MINI-REVIEW

Feasibility of Computed Tomography Colonography as a Diagnostic Procedure in Colon Cancer Screening in India

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Abstract

Computed Tomography Colonography (CTC) is a medical imaging technology used in identifying polyps and colon cancer masses in the large intestine. The technique has evolved a great deal since its invention and has become a routine diagnostic procedure in Western countries due to its non invasiveness and ease of use. The objective of our study was to explore the possibility of CTC application in Indian hospitals. This paper gives an overview of the procedure and its commercial viability. The explanation begins with the domain aspects from gastroenterologist perspective, the new way of thinking in polyp classification, the technical components of CTC procedure, and how engineering solutions have helped clinicians in solving the complexities involved in colon diagnosis. The colon cancer statistics in India and the results of single institution study we carried out with retrospective data is explained. By considering the increasing number of patients developing colon malignancies, the practicality of CTC in Indian hospitals is discussed. This paper does not reveal any technical aspects (algorithms) of engineering solutions implemented in CTC.

Keywords: ACRIN protocol 6664 - adenomas - bowel preparation - computed tomography colonography - neoplastic

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Introduction

Polyp is the abnormal growth of tissues found in the inner wall of the colon. They may arise from either mucosal layer or sub mucosal layer. Down the line, they may regress or grow further and can become malignant. The malignant version is called colon cancer and they can occur in any part of the colon (including Hepatic flexures and Splenic flexures). There are several clinical diagnostic procedures being used. Few are Colonoscopy, Flexible Sigmoidoscopy, and CTC (ACR practice guidelines, 2009). These procedures are employed based on the clinical task. CTC or Virtual Colonoscopy is a medical imaging technique used for finding the polyps of different shapes and sizes using the computer software. It is a non invasive procedure which involves CT scan of the patient and using image processing algorithms and techniques; the polyps are identified either through automated (CAD-Computer Aided Diagnosis of polyps) /semi automated software with Radiologist's intervention.

In our work, the broad notion of the discipline was to solve the problems in GI diagnosis through medical imaging. This is an interdisciplinary work involving Engineering, Radiology and Gastroenterology. The specific area of investigation was to solve the technical problems in CTC for accurate colon polyp classification with respect to size and shape. Within the scope of the study, extensive literature search was done using MeSH (Medical Subject Headings), MEDLINE and EMBASE databases. Review articles, product brochures of commercially available CTC solutions and conference proceedings were also searched for additional studies. Nearly 250 publications (2007-2013) were downloaded. Based on the relevance, adequacy and with deductive approach, the numbers were scaled down to 65. The statistics published from American Cancer Society (2013) and National Cancer Registry programs, India (2011) were also considered. These reports give the number of incidences of different cancers. Up to our knowledge; there was no literature which talks about the CTC procedure efficacy in Indian hospitals.

Clinically Significant Polyps

Polyp by definition is benign in nature and is called precursor of colon cancer. Not all colon cancers arise from polyps. Its importance can be decided by looking in to three major parameters, i.e. Size, Shape and Type.

The size of the polyp is the maximum diameter measured within the mass excluding the stalk of the

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peduncle (Figure 1, 2). Several authors have considered 1mm-5mm (small or sessile or Diminutive), 6mm-9mm (medium or Pedunculated) and >10mm (large or mass) as the classification schemes (Bogononi et al., 2005; An et al., 2008; Lieberman et al., 2008). Size measuring greater than 10mm has more likelihood of becoming malignant. Nowadays 6-9mm range is also considered clinically significant as they show advanced histology (Chu et al., 2011). Size of 1-4 mm is least significant. Sleisenger et al. (2010) have discussed the classification of sizes as <10mm, 10-20mm and >20mm and diameter of >10mm have more tendency to become cancerous.

The shape of the polyp is classified in to Flat, Sessile, Pedunculated and Mass. The growth of a polyp as seen in Colonoscopy is shown in Figure 2 (A1, B1 and C1). Sessile may look like flat or depressed which has a broader base. They are more difficult to identify and treat (Summers, 2010). Pedunculated polyp stalks out or projects from the mucous membrane (protrudes towards lumen) of colon. Sessile have less chances of becoming malignant when compared to pedunculated. Mass is the tumor which is malignant most of the time.

