Chapter 2
Biomarkers as the Promising Tools for Early Detection of Gastrointestinal Cancer

Pallaval Veera Bramhachari and Nageswara Rao Reddy Neelapu

Abstract Gastrointestinal cancer is one of the most prevalent types in the world and which is poorly understood at the molecular level. Early detection of gastric cancer is still a problem and detection of cancer at an early stage will help plan the selection of an appropriate treatment plan and effective monitoring of diseases. Literature reports the use of biomarkers and methods for early detection of cancer. This chapter summarizes the burden of cancer, especially gastrointestinal cancer, methods for diagnosis of cancer, the importance of biomarkers and early detection of cancer, biomarkers and their classification, and biomarkers for gastrointestinal cancers which could be potentially used for early diagnosis, and accurate prediction of therapeutic approaches.

Keywords Biomarkers · Burden of cancer · Cancer · Early detection of cancer · Gastrointestinal cancer · Technologies for early detection of cancer

2.1 Introduction

Global cancer burden shows that 43.8 million people are living with cancer (GLOBOCAN Database 2018). The new global cancer burden in 2018 is 18.1 million new cases, whereas the lethality of cancer is 9.6 million cancer deaths in the year 2018 (GLOBOCAN Database 2018). The burden of cancer is different in different regions, where 50% of the cancer cases were registered in Asia, 25% cases accounted to Europe, and the rest of the cases are distributed across the different parts of the world (GLOBOCAN Database 2018). Gastrointestinal cancer (GI) is the

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P. Veera Bramhachari, N. R. R. Neelapu (eds.), *Recent Advancements in Biomarkers and Early Detection of Gastrointestinal Cancers*, Diagnostics and Therapeutic Advances in GI Malignancies, https://doi.org/10.1007/978-981-15-4431-6_2

third-highest based on lethality and fourth-highest based on morbidity of all cancers. The gastrointestinal cancer burden can be assumed from the new and death cases registered. Nearly ~1,033,701 new cases and ~782,000 deaths were recorded for gastrointestinal cancer in 2018 (GLOBOCAN Database 2018). Statistical techniques like Bayesian inference methods, capture-recapture methods, Mortality and Incidence Analysis Model (MIAMOD), and Prevalence and Incidence Analysis Model (PIAMOD) are the methods used to measure the burden of cancer on population (Sharifian et al. 2016). This chapter discusses in detail how the diagnosis and early detection of cancer can relieve the burden of cancer. Also, the details of biomarkers and their types that can be used for early diagnosis of gastric cancer are discussed. This helps in understanding the role of biomarkers for early diagnosis of gastric cancer.

2.2 Diagnosis and Importance of Early Detection of Cancer

Diagnosis is a very important aspect to confirm the disease, especially cancer. The diagnosis of cancer provides an opportunity to treat the diseases appropriately. But, by the time the patient is diagnosed with cancer; the patient is in an advanced stage of cancer with his life at risk. To save their lives, cancer patients can be diagnosed early. Therefore, this section provides details on the diagnosis of cancer and the importance of early detection of cancer.

2.2.1 Diagnosis of Cancer

Broadly, there are four types of tests like tumor testing for biomarkers, cytogenetic tests, gene tests, and biochemical tests available for diagnosis of cancers. This section discusses briefly the tests for diagnosing cancers or tumors.

2.2.1.1 Tumor Testing for Biomarkers

Samples of blood, body tissue, bodily fluids, tissue biopsies, and urine are used for testing tumor biomarkers. Molecular or genetic tests identify molecular features of genes or DNA in cells of cancer or tumor. These molecular features are specific biomarkers for cancer. PCA3 and T2: ERG are the biomarkers of prostate cancer identified by gene testing (Füzéry et al. 2013; Paddock 2019).

2.2.1.2 Gene Tests

Molecular tests look for biomarkers like genes (inside chromosomes), extra copies of a gene (duplicated or amplified genes), missing genes (gene deletions), incorrectly placed genes (translocated genes), changes in genes (mutated genes) in small tissue samples, blood tests, liquid biopsies, and biopsy (tissue testing). Specific biomarkers like *HER2* or *EGFR* (single-gene test) or gene-expression panels for many biomarkers are the molecular tests used for the diagnosis of cancer (Chanley 2018).

