Chapter 6. Colorectal Cancer

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Abstract
The incidence and mortality rates of colorectal cancer are rising in upper-middle-income countries. Moving toward organized screening will improve outcomes. We present new recommendations concerning feasible and cost-effective interventions in countries at four different resource levels, ranging from basic (low income) to maximal (high income).
Introduction
Adenocarcinoma of the colon and rectum (colorectal cancer, CRC) is the third most common cancer, the fourth most common cause of cancer death, and the second most common cancer in terms of the number of individuals living with cancer five years after diagnosis. An estimated 1,234,000 people are diagnosed with CRC annually; approximately 608,000 people die from CRC annually (IARC 2008); a total of 3,260,000 individuals are living with CRC.

CRC arises from the epithelial cells that line the large bowel, or colon and rectum. The adenoma-carcinoma sequence is the dominant molecular pathway of CRC carcinogenesis, in which genetic mutations accumulate that drive the progression from normal lining (mucosa), through the development of premalignant lesions or polyps (adenoma), to invasive cancer. The roles of other, more recently described molecular pathways, such as the serrated neoplasia pathway, are being clarified.

Randomized controlled trials have shown that screening is associated with a reduction in CRC mortality; in several high-income countries, organized population-based screening programs have been introduced beginning in 2006. Some screening tests detect cancer at an early stage when treatment is less arduous and more often results in cure. Other screening tests have the ability to detect adenomas as well as cancer. Screening provides the opportunity to identify and remove adenomas and thereby to prevent the development of the disease (Lieberman 2012).

In general, the burden of disease, as measured by incidence and mortality rate, tracks the World Bank grouping of countries into low-, lower-middle, upper-middle, and high-income: the lowest income countries have the lowest burden of disease. The ability to intervene to introduce screening and to offer access to high-quality treatment is a function of resource availability, which is associated with income level. The ability of countries to develop interventions increases with income, suggesting a progression in policy options as country income increases.

In our discussion of policy options, we use a slightly different typology than income for resource availability, following Anderson and others (Chapter 3 this volume). The resources available at a health facility can be described as basic, limited, enhanced, and maximal. The basic level corresponds approximately to the situation in low-income countries, the limited level to the situation in rural areas of both lower-middle and upper-middle countries, the enhanced level to the situation in urban areas of lower-middle and upper-middle countries, and the maximal level to the situation in high-income countries. We provide suggestions for appropriate screening and treatment strategies that correspond to these different resource levels for policy makers to consider.

Burden and Epidemiology of Colorectal Cancer
Colorectal cancer is the third most common cancer in men (663,000 cases, 10.0 percent of the total worldwide) and the second most common in women (571,000 cases, 9.4 percent of the total) worldwide. Almost 60 percent of the cases occur in high-income regions. Incidence rates vary 10-fold in both sexes worldwide: the highest rates are in Australia/New Zealand, Canada the United States, and Western Europe; the lowest rates are in sub-Saharan Africa (except southern Africa) and south Asia; the rates are intermediate in Latin America and the Caribbean.
Incidence rates are substantially higher in men than in women (the overall sex ratio of the age-standardized rates is 1.4:1) (IARC 2008). CRC incidence and mortality rates vary widely across regions (maps 6.1 and 6.2).

As observed for incidence, mortality rates in general are lower in women than in men. There is less variability in mortality rates worldwide (sixfold in men, fivefold in women), with the highest mortality rates in both sexes estimated in Eastern and Central Europe (20.1 per 100,000 for men and 12.2 per 100,000 for women), and the lowest in the sub-Saharan Africa and south Asia 3.5 and 2.7, respectively) (IARC, 2008).

Incidence rates have stabilized or are declining in many high-income countries. Initially, the stabilization or decline may have been due to declines in some risks, such as smoking; more recently, the change is likely to be due to increased screening. Figure 6.1 presents one of the longest consistent time-series available, for the state of Connecticut, United States, from 1940 to 2009. Incidence rates increased rapidly until the 1980s and then declined. The peak in the 1980s represents the introduction of screening (primarily with fecal occult blood tests) and is consistent with an initial increase in incidence with screening because of detection of early stage and preclinical disease. The decline post-1985 likely represents the impact of screening, as well as a decrease in risk factors such as smoking. The inverted U-shaped curve is more pronounced for men than for women. Incidence rates are now declining to the lowest level since the 1940s (Edwards and others 2010).
Figure 6.1 Colorectal Cancer Incidence in Connecticut, United States, 1940-2009

Note: Rates are age-adjusted to year 2000 U. S. standard population. Data from 1940−97 are from SEER*Stat Database: Incidence, Connecticut Historical, August 1999 Sub (1935−97); data from 1985−2009 are from the Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence-Based Mortality, SEER 9 Regs Research Data, November 2011 (National Cancer Institute 2012). Data from the two files are consistent for 1985 to 1997.

Trends for the United States as a whole are similar to those for Connecticut, but data are not available as far back as 1940 in a continuous series. A declining trend in mortality is also seen in some other high-income countries, including Australia, Denmark, and Japan (figures 6.2a, 6.2b). Incidence has not yet begun to decline in these three countries, likely because a “bulge” in reported cases occurs as CRC is detected at increasingly earlier stages. One would eventually expect to see incidence rates decline as in the United States once a steady-state is reached in screening.