Based on the manner how the cells are organized when observed under microscopic examination (Histology), primarily polyp types are classified in to Inflammatory, Hyperplastic and Adenomatous (or adenomas). Adenomas are most common and larger adenomas have more tendencies and the malignant potential increases when size is >10mm. Adenomas are further classified as Tubular, Tubulovillous and Villous adenoma. Villous adenomas and Tubulovillous (cells that are organized as tubular and villous structure) are more likelihood when compared to tubular adenomas.

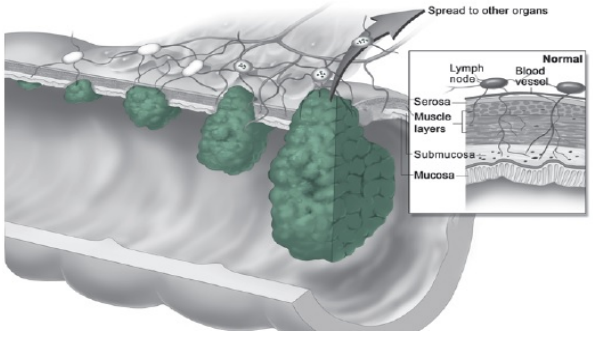

Figure 1. Polyp Growth (Source: American Cancer Society, 2013)

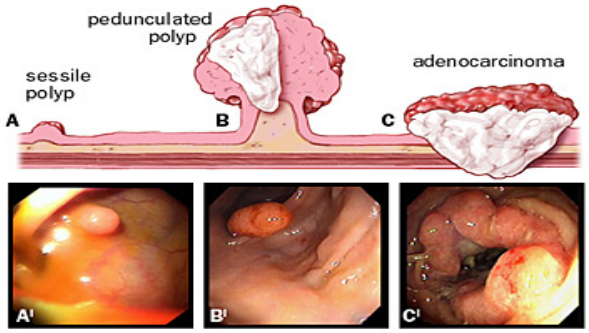

Figure 2. The Polyp Growth (A1, B1, and C1) Shown in Colonoscopy (Source: John Hopkins Cancer Center)

If there is a single or multiple polyps, then patient with multiple can develop additional in future. Malignant potential increases when there are more than 3-4. More than 80% of the polyps found are adenomatous type (Chu et al., 2011; Hodadoostan et al., 2010). Adenomatous which are 5-9 mm in length have a 5-10 % chance of becoming cancerous in 5-10 years. And of 10-15 mm length have 10-15 % chance in 5-10 years. The classification scheme as explained is shown in Figure 3.

Once polyps are identified, to know whether the cells are neoplastic (cancerous) or non-neoplastic (non cancerous), the tissue samples are referred to histopathology. They can be removed through polypectamy. The challenging job of the gastroenterologist is to diagnose a patient for the polyps with more accuracy in terms of shape, size and its type. This helps in avoiding the patient from developing the colon cancer in the near future.

CTC Procedure

CTC is a non invasive procedure involving the CT scan of the patient with the standard protocol and the images are interpreted to know the CT findings. CT modality is used which provides accurate tissue density information with less geometric distortions of the anatomy. ACRIN and ACR jointly define the protocol (Johnson et al., 2006) for performing the CTC procedure. Scan is performed by considering the safety of the patient as ionizing radiation can induce the side effects. Multi slice helical CT scan is recommended as it takes less time and radiation exposure to the patient is less. Recommended number of slices for scanning is 16, 64 or 128. Motion artifacts due to bowel peristalsis can be reduced with higher number of slices. The steps followed in the CTC procedure are, *i)* Bowel preparation through a low residue diet (2 days before the scan). Stool may prevent the CT scanner from taking clear images of colon lining and