2.2.1.3 Cytogenetic Tests

The structural abnormalities in chromosomes leading to cancer can be diagnosed with cytogenetic tests. Samples of blood cells, tissues, and bone marrow can be used to measure the abnormalities in the chromosome. The specific changes in the chromosomes can act as biomarkers to screen or diagnose cancer. A change in the Philadelphia chromosome is the biomarker and the common feature of blood cancer (chronic myeloid leukemia) (Chanley 2018).

2.2.1.4 Biochemical Tests

Mutated genes express abnormal proteins and biochemical tests identify these proteins which serve as biomarkers. For example, the gene test uses the HER2 gene, whereas biochemical tests look for HER2 protein in the tissue sample. The tests described above identify a biomarker in the cancer cells and help in characterizing the specific nature of cancer. Understanding biomarkers related to cancer may help to get the best treatment for cancer and also show whether cancer is responding to treatment or not (Chanley 2018).

2.2.2 Importance of Early Detection of Cancer

The importance of early detection of cancer can only be addressed when it is understood, why some cancers are diagnosed late? how finding and treating cancer at an early stage can save lives? and how early diagnosis can improve survival? Some cancers are diagnosed late and the reason for the delay in cancer diagnosis is low awareness of cancer signs and symptoms among the general public, health care providers, physicians, and nurses (Why is early diagnosis important 2019). The signs and symptoms of cancer can be abnormal bleeding, chronic hoarseness, lumps, persistent indigestion, and sores that fail to heal. Education promoting sessions on cancer signs and symptoms would create awareness and encourage screening or early diagnosis of cancer. Early detection of cancer greatly increases the chances for

successful treatment, whereas if cancer is diagnosed late then treatment becomes more difficult, decreasing the chances of survival of the patient. Early diagnosis is particularly relevant for cancers of the breast, cervix, mouth, larynx, colon and rectum, and skin. Some predictions estimated, how early diagnosis can improve the survival of cancer patients. In the case of bowel cancers, nine of the ten patients can survive if diagnosed at an early stage (Why is early diagnosis important 2019). In the case of breast and ovarian cancer, 90% of women survive for more than 5 years if diagnosed at an early stage when compared with women who are diagnosed at an advanced stage (Why is early diagnosis important 2019). In the case of lung cancer, 80% of patients survive for a year if diagnosed at an early stage when compared with patients who are diagnosed at an advanced stage (Why is early diagnosis important 2019). These advantages demonstrate the importance of early diagnosis of cancer. The role of biomarkers in early diagnosis of cancer is well known and established. Further, details on the importance of biomarkers would provide an understanding of the early diagnosis of cancer.

2.3 Importance of Biomarkers

Biomarkers are the molecules produced by the tumor or cancer cells in the body due to changes in genes, DNA or RNA that transform the normal properties of the cell and develop the cell into cancer cells. Biomarkers can determine the characteristics of a tumor or cancer, and also the severity or grade of cancer. Understanding the characteristics of a tumor or cancer allows physicians to customize treatment to cancer. This paved path and revolutionized the treatment of cancer by approaches like personalized medicine or precision medicine. Hence, cancer or tumor biomarkers can be identified through gene or molecular testing and can be characterized to understand the paint a specific picture of a tumor. Once the biomarker is recognized, targeted therapy can be designed for specific cancer with reduced cost and side effects.

2.4 Biomarkers Available for Early Detection of Cancer

Biomarkers are classified based on disease state, types of biomolecules, and other criteria (Radhika et al. 2016) (Fig. 2.1).

