Colorectal cancer

Colorectal cancer is a malignant growth of the large bowel (Figure 1). Most colorectal cancers arise from benign adenomatous polyps; if these polyps can be detected at an early premalignant stage and removed, mortality from colon cancer can be significantly reduced.

The progression from a small - often polypoid - adenoma to a colorectal cancer takes a relatively long time. This gives a long window of opportunity for detection. Treatment becomes much simpler and effective when a cancer is detected early, and this is particularly true when a polyp is detected before it can even become cancer.

The large majority of colorectal polyps are thought not to develop into colorectal cancer. This concerns a large percentage of adenomas and is even more the case in hyperplastic polyps. The risk of a polyp becoming cancer increases with the size of the polyp: a large polyp (larger than 10 mm) has a 5-10% likelihood of becoming a cancer in 10 years time, while this likelihood is lower than 1% for small polyps (smaller than 5 mm) [1].

Epidemiology

Colorectal cancer is the third most common cancer worldwide and the fourth leading cause of cancer deaths worldwide. In the USA it occupies the second place: only lung cancer claims more lives. The worldwide prevalence of colorectal cancer exceeds 3.5 million and amounts to about 1 million [2] in the USA. It is estimated that there will be about 1 million new cases diagnosed in the USA in 2006. The number of deaths due to colorectal cancer in the same year is slightly below half a million.

Detection and treatment

Diagnosis

A variety of common and experimental screening and diagnostic tests are shown in Table 1.

Most guidelines recommend a combination of diagnostic methods. The American Cancer Society prefers an annual FOBT and a flexible sigmoidoscopy every five years since it is the most cost-effective screening strategy today [3]. Patients have generally been reluctant to undergo colorectal screening for reasons of modesty and the unpleasantness of the colon-cleansing process.

Treatment

Surgery (colectomy) is the primary treatment for colorectal cancer. Other therapies, such as radiation or chemotherapy, are an option depending on how far the cancer has penetrated into the wall of the bowel and whether it has spread to the lymph nodes or other parts of the body. In the premalignant stage, adenomatous polyps can be simply removed using an endoscope.

CT colonography

CT colonography is an imaging technique that simulates optical colonoscopy, enabling inspection of the inner colon wall to detect the presence of polyps or cancer. CT colonography

Clinical applications

Computer-aided detection of polyps and colorectal cancer

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Figure 1. Anatomy of the colon.
Table 1. Common screening and diagnostic procedures to detect colorectal cancer and polyps.

<table>
<thead>
<tr>
<th>class</th>
<th>technique</th>
<th>description</th>
<th>status</th>
</tr>
</thead>
<tbody>
<tr>
<td>digital rectal exam</td>
<td>fecal occult (hidden) blood test</td>
<td>non-invasive, cheap, easy blood test to perform, but sensitivity is low and specificity is medium</td>
<td>recommended</td>
</tr>
<tr>
<td>DNA test</td>
<td>analyzing DNA from stool samples and detecting mutations can indicate colorectal neoplasia. Still experimental, but expected high sensitivity and specificity</td>
<td>experimental</td>
<td></td>
</tr>
<tr>
<td>proteomics</td>
<td>detect proteins that may serve as biomarkers of early disease by analyzing a blood or feces specimen. No mature, validated proteomic technology currently available for the clinic.</td>
<td>experimental</td>
<td></td>
</tr>
<tr>
<td>endoscopy</td>
<td>sigmoidoscopy</td>
<td>examine the last part of the large bowel with a 60 cm flexible endoscope. High sensitivity and high specificity</td>
<td>recommended</td>
</tr>
<tr>
<td>endoscopy</td>
<td>colonoscopy</td>
<td>examine the entire large bowel with a 160 cm flexible endoscope. High sensitivity and high specificity. Considered the gold standard in the detection of colorectal cancer.</td>
<td>recommended</td>
</tr>
<tr>
<td>imaging</td>
<td>double contrast barium enema (X-ray)</td>
<td>medium sensitivity and specificity</td>
<td>recommended</td>
</tr>
<tr>
<td>imaging</td>
<td>virtual colonoscopy (CT/MR)</td>
<td></td>
<td>becoming accepted</td>
</tr>
<tr>
<td>imaging</td>
<td>molecular imaging</td>
<td></td>
<td>research</td>
</tr>
</tbody>
</table>

