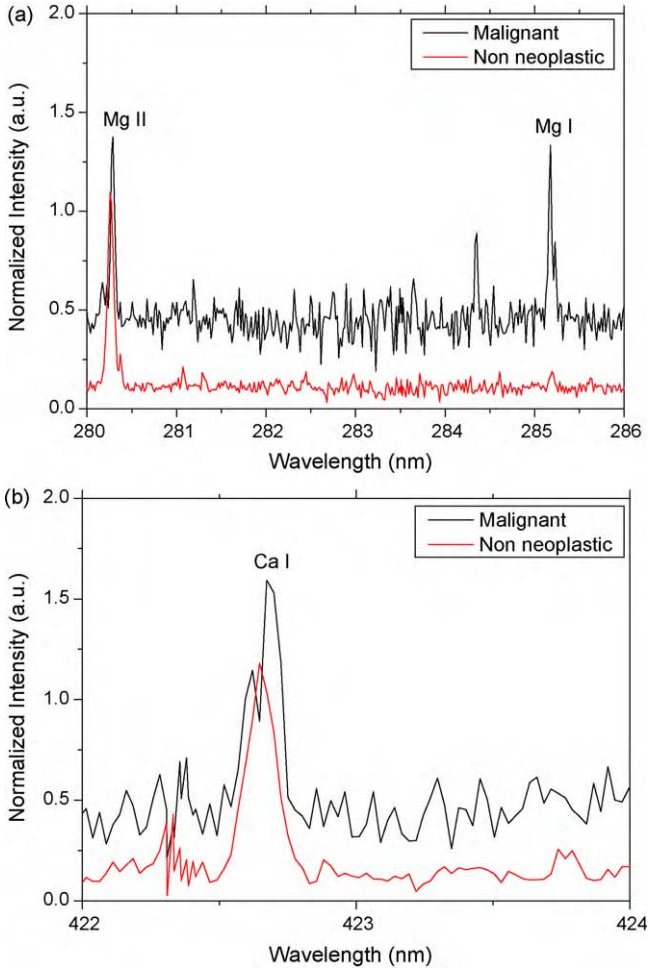

Fig. 2. The normalized intensity of (a) Mg II (280.2 nm) and Mg I (285.2 nm) spectral lines for breast samples and (b) Ca I (422.6 nm) spectral line for colorectal samples. Both spectra are obtained on soft tissues at room temperature.

