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Application of Fourier Transform-Infrared Spectroscopy as a Tool for Early Cancer Detection

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Abstract

The absence of sufficiently reliable, cost-effective and non-invasive approaches for detection of cancers at initial stage fuel a search for new and effective diagnostic methods to screen and prevent cancer. Fourier transform infrared (FTIR) spectroscopy is a vibrational method which detects changes in vibration of molecular bonds using infrared radiation in tissues and cells. FTIR detects biochemical changes within the sample and can be used to find biomarkers for early detection of various cancers in the region of mid infrared range of 4000 to 400 cm^{-1}. It provides precise database on molecular finger printing of the characteristic FTIR peak frequencies for researchers aiming to study biological samples such as cells, tissue sections, bio fluids and fixed cytology. Promising role of FTIR as a specific and sensitive analytical tool to differentiate between unaffected and malignant cells in breast, colon, skin, ovaries, lung, cervix, and oesophagus carcinoma has been already reported. The biochemical changes within tumor and normal cells are normally detected at the "fingerprint region" of 1800 to 950 cm^{-1} by measuring the change in frequency of vibration of the molecules. In this review, we present application of FTIR spectroscopy in cancer biology. Thus this review is aimed to brief the potential role of FTIR in detection of various types of cancers.

Keywords: FTIR spectroscopy, Absorption spectra, Infrared spectroscopy, Biological tissues, Cancer diagnostics

1. Introduction

Cancer is a multistep disease which involves addition of irreversible and transmittable genetic abnormalities and presence of epigenetic variations in susceptible cells [1, 2]. It involves an array of mutations [3] and change in response to the cell microenvironment [4], evasion of host immune responses[5] and metastasis of cancer cell phenotypes which ultimately leads cells resistant to chemotherapy.

Tumor detection at initial stages is a major concern in cancer diagnosis. Cancer screening involves costly and lengthy procedures for evaluating and validating cancer biomarkers. Rapid or one step method preferentially noninvasive, sensitive, specific and affordable is required to reduce the long diagnostic processes. However, gold standard for cancer diagnosis is the histopathology of the tissue biopsies which is further an invasive and time consuming practice and requires expertise of pathologists. There is a need to develop cancer detection and diagnosis techniques allowing non-destructive, quicker diagnosis with more accuracy and sensitivity.

Recently spectral methods are being used for the evaluation of malignancies and screen techniques for various cancers [6]. Infrared spectroscopy (IR) is used to study structural components of cell, based on vibrational spectral analysis such as intensity, band shape, frequency and band splitting [7]. The use of FTIR methods for the non-destructive investigation of biological samples is gaining popularity in research aiming its potential usage in histological and cytological diagnosis [8].

FTIR spectrometer consists of two perpendicularly plane mirrors (fixed and moving mirror), a semi-reflecting film, and the beamsplitter which bisects the planes of these two mirrors as shown in Fig. 1[9]. When a beam of monochromatic radiation is passed into a beamsplitter, half of the incident radiation will be reflected to fixed mirror while rest half will be transmitted to the moving one. Then these two beams are reflected from both mirrors which recombines and interferes at the beamsplitter. Further, half of the beam reflected from the fixed mirror is transmitted through the beamsplitter while remaining half is reflected back in the direction of the source. The beam which arises from the interferometer at 90^{o} to the incident beam is referred as transmitted beam which is detected in FTIR spectroscopy.

It is a non-destructive method which detects any change of molecular functional group in tissue or cells being visualized in mid infrared region. Biochemical changes among unaffected and tumor cells fall within 1800 to 950 cm^{-1} range which ensures FTIR spectroscopy a reliable method to study structural changes in cells of various human cancers at the molecular level [10]. FTIR is a sensitive instrument which differentiates between normal cells and neoplastic in colon [11], prostate [12], breast [13], cervical [14], gastric [15], oral [16] and oesophagus [17]. Furthermore, only small quantity of sample is needed for analysis, and is reagent free with fast analysis of biochemical variations at the molecular level, and can be further clubbed with computational and statistical multivariate methods for data analysis to gather additional information from spectra.