Preparation
Bowel preparation is required to remove residual stool and fluid within the colon, since this can mimic or obscure polyps and other masses. Cleansing is achieved by the ingestion of a cathartic or laxative that evacuates the colonic contents. The stool or fluid that still remain are often marked by administering an oral contrast agent (barium or iodine) to differentiate retained stool from soft tissue. This technique is referred to as fecal tagging. Since the colon is a very flexible structure it needs to be inflated before its inner wall can be inspected. Colon insufflation is performed manually or automatically with a rectal catheter using ambient air or CO₂. The latter has the advantage of fast resorption by the colon wall.
Acquisition
Image acquisition is done using a multidetector CT scanner (Figure 2). The patient is usually scanned in two positions: supine and prone. This double scanning is done to allow for proper distension of all bowel segments and is helpful as residual fluid and stool may move to the dependent side, while polyps remain attached to the wall.

Typical multislice CT acquisition parameters are: 120 kV, 20-250 mAs - depending on patient size and accepted radiation exposure - and between 1 and 2.5 mm slice thickness. Because of the large contrast between soft tissue and air the dose can be lowered significantly with respect to a standard abdominal scan without sacrificing polyp detection performance [4]. This will however reduce diagnostic accuracy for extracolonic findings.

Visualization
After the acquisition, the volumetric dataset can be visualized and inspected. The most commonly used display is the primary two-dimensional (2D) mode in which large axial images are displayed to detect abnormal polypoid shapes on the colon wall. Three-dimensional (3D) visualizations are added for problem solving and to better discriminate polyps from (complex) folds by providing additional morphological information. An overview image of the colon can serve as a navigation aid. An example of primary 2D viewing is shown in Figure 3. A small polyp in the sigmoid colon is quite obvious in the 3D visualization (supine scan).

In primary 3D reading endoluminal images are primarily used to detect polypoid shapes, while the original CT slices are used for problem solving. These endoluminal or “virtual endoscopy” images mimic the images seen on a real endoscope by providing internal perspective visualizations of the colon wall. Recent studies have shown the advantage of primary 3D viewing [5, 6]. In the unfolded display this 3D viewing is taken a step further to provide a complete view of the colon wall. This allows the user to immediately see polyps behind the folds, leading to significantly less inspection time [7] and better colon surface visibility [8] as compared to ante- and retrograde endoluminal displays. Figure 4 shows a primary 3D display mode with an “unfolded” display. The same small polyp is visible and demonstrates the power of the “unfolded” display to look behind the haustral folds.

It is important to note that 2D and 3D visualizations are complementary and should always be combined, whatever the primary reading method is.

Navigation
Navigation though the data is straightforward in a 2D display paradigm, since it only requires scrolling through the original axial CT slices. When navigating in a primary 3D display mode the user has to follow the tortuous centerline of the colon, which is very difficult to do manually. Automatic methods of finding the colon centerline are therefore used [9, 10]. This increases the speed of working and reduces user-dependency [11]. When navigating through the colon in supine position, the user should also verify whether the lesion is visible in prone position. By comparing the scans the user can often differentiate between fecal material and polyps, since fecal material is
often subject to gravity. Because this matching can be quite time-consuming, the user can be assisted by automatic matching of both scans, so that the user is guided to the corresponding position in the second scan [12]. This may reduce the inspection time and increases the confidence that a detected lesion is indeed a polyp. As an example the small polyp that was already shown in the supine scan in Figure 3 and Figure 4 is automatically matched with its prone counterpart in Figure 5.

Computer-Aided Detection

Role
The role of Computer-Aided Detection was summarized in an editorial by Ronald M. Summers in Radiology [13]:

Computer-aided detection (CAD) has been proposed as a solution to interpretation of the ever-expanding amount of radiologic information. CAD is best for two types of tasks: tedious tasks, such as looking for a "needle in a haystack" (e.g., a very small lung nodule at chest computed tomography [CT]), and tasks that involve a complex combination of multiple image features (e.g. breast mass detection at mammography). CAD is also helpful if there is high interobserver variability or a lack of trained observers.