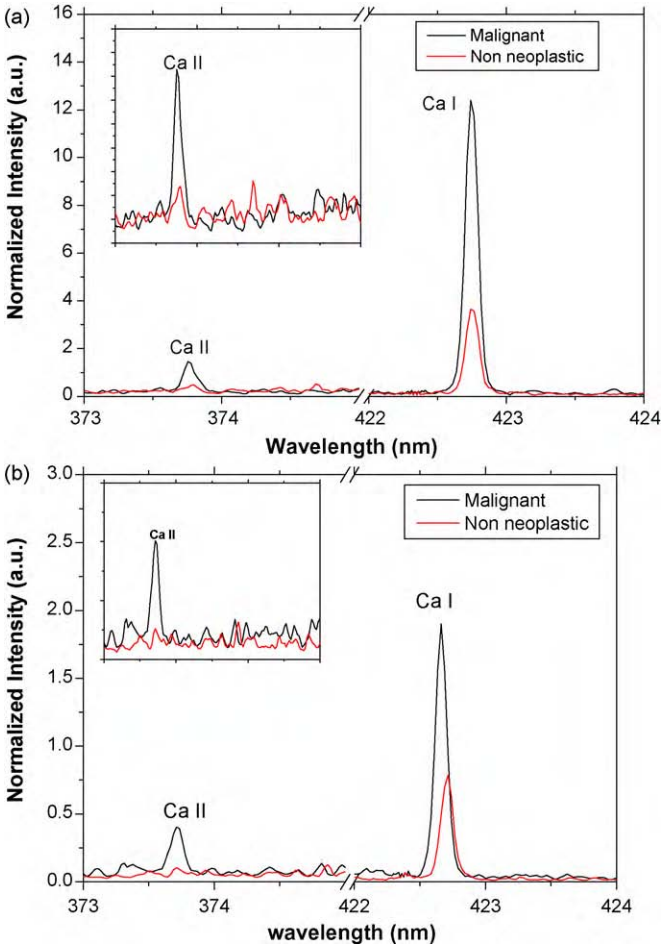

Fig. 3. The normalized intensity of Ca II (373.6 nm) and Ca I (422.6 nm) spectral lines for (a) breast and (b) colorectal frozen samples.

285.2 nm respectively for different types and grades of both breast and colorectal tissue and the same can be said for Ca I and Mg II at 422.6 nm and 280.2 nm respectively for both breast and colorectal cases. The above mentioned histograms remarkably reveal the significant increase and clear distinction of the intensities for the chosen lines in malignant samples compared with non-neoplastic samples of the same individuals.

Statistical analysis of the obtained results was performed using the statistical package (SPSS v13). ANOVA test was carried out to compare the intensity of the four chosen spectral lines for calcium and magnesium elements of tumorous and non-neoplastic in both types of tissue samples. The descriptive statistics table for the corresponding cases is shown in Table 3. The suggested comparison for breast samples emphasized high significant values ($P = 0.00001$ and 0.0003) by choosing Ca II and Ca I spectral lines respectively. The significant values of the suggested comparison for the same samples remain high ($P = 0.001$ and 0.002) using Mg II and Mg I spectral lines respectively. On the other hand, high significant values ($P = 0.001$) were obtained in the colorectal cases for both Ca spectral lines and similarly high significant values ($P = 0.001$ and 0.009) were got when selecting Mg II and Mg I spectral lines, i.e. the chosen spectral lines of calcium and magnesium elements have a remarkable role in the discrimination between malignant and neoplastic in both types of tissue samples. Moreover, when the intensities of the chosen spectral lines for calcium and magnesium elements in malignant breast tissue samples have been compared to those of colorectal tissue samples, it was clearly demonstrated that there is a high significant value ($P = 0.0008$) as the intensities of the chosen spectral lines for calcium and magnesium in breast tumours are higher than those in colorectal ones. This observation can be attributed to the influence of many factors in the distribution of calcium and magnesium ions in the breast and in the colorectal tract which include difference in the blood supply, the proliferation, size and the hormonal disturbance. All these factors in addition to the different vasculature architecture, capillary permeability and tumor interstitial diffusivity are more predominant in the breast tissues than in the colorectal tact.

Table 2
The improvement of S/N for the four chosen spectral lines of Ca and Mg by using liquid nitrogen to solidify the tissue samples in LIBS technique.

	Ca II	Ca I	Mg II	Mg I
S/N for breast samples using liquid nitrogen	6.12	37.8	17.01	8.98
S/N for colorectal samples using liquid nitrogen	5	36	11.48	6.75
S/N for breast samples without using liquid nitrogen	2.36	3.35	2.68	2.41
S/N for colorectal samples without using liquid nitrogen	2.1	9.81	9.1	4.31

Table 3
The descriptive statistics of the intensity of Ca and Mg spectral lines for breast and colorectal cases.