FTIR spectroscopy is a potent analytical, biochemical and imaging technique which offers information on the molecular configuration of biological samples at an energy or wave number related to the bonds between its atoms [18]. Micro imaging FTIR is capable of differentiating between unaffected and malignant tissues by comparing spectra's for change in an array of diagnostic bands rising from phosphate, C – O and CH stretching vibrational modes [19]. Chemometric methods like principal component analysis (PCA) and hierarchical clustering analysis (HCA) are widely used to separate spectra of normal and neoplastic zones. Despite the technological improvements in past three decades, biomedical applications of FTIR-based analytical technique have not yet properly come into the scientific forefront. This technique has been successfully used for analysis of various biological samples; however its application in cancer research and clinical diagnostics still remains untried. In this article, we present a brief overview of use of FTIR for detection and diagnosis of various cancers.

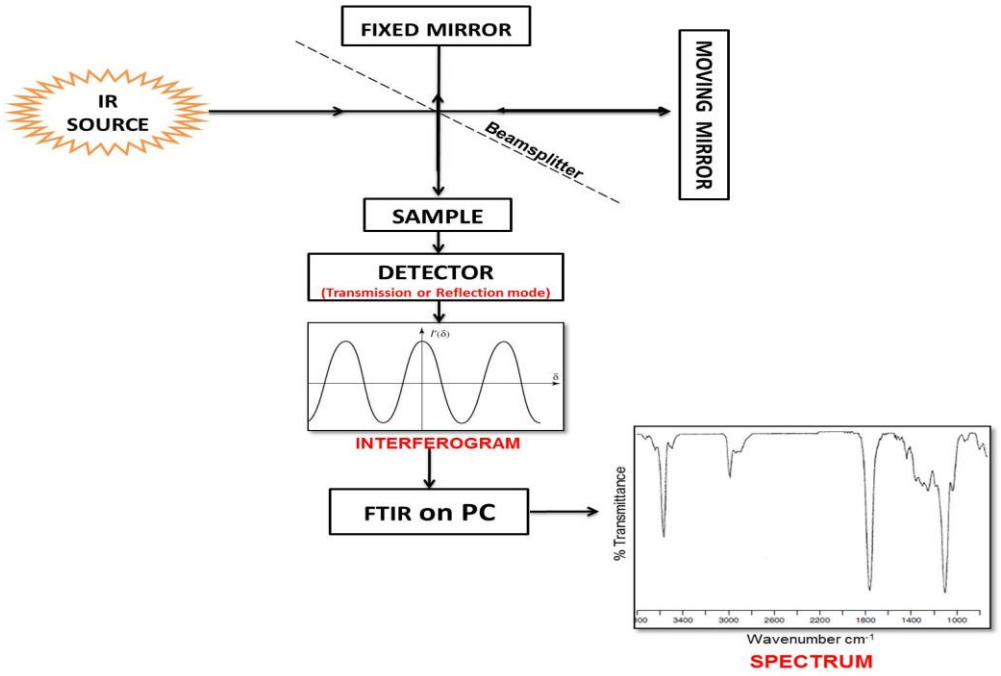

Figure 1: Brief mechanism of FTIR for detection (Adapted and modified from [9])

2. Breast Cancer

Breast cancer has beaten cervical cancer in incidence and is the second leading cause of death worldwide in women after lung cancer. Conventional diagnostic method such as mammography has around 66% sensitivity and 92% specificity [20]. Also recent studies have shown that screening procedures like mammography does not decrease mortality and may increase unwanted surgical procedures hence causing patient anxiety [21]. Furthermore, mammography has limitation with women with dense breasts and high-risk patients and to confirm its findings it may involve further diagnostic methods such as ultrasound or magnetic resonance imaging [22].