The first type of “needle in a haystack” tasks described corresponds very well to lesion detection in CT colonography, where large amounts of data (two abdominal CT scans of 500-1300 slices each) should be read to detect polyps and cancer. Such lesions are easily missed, and computer assistance will be helpful in reducing these observational oversights (so called perceptive errors).

Reader paradigms
Most CAD is used in a second-reader paradigm, where the physicians analyze the study without the help of CAD, make a decision, and only then consult the CAD. In the first-reader paradigm, the CAD reads the case first, makes a preselection of interesting locations to inspect further and the physician then only looks at the results of the CAD to make a diagnosis. This can provide faster reading, but the CAD algorithm must be sufficiently reliable and of high sensitivity for detecting polyps. Current examples of CAD in radiology are all in the second-reader paradigm.

The second-reader paradigm will probably increase the performance of an expert, but will also increase the reading time because of the extra check of CAD results that has to be done. Some studies indicate that the sensitivity of an expert in detecting medium and large polyps can be improved by around 10-15% when using CAD as a second reader [14, 15, 16]. Care should be taken in these numbers since all CAD findings should first be judged by the human reader who should keep all true polyps and reject the over detections of the CAD algorithm.

Computer-aided detection can also play a role in narrowing the gap between less experienced readers and experts [17, 18]. This will be particularly useful when screening programs
emerge and large numbers of new readers begin to participate in screening programs. Again, the final diagnosis is made by the human reader who also determines the final performance.

**CAD techniques**
A CAD algorithm should look for blob-like structures on the colon wall and take into account a large variety of possible polyp shapes, locations, data quality and scan settings. The polyp CAD systems discussed in literature all follow a similar framework consisting of the following three steps:

- segmenting the colon wall
- identifying and segmenting candidate polyps
- reducing false positives based on feature values.

**Step 1 - Segmenting the colon wall**
Segmenting the colon wall reduces the search area in which polyps need to be detected. It reduces processing time and avoids finding lesions located outside the colon. Segmentation of the colon wall is typically done starting with voxel thresholding and seeded region growing in the colon lumen, followed by a step to segment the adjacent colon wall. An example is shown in Figure 6 where the segmented colon wall is displayed in red and thresholded colon lumen in green, both superimposed on the original CT image. The non-colon elements such as lungs, small bowel and air outside the patient are removed using anatomical knowledge.

Examples have been published by Peters [19], Yoshida [20], Paik[21], Kiss [22] and Summers [23]. Processing can be either volume based – using voxels as the unit to compute – or surface based using an explicit triangularized representation of the colon wall surface.

**Step 2 - Identifying and segmenting candidate polyps**
Polyp candidates will be detected within the limited search area. In this step it is necessary to find as many true polyps as possible. Any over detections will be removed in the next step.

Since polyps protrude inward from the colon wall and have a cap-like structure, they can be detected using shape features. Examples of such shape features are volumetric shape index [20, 25, 26, 27, 28], geometric features [22, 23], sphere-fitting, overlapping surface normals [21] and slope density functions [22]. All these shape-based detection methods assume that the polyp is sufficiently cap-like. Flat lesions will therefore be difficult to detect using these methods. Unfortunately this type of lesions is also challenging for a trained observer.

All individual voxels or surface elements that are detected are then accumulated in a polyp segmentation. This is typically done by doing a connected component region growing or using a polyp model [29]. An example of a segmented lesion is shown in Figure 7. The individual voxels of the voxel-based segmentation are shown as a red overlay.

**Step 3 - Reducing false positives based on feature values**
The last step serves to limit the amount of false positive detections. In general this is necessary due to the large number of detections in the previous step. A set of feature values can be calculated for all segmented candidate polyps. These features are more specific to polyps than the features used in the detection step. Based upon the calculated features a system has to differentiate polyps from non-polyps. The purpose is to eliminate false positives without eliminating true positives.

Feature values that are typically used in literature can be subdivided into three categories:

- size based features such as lesion size or colon wall thickness
- shape based features such as average gradient concentration, average shape index, gaussian and mean curvature, sphericity, and slope density functions
- gray value based features such as average CT value, variance of CT value, polyp densitometry, region density [30].