	Spectral line	Mean value of malignant samples	Mean value of non-neoplastic samples	*P* value
Breast cases	Ca 373.6	1.85 ± 0.09	0.679 ± 0.09	0.00001
	Ca 422.6	7.08 ± 0.14	2.66 ± 0.12	0.0003
	Mg 280.2	1.554 ± 0.3	0.77 ± 0.2	0.0001
	Mg 285.2	0.917 ± 0.2	0.465 ± 0.1	0.002
Colorectal cases	Ca 373.6	0.898 ± 0.09	0.405 ± 0.09	0.001
	Ca 422.6	2.51 ± 0.14	1.45 ± 0.12	0.001
	Mg 280.2	0.78 ± 0.3	0.421 ± 0.2	0.001
	Mg 285.2	0.507 ± 0.2	0.286 ± 0.1	0.009

LIBS spectra show an obvious increase of the intensity of the chosen spectral lines for calcium element in the tumorous samples compared to the non-neoplastic ones for both breast and colorectal tissues. There is a reasonable evidence to suggest that calcium may play an important role in the development of cancer disease [15]. According to a 1998 Harvard School of Public Health study of 47,781 men, it was found that those consuming between 1500 mg and 1999 mg of calcium per day had about double the risk of being diagnosed with metastasis (cancer that has spread to other parts of the body) prostate cancer as those getting 500 mg per day or less [15]. And those taking in 2000 mg or more had over four times the risk of developing metastasis prostate cancer as those taking in less than 500 mg among 526 men diagnosed with prostate cancer and 536 similar men not diagnosed with the disease. That study found a 50% increase in prostate cancer risk and a near doubling of risk of metastasis prostate cancer among men consuming high amounts of dairy products, likely due to the high total amount of calcium in such a diet. In a Harvard study on the same topic, published in October 2001, they looked at dairy product intake among 20,885 men and found men consuming the most dairy products had about 32% higher risk of developing prostate cancer than those consuming the least. This remarkable increase in the intensities of the chosen spectral lines for calcium can be attributed to the fact that people with cancer often have hypercalcemia. Actually, it is the most common life-threatening metabolic disorder associated with cancer. Hypercalcemia is commonly attributed to either the cancer treatment or

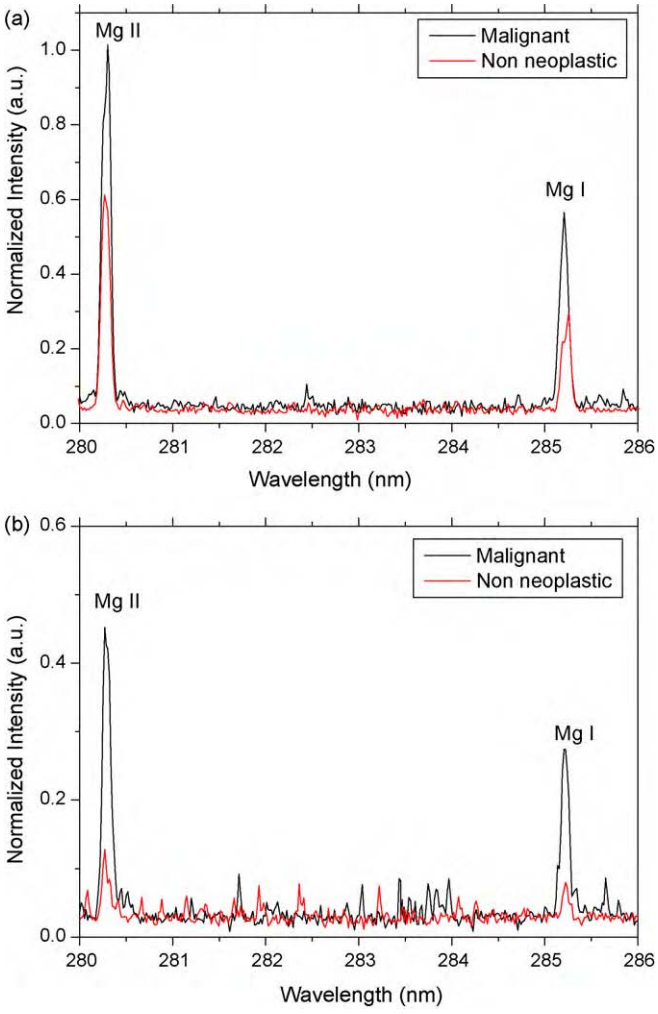

Fig. 4. The normalized intensity of Mg II (280.2 nm) and Mg I (285.2 nm) spectral lines for (a) breast and (b) colorectal frozen samples.