Moreover alternative diagnostic approaches such as thermography, trans-illumination and positron emission tomography have less sensitivity or specificity than mammography [23]. Sensitivity and the specificity of tumor markers such as cancer antigen 15-3, the extracellular domain of HER-2 protein, carcinoembryonic antigen, and tissue polypeptide antigen are very low at initial stages of the disease [24].

FTIR analysis of 25 breast cancer tissues by Mehrotra et al[25] showed shifting of vibrational spectra of breast malignant and unaffected tissues containing lobular, ductal, and adenomas carcinoma in the fingerprint region from 1097 cm^{-1} to 1076 cm^{-1} respectively. FTIR coupled with PCA-LDA (linear discriminant analysis) is used to explore the serum in breast cancer patients [26]. Serum samples of 43 breast cancer and healthy serum samples were collected and analyzed by PCA-LDA method. Major differences in the spectra of control and cancer groups were observed and it was related to the differences in protein conformation in serum samples. The sensitivity, specificity and accuracy of control and breast cancer patients were recorded as 84%, 74%, 83% and 76%, 72% and 80% respectively. Some other groups also reported the use of IR spectroscopy for the recognition of breast cancer [27]. ATR spectroscopy is used for the comparative study of pubic hair and scalp samples from normal healthy control and breast cancer patients[28].It was observed that breast cancer showed decreased beta-sheet and or disorder structures compared to alpha-helix and C-H lipid content than healthy control. It can be summarized that FTIR spectroscopy, together with multivariate data analysis is able to discriminate

between healthy and cancerous breast samples with greater accuracy, sensitivity and specificity.

3. Cervical cancer

Cervical cancer leads to nearly 12% mortality and morbidity among women worldwide of all cancers. Conventional cervical screening techniques lack sensitivity and specificity so low-cost robust, specific and sensitive screening technique is urgently required [29]. FTIR spectroscopy can be applied to understand the underlying changes during alteration between various cervical classes from normal to low-grade to high-grade and be developed into a bio-spectroscopy screening tool.

Cervical cells comprise specific changes at molecular level which is detected by absorption bands in the infra-red spectrum [30]. FTIR coupled with PCA was used to study cervical cells from 272 patients suspected with cervical tumor. PCA spectra of normal epithelial cells profile were distributed into two groups; normal epithelial cells displayed type 1 showing strong glycogen bands at 1022 cm^{-1} and 1150 cm^{-1} and a displaying distinct symmetric phosphate stretch at 1078 cm^{-1} [31]. However, decrease in glycogen-band intensity and prominent asymmetric and symmetric phosphate modes were recorded in type 2 spectra confirming dysplastic or malignant group. Similar study performed by Wong et al. [32] and group found significant differences between IR spectra of normal and malignant cervical epithelial cells. ATR-FTIR along with PCA and variable selection techniques segregated normal (negative for malignancy; n=43) from squamous intraepithelial lesion (n=40) in blood plasma samples [33].These results indicate the potential use ATR-FTIR spectroscopy as a screening tool for pre-cancerous cervical tumors, in turn reducing cervical cancer incidence. A total of 800 cervical scrapings were screened with FTIR spectroscopy and results were compared with the cytological findings and the results suggested that FTIR separates normal from abnormal cervical cells with the sensitivity and specificity of 85% and 91% respectively [14].

4. Colorectal cancer

Colorectal cancer (CRC) represents fourth widespread malignancy with the annual death rate of 1.2 million people in developing and third most common cause of cancer deaths worldwide with 0.6 million deaths annually [34]. The survival rates of patients diagnosed with colorectal cancer are linked with the tumor stage. Although progress has been made to improve the quality of current diagnostics and screening methods for CRC, the sensitivity and specificity of conventional tests still need to be improved [35].