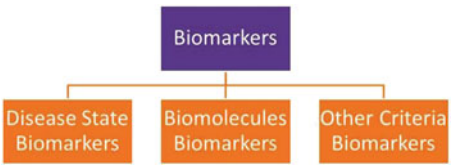

Fig. 2.1 Biomarkers and classification of biomarkers

2.4.1 Disease State Biomarkers

The disease state biomarkers available for early detection of cancer include risk assessment biomarkers, screening/detection biomarkers, diagnosis biomarkers, prognosis biomarkers, prediction biomarkers, and monitoring biomarkers (Radhika et al. 2016). Risk assessment biomarkers are associated with detecting the risk concerning predisposition of gene mutations in individuals which can lead to cancer. Risk assessment biomarkers can help in identifying the risk of cancer at an early stage (Radhika et al. 2016). Screening or detection biomarkers are real-time indicators like antibodies, serum proteins, circulating tumor cells, and DNA fragments in the bloodstream reflecting cancer or tumor. These indicators or biomarkers help in screening or detecting cancer or tumor (Radhika et al. 2016). Diagnosis biomarkers can determine, confirm the primary origin of cancer or tumor in the biopsy sample (Radhika et al. 2016). Prognosis biomarkers provide information about a patient's expected outcome, regardless of therapy. Sometimes, cancers are more aggressive than others and prognosis biomarkers can help in determining which cancers may grow rapidly and/or metastasize (Radhika et al. 2016). Prediction biomarkers are used to predict a patient's response to the drug and its dose when used for cancer treatment. Cancer is a heterogeneous disease, and different cancers respond differently to the same treatment methods and prediction biomarkers are used to predict a patient's response to the treatment (Radhika et al. 2016). Monitoring biomarkers are used to predict and monitor a patient's cancer recurrence after treatment. Thus, risk assessment biomarkers, screening/detection biomarkers, diagnosis biomarkers, prognosis biomarkers, prediction biomarkers, and monitoring biomarkers are available for early detection of cancer (Fig. 2.2). Biomarkers used for early detection of gastrointestinal cancer are listed below in Table 2.1. These biomarkers can be employed by different technologies available for early detection of gastrointestinal cancer.

2.4.2 Biomolecule Biomarkers

The biomolecule biomarkers include DNA biomarkers, RNA biomarkers, protein biomarkers, glycol biomarkers, metabolite biomarkers, and serum biomarkers (Radhika et al. 2016) (Fig. 2.3). Certain races or populations are susceptible to cancer, who are either predisposed or acquire genetic material hereditarily via DNA. These are known as biomarkers of genetic susceptibility or DNA biomarkers (Biomarkers Definitions Working Group 2001). MicroRNAs, circulating microRNAs, and plasma microRNAs are a few examples of RNA biomarkers. MicroRNAs are endogenous single-stranded non-coding small RNA molecules that are secreted into the circulation and exist stably. These, microRNAs exhibit aberrant expression under different physiological and pathological conditions. These differentially expressed circulating microRNAs are the potential biomarkers for cancer screening (Wang