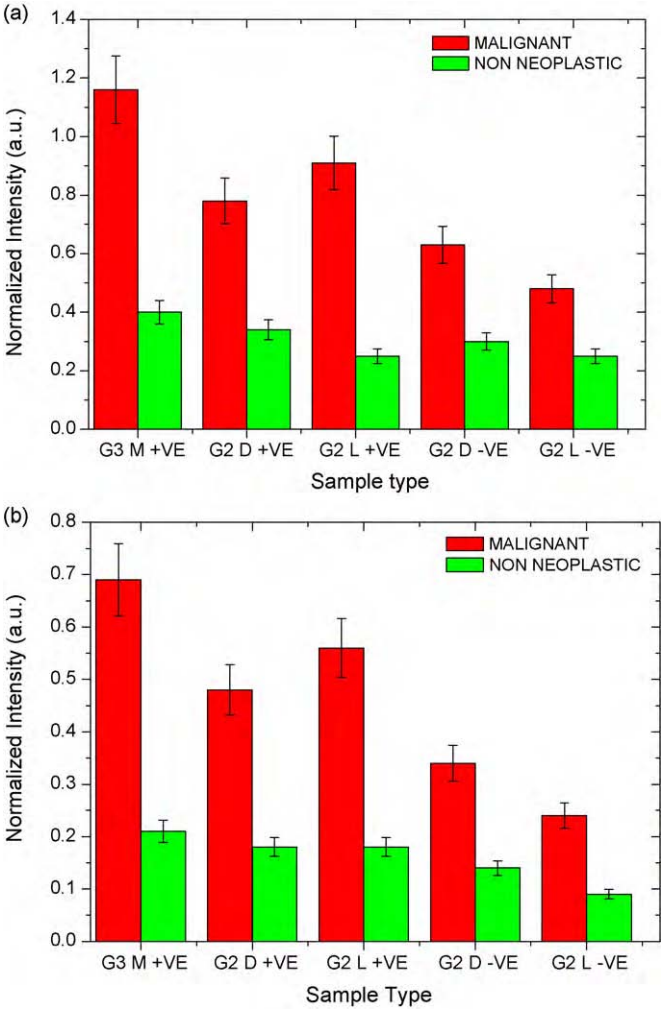

Fig. 5. Comparison between intensity of (a) Ca II (373.6 nm), (b) Mg I (285.2 nm) for different types of breast cancer.