Techniques from statistical pattern recognition are used to differentiate polyps from non-polyps [31]. These can be based on training from labeled polyp and non-polyp examples, or trained from data that is not annotated (so-called unsupervised training).
Performance
The performance of a CAD algorithm is a trade-off between true detection (sensitivity) and over-detection (false positives). Every CAD algorithm is designed to detect as many real polyps as possible, but will always find other structures that are not polyps. Most CAD algorithms attach a score to every polyp candidate. Above a certain threshold value of the score the candidate will be classified as a polyp. This threshold is variable and often under user control. Since it influences the performance directly, it must be taken into account when presenting performance results.

The algorithm performance for different threshold values can be graphically shown in a Free-response Receiving Operating Curve (FROC) [32]. Sensitivity and corresponding number of false positive detections can be calculated and plotted for each threshold value of the polyp score, as shown in Figure 8.

Standalone performance
The performance of the CAD system being developed was validated using data from 184 patients containing 142 polyps. Not all patients had both prone and supine scans, and the images were acquired with different scanners and protocols. Only polyps larger than or equal to 6 mm were considered.

We compared the CAD findings with “ground truth” annotated polyps of 6 mm and larger. The polyps visible on CT were considered the reference standard. The FROC curve obtained when varying the score threshold is shown in Figure 8. Results are shown on a per-polyp basis, i.e. combining the two scans when available. When a polyp is found on one scan it is sufficient to be counted as a true detection.

Using this research CAD system we obtained a sensitivity of 88% while generating seven false positives per scan. A lower number of false positives is possible but at the expense of a decreased sensitivity. These results were generated on data that were not used in the development and training of the algorithm.

Performance of CAD as a second reader
The added value of CAD to the observer performance in a second reader setting was tested on a database of 49 patients (scanned in prone and supine positions) out of a comparative study of colonoscopy and CT colonography. All data was independently read by two experienced observers and the CAD algorithm. The results of this study have been published in A.H. de Vries et al. [14]. Results of both observers, CAD and the combination of observer and CAD as second reader are shown in Table 2. As a reference we used polyps identified on optical colonoscopy that were visible on CT in retrospect.

The use of CAD combined with the observer initial results can improve polyp detection by 16-18% for polyps ≥ 5 mm and 14-21% for polyps ≥ 10 mm. CAD presented on average four over-detections per case. Note that in the study the additional CAD results were not yet presented to the observer, therefore this represents the maximal possible improvement in sensitivity of the observer when aided by CAD.

Conclusion
In the past decade virtual colonoscopy has matured from the research department and gained increasing clinical use as a primary method for colon imaging to detect colorectal cancer and polyps. New developments in both data

<table>
<thead>
<tr>
<th>Observer I</th>
<th>Observer II</th>
<th>CAD</th>
<th>Observer I with CAD as 2nd reader</th>
<th>Observer II with CAD as 2nd reader</th>
<th>Additional value CAD Observ. I</th>
<th>Additional value CAD Observ. II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity polyps ≥ 5mm</td>
<td>30/38 (79%)</td>
<td>28/38 (74%)</td>
<td>31/38 (82%)</td>
<td>36/38 (95%)</td>
<td>36/38 (95%)</td>
<td>6/38 (16%)</td>
</tr>
<tr>
<td>Sensitivity polyps ≥ 10mm</td>
<td>17/21 (81%)</td>
<td>17/21 (81%)</td>
<td>19/21 (90%)</td>
<td>20/21 (95%)</td>
<td>20/21 (95%)</td>
<td>3/21 (14%)</td>
</tr>
</tbody>
</table>
acquisition and image post processing have improved results and reduced cost and will continue to do so. CT scanners have become better and faster allowing for high-resolution isotropic data within seconds. Advanced visualization and navigation tools and especially the introduction of CAD are expected to increase the detection performance of human readers, including less experienced experts, and eventually reduce reading time.

In the near future CAD systems will have to be extensively validated by multiple readers on different types of data with varying acquisition settings and patient preparations. Further research will be aimed at improving patient safety and comfort by reducing radiation dose and patient preparation. All these developments help in preparing CT Colonography for prime time: becoming the population survey method of choice for colon cancer screening.

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References