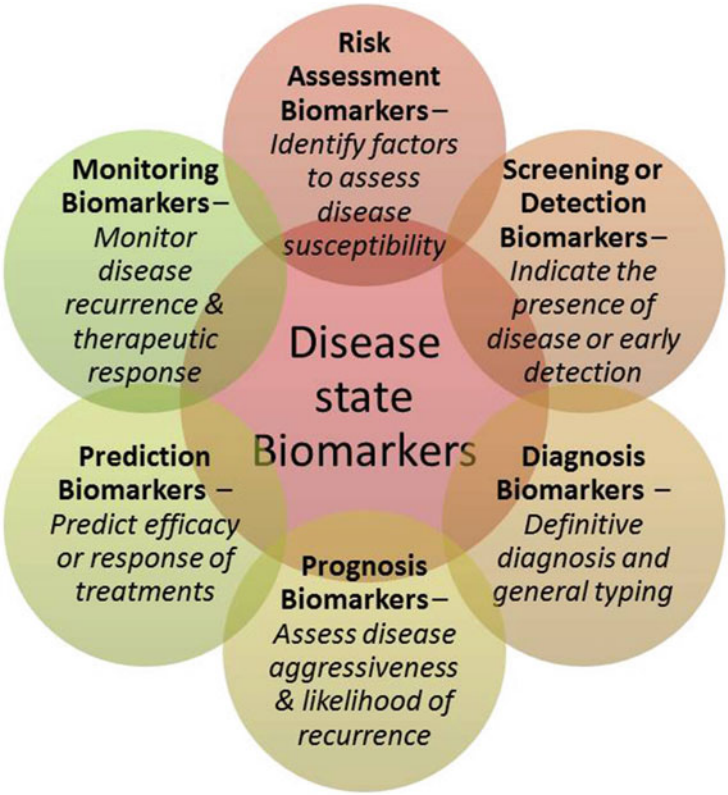

Fig. 2.2 Disease biomarkers available for early detection of cancer

et al. 2018). Circulating microRNAs in the serum generating microRNAs expression profiles are known as serum microRNAs (Wang et al. 2013). Circulating microRNAs when isolated from plasma of human subjects and generate expression profiles on microRNAs are known as plasma microRNAs (Wozniak et al. 2015). These, circulating microRNAs have several clinical applications like a diagnosis of cancer, classification of the tumor, monitoring, and outcome prognosis. Proteins causing disease or associated with susceptibility of the disease are known as protein biomarkers (Biomarkers Definitions Working Group 2001). Immunoassays and mass spectrometry assays are the two types of protein biomarkers assay platforms available for the discovery of protein biomarkers (Walid and Klaus 2010). These protein biomarkers have several clinical applications like a diagnosis of cancer and the classification of the tumor. Reactive oxygen species like hydroxyl radicals (HO$*$) have generated which damage DNA, i.e., thymidine during oxidation forming thymidine glycol (5,6-dihydroxy-5,6-dihydrothymidine). Thymidine glycol is a biomarker that is excreted via urine and can be estimated as a biomarker for its disease state (Makropoulos et al. 2000). Volatile or metabolite biomarkers are

Table 2.1 List of biomarkers for gastrointestinal cancer

S. no	Biomarkers	References
1	HER2 (ERBB2), EGFR, VEGFA, NOTCH1, p-mTOR, MMP1, MMP7, TGFB1, MET, HER3 (ERBB3), SHH/PTCH1/SMO, FGFR2, CASOX9, TP53, PTEN, ALDH, PIK3	Elimova et al. (2015)
2	PD-L1	Curea et al. (2017)
3	ADAM23, GDNF, MINT25, MLF1, PRDM5, RORA	Watanabe et al. (2009)
4	BARHL2	Yamamoto et al. (2016)
5	PVT1	Yuan et al. (2016)
6	CagA	Saju et al. (2016)
7	VacA	Ghotaslou et al. (2018)
8	Gastrokine 1	Altieri et al. (2017)
9	CEACEM6, APOC1, YF13H12, CDH17, FUS, COLIA1, COLIA2, APOE	Yasui et al. (2004)
10	OLFM4, HOXA10, DSC2, TSPAN8, TM9SF3	Oue et al. (2015)
11	CCNB1 and CCNB2	Wang et al. (2015)
12	ZNF331, ZSCAN18, CDO1	Marie Vedeld et al. (2015)
13	KLK6	Paliouras et al. (2007)

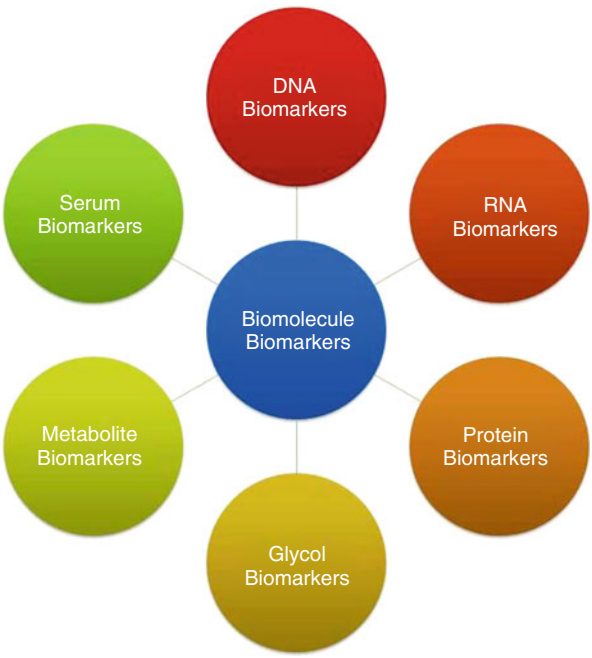

Fig. 2.3 Biomolecule biomarkers and their classification

volatile organic compounds (VOCs) released from human body fluids by endogenous metabolic processes. Expressions of VOCs bring in pathophysiological changes leading to disease, and several disease-specific volatile biomarkers have been identified and used in diagnostic aids (Kwak and Preti 2011). Serum biomarkers are substances synthesized by the tumor or cancer cells and released into circulation or expressed at the cell surface in large quantity changing quantitatively the serum during tumor or cancer development (Kato and Torigoe 1977).