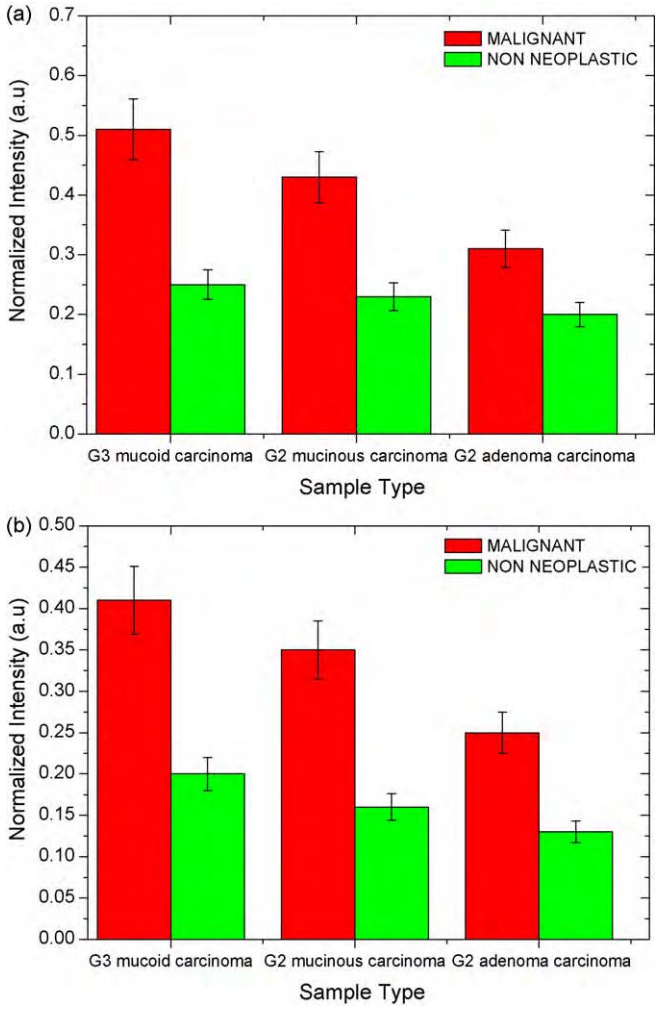

Fig. 6. Comparison between intensity of (a) Ca II (373.6 nm), (b) Mg I (285.2 nm) for different types of colorectal samples.

the cancer itself. Cancers of the breast, lung, colon and kidney are frequently associated with hypercalcemia. It also occurs frequently in association with certain cancers of the blood, particularly malignant myeloma. It is seen most often in patients with tumors of the lung (25–35%) and breast (20–40%), according to the American National Cancer Institute. Cancer causes hypercalcemia in two ways, when a tumor grows into the bone; it destroys bony tissue (osteolysis) and when the bone is not involved, factors secreted by cancer cells can increase calcium levels (humoral hypercalcemia of malignancy) [16]. The two mechanisms may operate at the same time. Because immobility causes an increase in the loss of calcium from bone, cancer patients who are weak and spend most of their time in bed are more prone to hypercalcemia. Cancer patients are often dehydrated because they take in inadequate amounts of food and fluids and often suffer from nausea and vomiting. Dehydration reduces the ability of the kidneys to remove excess calcium from the body. Hormones and diuretics that increase the amount of fluid released by the body can also trigger hypercalcemia. This hypercalcemia has a critical action by down-regulating 1,25 D^2, the active form of vitamin D. The 1,25 D form has been hypothesized to play an important role in carcinogenesis through inhibition of tumor growth and proliferation in metastases [17].

Similarly, the measured LIBS spectra of the tissue samples show a noticeable increase of the intensities of the chosen spectral lines for magnesium element in the tumorous samples compared to the non-neoplastic ones for both breast and colorectal tissues. This increase can be justified in view of the important role that magnesium plays in the biosynthesis of proteins which play a key role in cells multiplying intensity. Over 300 different enzymes systems rely upon magnesium to facilitate their catalytic action, including ATP metabolism, creatine-kinase activation, adenylate-cyclase, and sodium–potassium-ATPase. It is known that carcinogenesis induces magnesium distribution disturbances, which causes magnesium mobilization through blood cells and magnesium depletion in non-neoplastic tissues. Perhaps this is the reason of the increased need of this element in the neoplasmic tissues [18,19]. Kohli et al. as well as Tansy and Kendall found that magnesium level in the organism comes back to norm in patients undergoing chemotherapy or radiotherapy [20,21]. This confirms the role of magnesium in tissue metabolism. Changes in magnesium concentration can be used as an additional, essential coefficient enabling the estimation of tumor development.

In good agreement with our results, Kumar et al. [22] observed in their research on dogs that the intensity of the Ca lines and the Al lines 394.4 nm and 396.15 nm were found weaker than the malignant tissue cells. They showed that the intensity ratios of Ca/K and Na/K are higher in the malignant tissue spectra. The Mg/K and Al/K are comparable in the normal and malignant tissue spectra. They indicated that the concentration of trace elements like Ca, Al, and Mg are higher in malignant cells in comparison with that in normal cells.