CRC at early stages from colonic tissue samples has been identified by FTIR spectroscopy in several studies [36, 37]. Solid tumor affects the cellular blood components and it was suggested that spectral analysis of whole plasma can be done to predict neoplasms rather than locating a change in protein or other molecule from a tumor [38]. Significant differences were observed in the spectra of phosphodiester and glycogen region of normal, dysplastic, and carcinoma cells collected by a cytobrush and Ayre spatula in the CRC patients [39]. Shifting of peak position in spectra with malignant transformation was also observed in many studies [14, 40]. ATR-FTIR spectroscopy with multivariate analysis methods is also used for screening pre-cancerous cervical lesions [33]. The spectral changes observed by FTIR reflect significant changes in the structure of main structural molecules in the malignant tissue. In another study significant difference in the FTIR spectra of normal and cancerous colon biopsies was observed in the spectral region of 1800-900 cm^{-1} by combining ATR-FTIR microspectroscopy with chemometric method [41]. The results revealed with an accuracy, specificity, and sensitivity of 93.3%, 100%, and 88.2%, respectively.

5. Lung Cancer

Lung cancer is the leading cancer in the world with 1.69 million deaths annually according to WHO 2018 report. Due to the diagnosis at later stage more than 90% of patients die within five years. Existing diagnostic techniques such as chest X-ray, bronchoscopy and computerized tomography is used in lung cancer detection though they are not

effective for detecting at early stage [42]. Effective ways to detect lung cancer at early stage should be developed to reduce high incidence and mortality rate. FTIR has been effectively used for the diagnosis of lung cancer on sputum, pleural fluid and lung tissue. Sputum sample from the suspects with sufficient presence of bronchial epithelial cells was assessed for detection of lung cancer. Cell pellets were analyzed by FTIR micro-spectroscopy and the characteristic spectra for pre-identified tumor and unaffected bronchial cells were generated. With the help of HCA and PCA statistical methods, spectral subgroups are easily visualized and interpreted on the basis of patterns of differences in absorbance levels. It was suggested that FTIR in sputum cells showed high sensitivity and specificity in diagnosing the disease within a small range of significant wave numbers [10]. Another study was performed on 161 patients with initial cancer suspicion with the FTIR analysis of blood sample to identify non-small cell lung carcinoma (NSCLC) [43]. Biochemical differences between blood samples of control and lung carcinoma patients were detected in the spectra and an accuracy of 80% was achieved in separation of squamous cell and adenocarcinoma patients. It was suggested that this method could be a diagnostic tool for NSCLC with enhanced performance.

Serum samples were also exploited by FTIR spectroscopy to compare healthy control and lung cancer patients as it reflects pathological and physiological changes in humans. It was observed that the A1080/A1170 ratio (the relative content of nucleic acids) may be useful criteria for differentiating healthy serum from lung cancer. Pleural fluid was used to understand structural changes associated with lung cancer using microscopic FTIR spectroscopy [44]. Significant spectral difference was measured between lung cancer and normal samples ratio at 1030 and 1080 cm^{-1} wavenumber (glycogen and phosphodiester groups of nucleic acids). Zhang et al. observed relative intensity ratios I1080/I1160, I1240/I1310, I1460/I1400 and I1640/I1550 plays a major role in distinguishing non-cancerous and cancerous tissues by comparing FTIR spectra [45] and also the ratio of H1045/H1467 is used to segregate normal tissues from malignant lung tissues spectra [46].The sensitivity and specificity of ATR-FTIR were found to be 96.7% for the detection of malignant lung tissue in the pilot study performed to differentiate malignant and nonmalignant lung tissues [47].

Based on these studies, it is suggested that sensitivity and specificity of FTIR spectra method is highly efficient compared to the current methods of lung cancer detection. Thus, this technology is a non-invasive, cost-effective and high-throughput technique for screening lung cancer. Since FTIR spectroscopy can reflect changes at molecular level, it can used as a tool for early cancer detection.

6. Bladder cancer (BC)

Bladder cancer is ninth most common malignancy in humans worldwide. The most common symptom of BC is hematuria that occurs in 80-90% of the cases [48]. It has a high risk of recurrence that requires a lifelong follow-up and it is a costly process [49]. There is a need of accurate, minimally invasive and cost-effective screening method for BC detection so that malignancy can be detected at an early stage. Cystoscopy followed by the pathological confirmation is a gold standard to detect BC but it fails to detect flat lesions (carcinoma in situ) and small papillary tumors and is an invasive method [50].