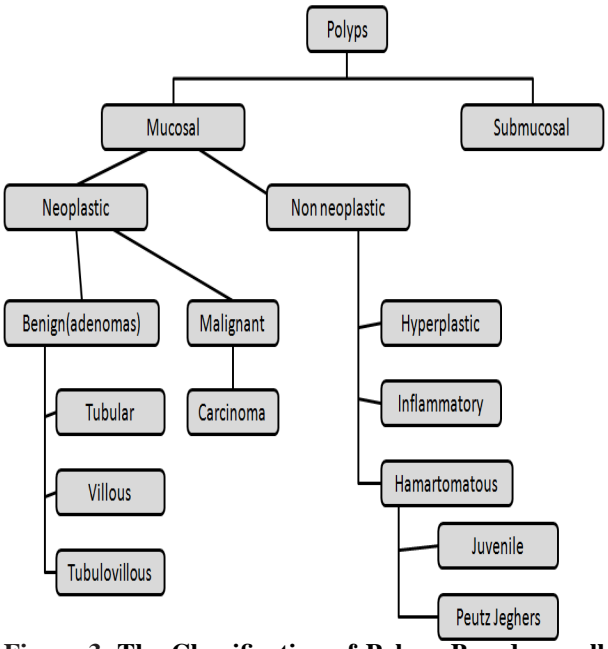

Figure 3. The Classification of Polyps Based on cell Type (Source: Sleisenger et al., 2010)

hence bowel cleansing is an important step. *ii)* Optional stool tagging or fecal tagging using oral contrast (they show different attenuation coefficients or Hounsfield units). *iii)* Intravenous contrast is not used to enhance the lesions. *iv)* Insufflations with room air or CO_2 to distend the colon for better visualization. *v)* Scans in Supine and Prone position as polyp may be obscured if seen in only one position scan (Punwani et al., 2009). *vi)* Breath hold technique is recommended to avoid the bowel peristalsis. *vii)* Interpreting the CT images through CTC software by looking in to the 2D MPR images and the 3D visualization which is called endoluminal fly through.

CT Imaging

ACRIN is the largest multicenter study to compare the CT results with Colonoscopy (Chu et al., 2011). The recommended CT scan parameters are slice thickness of 1-3 mm (results in best possible 3D volumetric data with isotropic resolution), reconstruction interval of 1-1.25mm, effective mAs of 50, kV=120, mA=200-300 (higher mA, less the quantum noise in the resultant image). Fine tuning any of these parameters is clinical task dependent. Radiation exposure to the patient is a concern in CTC (For CTC, the universal global quality metric-CTDIvol, is fixed). Nowadays technology has improved a lot and many CT devices have achieved As Low As Reasonably Achievable (ALARA) principle which has reduced the radiation exposure (Rockey, 2010) drastically. Normally the patient is exposed to ~8 mSv of radiation during CTC involving both position scans (Berrington et al., 2011) and a person can develop cancer when he is exposed to >60mSv of radiation in his lifetime. Still if we consider the health benefit and risk ratio, out of 35 patients in 1 lakh population only one person can develop cancer due to cumulative CT scans (Berrington et al., 2011).

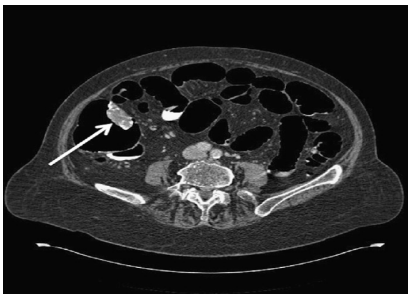

Figure 4. The Axial CT Scan Showing the Cancer Mass in Ascending Colon (Source; Halligan S, 2013)

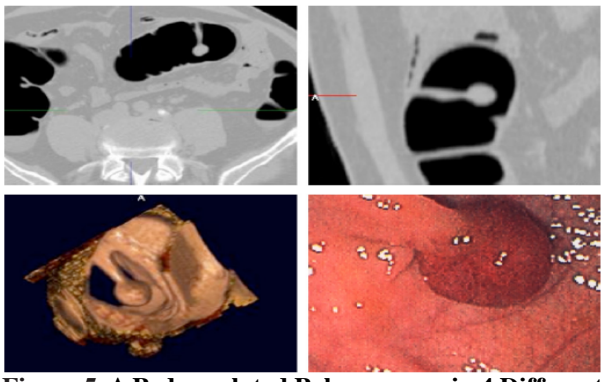

Figure 5. A Pedunculated Polyp as seen in 4 Different Visualizations. A) The Axial CT, **B)** The Sagital view, **C)** the volume rendering (3D visualization), **D)** The colonoscopy image. (Image source: Rockey et al., 2010)