Nasiadek et al. [23] investigated the cadmium, copper, zinc, iron, magnesium and calcium concentrations in uterine cancer and uterine myoma. Tissue levels of the six elements in 15 uterine cancers and 28 uterine myomas have been monitored using the atomic absorption spectrometry (AAS) technique. In agreement with our results, they found in uterine cancer tissues, a significant increase in Ca^{2+} concentration and an insignificant increase in Mg level were observed when compared to non-neoplastic uterine tissues. The same authors have also found a significant increase of Mg and Mg/Ca ratio in uterine myoma. The increase of the calcium content could be due to the enormous uncontrolled divisions of the cancerous cells.

In relevance with the present study, Durach et al. [24] reported that at a later cancerous stage, disturbances in Mg distribution in tumor tissues are even more complex. They proved that the disturbance in Mg distribution is associated with increased Mg level in the tumor tissues. Günther et al. [25] mentioned that the uptake of cellular Mg is possible when the normal cells are moderately depleted and are growing, but tumor cells, e.g. Ehrlich or Yoshida ascites tumor cells or tumorogenic pancreatic B cells or thymocytes rapidly reaccumulate Mg ions.

According to the pathological diagnosis for the breast cancer, it is well known that the prognosis of duct carcinoma and lobular carcinoma are almost the same, but when any type of them is accompanied by the spread to the lymph nodes, the prognosis becomes much less depending on the number of the affected lymph nodes and the metastasis of the disease. Moreover, the severity of the disease increases as long as the grade increases in the same type.

Fig. 5 shows the increase of the intensities of the normalised chosen spectral lines for calcium and magnesium elements with the increase of the metastasis and the grade of the neoplasia in breast cancer. Here it should be noticed that there is no clear pathological difference between lobular and duct carcinoma as both of them are considered to have the same severity.

Pathologically, the same can be said for colorectal cancer where the severity of the disease increases with increasing the grades in the same type. But the prognosis in this case of adenocarcinoma is much better than that of the mucoid carcinoma. Also here the prognosis is again affected by the presence or absence of lymph nodes metastasis as it increases in the absence of lymph nodes metastasis

and decreases by the presence of lymph nodes metastasis. It is clear from Fig. 6 that the maximum intensity of the normalised chosen spectral lines for calcium and magnesium elements is in grade 3 mucoid carcinoma with positive metastasis to lymph nodes cases and the least intensity of the same lines is in grade 2 adenocarcinoma with positive metastasis to lymph nodes.

4. Conclusions

Results reported in the present paper show that laser-induced breakdown spectroscopy (LIBS) provides new and fascinating possibilities for both detection and follow up of cancer diseases. The future substitution of much traumatic major surgery by simple fiber-optic procedures is a major challenge for doctors in collaboration with physicists. In the present study we have found distinct differences of calcium and magnesium spectral lines' intensity in LIBS spectra of non-neoplastic and malignant breast and colorectal tissue samples. The line intensity ratios of different elements can be used to determine the concentration ratio of the minor and trace elements in the tested tissue samples. The results of the present study show clearly that LIBS has great future potential as an in vivo diagnostic tool for cancer early detection and follow up of the therapy. Extensive efforts in this area are needed to obtain quantitative results for practical applications. Although optical spectroscopy has been shown successful in diagnosing cancer in a number of independent studies, but a further work and a stepwise approach are warranted to bring this system into clinical use. Finally this research could be seen as a promising avenue and could allow for an increased understanding of the underlying mechanism for the optical spectroscopic diagnosis of cancer. The increase in diagnostic specificity has the potential to reduce the number of unnecessary biopsies and to reduce delays in therapy. Other approaches like multi-spectral imaging approaches may increase diagnostic sensitivity for identifying pre-cancers not seen with traditional white light endoscopy. In the future, improving our understanding of the biological changes that can be assessed using spectroscopy will not only give a new impetus to improve optical techniques but also provide new tools to a better understanding of cancer biology.

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