2.4.3 *Other Criteria Biomarkers*

The biomarkers in other criteria include imaging biomarkers, pathological biomarkers, next-generation biomarkers, and in silico biomarkers (Radhika et al. 2016) (Fig. 2.4). Biologic feature of an image measured using techniques like CT, electroencephalography, magnetoencephalography, MRI to diagnose patients is known as imaging biomarker (Smith et al. 2003). Histopathologic techniques like electron microscopy, confocal laser scanning microscopy, immunohistochemistry, and in situ hybridization detect morphology of the disease state and improve diagnoses. These morphological and pathological features are known as pathological biomarkers (Novilla et al. 2014). Markers that are generated/identified using next-generation technologies like pharmacogenetics/pharmacogenomics, genotypic drug metabolism and transport, haplotype and SNP, RNA expression profiling, metabolomics, proteomics for the clinical outcomes during the development program are called next-generation biomarkers (Hogan et al. 2018). The different types of biomarkers are—pharmacogenetic biomarkers, pharmacogenomics biomarkers, genotypic drug metabolism biomarkers, drug transport biomarkers, haplotype biomarkers, SNPs, RNA expression profiles, metabonomics biomarkers, and proteomics biomarkers (Hogan et al. 2018). Computational or in silico methodologies are used to detect the pathological changes and connectivity of cells especially in

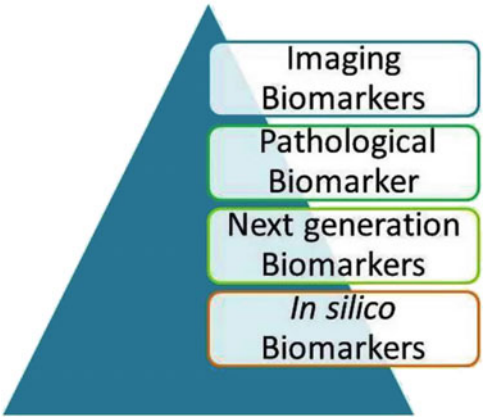

Fig. 2.4 Biomarkers in other criteria and their classification

neurons or any other tissues. These biomarkers are known as computational or in silico biomarkers (Siekmeier 2017). These biomarkers can be employed by different technologies available for early detection of gastrointestinal cancer. The different technologies available for early detection of cancer are DNA sequencing, next-generation sequencing technologies, "omics" technologies, nanotechnology, synthetic biology, next-generation sequencing panels (exomes to genomes), serum biomarker panels, ultra-sensitive nano-chips, nanosensors, nanodevices, biosensors, electrochemical biosensors, DNA biosensors, synthetic biology devices, etc.

2.5 Conclusions and Future Perspectives

Gastrointestinal cancer is one of the most prevalent, ranking third highest based on lethality and fourth-highest based on morbidity. Tumor testing for biomarkers, cytogenetic tests, gene tests, and biochemical tests are the tests available for the diagnosis of cancers. Early detection of gastric cancer is still a problem and the reasons for the delay in cancer diagnosis are low awareness of cancer signs and symptoms among the general public, health care providers, physicians, and nurses. The signs and symptoms of cancer are abnormal bleeding, chronic hoarseness, lumps, persistent indigestion, and sores that fail to heal. Promoting education and awareness of cancer signs and symptoms would encourage screening or early diagnosis of cancer. Early detection of cancer greatly increases the chances for successful treatment, whereas if cancer is diagnosed late then treatment becomes more difficult, decreasing the chances of survival of the patient. Early diagnosis is particularly relevant for cancers of the breast, cervix, mouth, larynx, colon and rectum, and skin. Biomarkers are used for early detection of cancer and biomarkers are classified based on disease state, types of biomolecules, and other criteria. The disease state biomarkers available for early detection of cancer are risk assessment biomarkers, screening/detection biomarkers, diagnosis biomarkers, prognosis biomarkers, prediction biomarkers, and monitoring biomarkers. The biomolecule biomarkers are DNA biomarkers, RNA biomarkers, protein biomarkers, glycol biomarkers, metabolite biomarkers, and serum biomarkers. The biomarkers in other criteria are imaging biomarkers, pathological biomarkers, next-generation biomarkers, and in silico biomarkers. Detection of cancer at an early stage using biomarkers will help to plan the selection of an appropriate treatment plan and effective monitoring of diseases.

Acknowledgments NNRR is grateful to GITAM (Deemed-to-be-University) for providing necessary facilities to carry out the research work and for extending constant support. PVBC is thankful to Krishna University for providing the necessary facilities to carry out the research work.

Conflict of Interest The authors declare that there is no potential conflict of interest.

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