In CT images, the polyp tissues show the homogeneous attenuation coefficients and the fecal matter shows the heterogeneous. By looking at the texture, geometry, size and the homogeneity in the Hounsfield units, polyps are reported as CT findings. v 4 shows an axial slice with Feet First Supine position scan. The arrow indicates the tumor mass from the mucosal layer which shows homogenous attenuation coefficients. By varying the window center and window width it is possible to visualize more anatomy details (Punwani et al., 2009; Kim et al., 2008) and the colon is best visible at window width of 1400 and window center of -350 (Poullos et al., 2010)

The 3D volume visualization of the patient data is an engineering marvel and has helped the doctors in visualizing the colon from different image planes (orthogonal Multi planar reformats, Figure 5.a, 5.b) and with volume rendering techniques (Figure 5.c). Most of the commercially available software supports both of these display techniques. Figure 5.d shows a pedunculated polyp stalked out from the mucous layer of colon (optical colonoscopy result of the same polyp shown in Figure 5.a-c). Several studies have shown the variation in sensitivity when assessed using both techniques and few have concluded that sensitivity is good in 3D when compared to 2D (Pickhardt et al., 2007).

Comparison between CTC and Colonoscopy

From the day of innovation of the CTC, several clinicians have done the investigations and over the period of time CTC software has matured enough in polyp measurement. Optical Colonoscopy results are still believed as the gold standard. But there are controversies in accepting this as the size measurement is poor for larger polyps (Cash, 2010; Pickhart, 2007). Few studies have reported that polyp are underestimated by ~2mm in CTC and is overestimated by ~2mm in Colonoscopy (Summers, 2010). Many have discussed the variation in sensitivity and specificity of CTC results when compared to the Colonoscopy. CTC mainly fails in identifying the smaller lesions of <5mm (Aswakul et al., 2012). Colonoscopy overtakes CTC in highly risk population as CTC fails for smaller lesions (Broadstock, 2007). If these go undetected, they may show advanced histology of becoming colon cancers.

It is difficult for CTC software to identify the polyps in Haustral folds of colon (Lafere et al., 2011). Different radiologists use different convention to assess the polyp (Atkin et al., 2013). The accuracy and sizes of measurement is highly variable among multisite studies and hence a standard protocol realization is required to conclude the sensitivity and specificity (Summers, 2010; Broadstack, 2007). Lieberman (2008) discusses that decision making of the observer is important in judging the polyp size and Inter observer variability in diagnosis has to be reduced. Despite CTC findings, still the tissue samples are referred to biopsy for the polyp type confirmation.

Few centers recommend the patient to Colonoscopy again and the results of both the procedures are evaluated for final conclusion (Lee, 2011; Pickhardt, 2010). Standard guidelines are needed to reduce the referral rate after CTC.

American Cancer Society (2013) reports that even though CTC is advantageous when compared with colonoscopy, CTC still can miss few polyps and sensitivity for polyps of >10mm is almost similar to that of Colonoscopy. With maturity so far, CTC has become a routine diagnostic procedure in western countries. Rather than relying on the conventional classification of polyp size as 1-5mm, 6-9mm and >10mm, measure it accurately and let the doctor decide its clinical significance for further analysis. This would avoid the variation in sensitivity and specificity.

Commercially available CTC Software

The list of few commercially available CTC software and the vendor details is shown in Table 1. The software has provided enough user interfaces for the doctors to handle the software for polyp measurement and visualization.