FTIR spectroscopy is broadly used in detection and characterization of BC using blood, tissue, urine [51, 52]. FTIR spectroscopy combined with chemometrics is an observer-independent, non-invasive, rapid and economical method used in detection of bladder tumor recurrence using bladder wash samples; sampled during cystoscopy [52]. Bladder wash samples of 71 patients (n=34; control and n=37; bladder cancer) were analyzed with FTIR and the results showed significant modifications in molecular content in the cancer group (significant shift in the wavenumber of CH_3 symmetric stretching band at 2877 cm^{-1}) and successful differentiation of two groups were achieved with 100% sensitivity. Malignant bladder and unaffected tissues show significant differences in their FTIR spectra due to changes in lipids, proteins, and nucleic acids during carcinogenesis [53]. Thus FTIR spectroscopy facilitates early and rapid detection of bladder tumor and suggests need of cystoscopy in tumor patients during the follow-up period. Table 1 show that FTIR can detect cancer progression in

various types of cancer using different types of samples.

7. Technological advancement based on FTIR

FTIR spectrometer with increased sensitivity and automatisation of modern bioinformatics and sample preparation methods made it possible to identify and validate spectrally distinct biomarkers for various cancers and inflammations in suspected cancer patients. With the help of advanced techniques such as Random Forest (RF) approach, absorbance spectra and their 1st and 2nd derivative spectra were identified which aids for achieving higher resolution and faster acquisition with increased sensitivity and specificity. Further, new and improved computing software has improved efficiency and speed to the execution of IR spectroscopy with functions such as sample presentation and control, classification, quantitative analysis, and identification through database searching and data handling.

8. Disadvantages of FTIR

Demand of highest standards of accuracy and reproducibility of measurements is required in the extraction of detailed data from FTIR spectra of human samples, which is limited by small spectral differences between diseased and healthy subjects in comparison to large background absorbance of the sample. Potassium bromide (KBr) used in sample preparation is a very hygroscopic material and thus reduces spectral quality in the course of the spectral acquisition, mainly during the first 20 min of FTIR measurements.

9. Conclusion

An FTIR detection method deals faster and reliable results than cytology reports, so it can be used as one of the primary diagnostic method for cancer screening. Significant changes were observed between the spectra of normal and malignant tissues studied by FTIR spectroscopy and it provides high-resolution spectra in shorter period. The spectral alterations show the modifications in the proteins, lipids, and nucleic acids of the cancerous tissues. It can be concluded that FTIR spectroscopy is a high-throughput method for screening of various cancerous tissues and could be used as an alternative method for identification and diagnosis. Degree of malignancy in various cancers could be documented on the basis of changes in spectra obtained by FTIR and by comparing it with the histopathological studies.

Table 1: Sample types for cancer detection by FTIR with spectral analyses

Cancer type	Sample type analyzed	Major peak/s	Assignment
Breast	Breast tissue, Serum	1076 cm^{-1}	Symmetric phosphate (PO_2) stretching
Cervical	Cervical smear	1084.4 cm^{-1}	Phosphodiester bond (PO_2^-) in nucleic acids
Colorectal	Exfoliated cells	1239.4cm^{-1}; 1085.1cm^{-1}	asymmetric and symmetric phosphate stretching
Lung	Sputum, pleural fluid, lung tissue	1656 cm^{-1}; 1577 cm^{-1}	amide I and amide II bands
Bladder	Blood, bladder tissue, urine, bladder wash	2877 cm^{-1}	CH_3 symmetric stretching band

Author Contributions

AK and JK performed the initial literature search, study design, data collection and prepared the original draft of the manuscript, which was subsequently read and substantially modified, analyzed and interpreted by JK and SB.

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Disclosure Statement

The authors declare no potential conflicts of interest.

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