It is not clear about how the technology works in various scenarios like polyps of different shapes and sizes (especially less than 10mm), fecal matter cleansing techniques and subtracting the oral contrast artificially through image processing, how to classify polyps when they are present in Haustral folds and what is the sensitivity of their methods etc. Practically it is difficult to explore the number of diagnostic centers offering this facility. Only based on the centers mentioned in the literature a rough estimation can be made.

Global and India Scenario of Colon Cancers

Colon cancer can be widely seen in western and European population and also in Asian countries. In the recent past years, India is also not an exceptional case. The main reasons for the onset of this cancer are lifestyle (physical inactivity, overweight, obesity, heavy intake of alcohol, processed meat, smoking and aging problems) (Chu et al., 2011). As per the statistics released

Table 1. Few of Commercially Available CTC Software (These are Listed based on the References from Different Literatures)

Software	Vendor
GE Advantage CTC™	General Electric (Danielle Hock)
Syngo Colonography CT™	Siemens Medical Solutions
iCADTM	Veralook (www.icadmed.com)
Virtual Colonography™	Philips (www.healthcare.philips.com)
V3D-Colon™	Viatronix (product brochure)
Computed Assisted Reader™	MediSight, London
Vitrea 2	Vital Images, Plymouth

Table 2. Predicted Colon Cancers in India between 2010 and 2020 (Source: Takiar et al., 2010)

ICD 10	Gender	2010	2015	2020
C18 - Colon cancer	Male	11613	12483	13420
	Female	11895	15205	19013

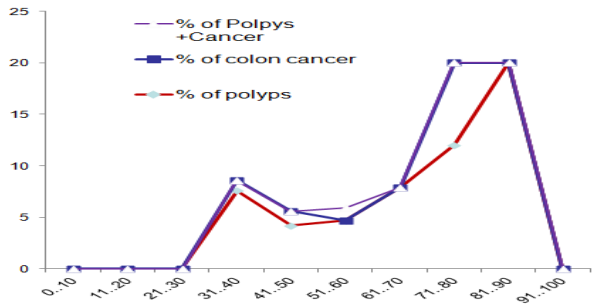

Figure 6. Frequency of Polyps among Age Groups

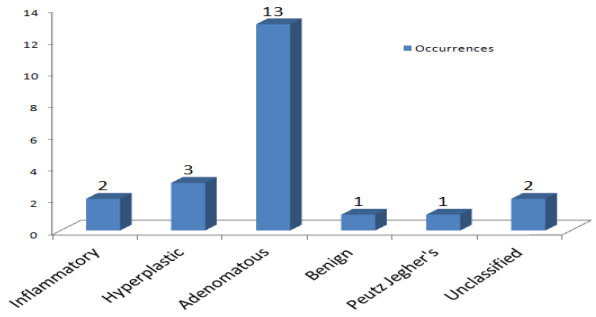

Figure 7. Different Type of Polyps Based on Histology

by American Cancer Society, in 2011, around 1, 41, 210 people were diagnosed and out of which 72% are related to Colon and 28% are related to rectum (ACS Facts and figures, 2013).

In Asian population also the colon cancer is increasing rapidly (An et al., 2008; Iinuma et al., 2008; Lohsiriwat et al., 2012). The numbers in India is shown in Table 2 (survey area was limited to few cities). Early diagnosis is the best possible way of preventing this disease. There were 6 papers in the last 5 years who have discussed about colon cancer in Indian population. Among them, few have focused on the colon cancer screening with the present and future numbers.

Takiar et al. (2010) have explained the projection of number of cancers in India during 2010 and 2020 using Crude Incidence rate in which they have emphasized on colon cancer also.

The numbers were derived from the population based cancer registry at few selected cities and the future trend was predicted using linear regression model. The recent article published by D'Souza et al. (2013) also has discussed the projected number of colon cancer among different age group in India. Imran et al. (2011) have explained the cancer scenario in India by comparing the colon cancer between India and United States. The inference from this study was, the possibility of increase in the colon cancer growth in future. Javid et al. (2011) have discussed about the colon cancer statistics in few selected cities and the numbers are based on crude incident rate and truncated incident rate. Tony et al. (2007) have discussed the histology of polyp occurrence in southern Indian population and have compared with other nations. Majority of polyps found in their study were adenomatous. Peedikayil et al. (2009) have studied the colon cancer distribution within the colon and have done the analysis on retrospective data. They conclude that colon cancer

distribution was more in the descending colon and the rectosigmoid junction.

Single Institution Study

To know the frequency and type of polyp in a single institution, we conducted a retrospective study in Kasturba Medical College, Manipal University, India. Patients diagnosed between Jan-June 2013 for any abdominal symptoms was considered. The diagnostic procedures were Flexible Sigmoidoscopy, Colonoscopy and polypectamy. Registry search was narrowed down only to Colonoscopy and Sigmoidoscopy along with biopsy results. Pseudopolyps were discarded. Redundant polyps were removed with the following strategy. If a patient undergo both Sigmoidoscopy and Colonoscopy procedures, and in both if same polyp was found, then it was considered as (1 patient, 1 polyp) and not 1 patient, 2 polyps. If different polyps were found in both the procedures for the same patient then it was considered as 1 patient, 2 polyps.

All together, 401 procedures were conducted during 6 months. 22 polyps and 4 colon cancers were found. These numbers are based on the diagnostic procedure and the biopsy results. Interesting fact is that the number of occurrences was more in the elderly people in the age group of 61-80. Figure 6 shows that the incidences are linearly increasing between 21-30 and 71-80 age groups. Majority of the diagnosed polyps were adenomatous (confirmed with biopsy results) (Figure 7). Many other authors also have reported the domination of adenomatous type in their study (Tony et al., 2007; Chu et al., 2011)

Current State of CTC in the World

In many developing countries, the differences of opinion and variations in the diagnosis results have led the CTC procedure not to gain wide popularity. As mentioned by Berrington et al. (2011). American Cancer Society recommends the CTC as screening tool whereas US preventive task force does not due to concerns about the harms (even though benefits are more than harms). Many hospitals in US (Cash, 2011) are using CTC as a routine diagnostic procedure for colon cancer screening. Some have even got the FDA approval for commercial use (iCADTM). As the western population show more number of colon cancers when compared to other countries, CTC has been accepted as a replacement diagnostic procedure of colonoscopy.

Feasibility of CTC in India

Though the CTC techniques has got acceptance from many diagnostic centers in United States and other countries, still it is not very much familiar and has not got wide acceptance in India for diagnosing colon cancer. The primary reason is, compared to western population, the colon cancer occurrence is less (but the numbers are increasing in the recent past years) and CTC as a diagnostic procedure is rare when compared to Colonoscopy. Secondary reasons are variations in the sensitivity and specificity decisions, differences of opinion (Mohandas, 2011), less number of experts to evaluate the ground truths, lack of references from Gastroenterology (we came to know this when discussed with few diagnostic centers) and the expensive diagnosis cost (Nair et al., 2013, have discussed about the cost of diagnosis, the difficulties in curing cancers due to late stage diagnosis and treatment of cancer in Indian hospitals). There has not been much statistics about usage of CTC in Indian hospitals, how many diagnostic centers have got this facility commissioned? How many of them are using for regular screening, are not known. By considering the advantage of this procedure where patient comfort is more important in aged population (our study and other papers also reveals that majority of the patients belongs to 50-90 years) and the advancement in the technology, with the common guidelines, protocols and sufficient training to the technicians to evaluate the ground truth, this can become a routine diagnostic procedure for colon cancer screening.

Discussion

In this paper, we have expressed our opinion from doctor's perspective about the feasibility of colon cancer diagnosis using the imaging technology, the necessity of new way of thinking in polyp classification, the standard protocol being followed and the comparison between two methods. The transition from conventional to the latest technology is essential if we look in to the increasing number of patients and the discomfort of colonoscopy. The Gastroenterologists has to come forward by referring the patients to this procedure. Certain technical limitations of CTC may be one of the reasons why this is not widely accepted in India. Down the line, due to the maturity of CTC software, we hope that CTC can rule the diagnostic centers for colon cancer screening in the future.

Acknowledgement

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We declare that we do not have any conflict of interest.

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