The increase in incidence and mortality in middle-income countries, such as China, Costa Rica, the Philippines, and the Russian Federation (figures 6.2a, 6.2b), is occurring prior to the onset of organized screening. The Russian Federation is particularly noteworthy, since mortality rates are so much higher than elsewhere relative to incidence, reflecting late-stage cancer detection. Even in lower-middle-income countries such as India, incidence rates are increasing. Data from low-income countries are very sparse, due to very limited availability and coverage of cancer registries.
Figure 6.2a Trends in Incidence and Mortality of CRC in Men, Selected Countries, 1970–2010

NOTE: PRELIMINARY ONLY

Source: (Bray et al – to be updated)
Note: Rates are age standardized rate per 100,000 men.
Figure 6.2b Trends in Incidence and Mortality of CRC in Women, Selected Countries, 1970-2010

NOTE: PRELIMINARY ONLY

![Trends in Incidence and Mortality of CRC in Women, Selected Countries, 1970-2010](image)

*Source:* (Bray et al – to be updated)

*Note:* Rates are age standardized rate per 100,000 women.

<<Figure 6.3 here>>

**Incidence and Mortality by Income Group**

We classified the age-adjusted incidence and mortality rates for CRC by World Bank groupings of countries into low-income, lower-middle-income, upper-middle-income, and high-income (figure 6.3). The incidence and mortality rates increase with increasing income grouping.

We also derived the incidence/mortality ratio as an approximation of the specific mortality rate using the data from Figure 6.3. The incidence-to-mortality ratio roughly represents the percentage of people with CRC who die of this disease. Although the lowest-income quartile had the lowest incidence and mortality CRC rates, approximately 80 percent of those developing CRC die from the disease. This is in strong contrast to the experience in high-income countries, where the incidence and mortality rates are much higher than in the low-income countries but only 37 percent of those with CRC die of this cancer. The corresponding figures for the lower-middle-income and upper-middle-income countries are 72 percent and 54 percent, respectively, indicating that better survival is associated with higher country income.
Risk Factors

Age, gender, and family history are independent risk factors for CRC. In terms of modifiable risk factors, epidemiological evidence supports roles for diet, lifestyle, and medications (Chan and others 2010). In general, diets high in red and processed meats are associated with an increased risk. In addition, smoking, excessive alcohol use (greater than two drinks per day for men or one drink per day for women), obesity, and a sedentary lifestyle are associated with an increased risk. Calcium supplements are associated with a modest reduction in risk. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) and use of post-menopausal hormones among women are all associated with reductions in risk. The rise in CRC incidence rates in low- and middle-income countries described is largely attributed to the adoption of “western” diets and sedentary lifestyles.

Interventions

Screening

CRC Screening Tests

In 2010, the International Agency for Research on Cancer (IARC), an agency of the World Health Organization, published a landmark document, “European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis” (von Karsa, Segnan, and Patnick 2010a). The recommendations are based on a comprehensive and systematic review of the scientific evidence. The guidelines reported that there is good evidence for the guaiac fecal occult blood test (gFOBT); when coupled with colonoscopy for those who test positive, gFOBT is associated with an approximately 15 percent reduction in mortality with biennial screening in average risk populations. Further, the guidelines recommend that the screening interval should not exceed two years. The gFOBT indirectly detects blood in the stool that may be due to bleeding from CRC. A positive test is not specific for the presence of human blood, however; it may reflect blood from ingested animal meats, for example.

Strong evidence to support the fecal immunochemical test (FIT) has emerged since publication of the European Union Guidelines (Quintero and others 2012; van Rossum and others 2008). The FIT uses an antibody against human globin, the protein part of hemoglobin. A positive FIT is specific for human blood. Use of the FIT is associated with higher adherence/compliance rates than with use of gFOBTs. The FIT is also superior to the gFOBT in terms of detection rates and positive predictive values for adenomas and cancer (Quintero and others 2012; van Rossum and others 2008).

Large-scale randomized controlled trials (RCTs) of flexible sigmoidoscopy (FS), coupled with colonoscopy for those who test positive, have shown reductions in CRC incidence (Atkin and others 2010; Schoen and others 2012; and Segnan and others 2011) and mortality (Atkin and others 2010; Schoen and others 2012) over a 10-year period. Evidence from the National Polyp Study, as analyzed as an observational cohort study, indicates that colonoscopy with polypectomy is associated with a reduction in CRC incidence and mortality (Winawer and others 1993; Zauber and others 2012). RCTs evaluating colonoscopy are underway in Europe.
and the United States. Indirect evidence from RCTs of FS supports colonoscopy, although the magnitude of benefit compared with FS is unknown. Nonetheless, when a less invasive screening test (gFOBT, FIT, or FS) is used, colonoscopy is required to investigate those with a positive (abnormal) screen, and it is the final common pathway to establish a diagnosis. Hence, having adequate colonoscopy resources is a key aspect in implementing CRC screening. Colonoscopy is also recommended for surveillance in those with advanced adenomas (size ≥1.0 centimeters, with villous histology, or high-grade dysplasia) (Lieberman and others 2012).

**Organized Versus Opportunistic Screening**

Screening is not simply a test; it is a process. The IARC defines an *organized* screening program as one with the following elements:

- An explicit policy with specified age categories, screening method, and screening interval
- A defined target population
- A management team responsible for implementation
- A health-care team for decisions and care and followup of patients with positive screening tests
- A quality assurance structure for every step in the process
- A process for monitoring, evaluating, and identifying cancer occurrence in the population, which generally means having a cancer registry (IARC 2010).

In contrast, *opportunistic* screening is conducted outside of an organized screening program, often delivered through fee-for-service reimbursement of physicians. Compared with opportunistic screening, organized screening focuses much greater attention on the quality of the screening process, including followup of participants (Miles and others 2004). Thus, a key advantage of organized screening is that it provides greater protection against the possible harms of screening. These include overscreening (ie, screening at too frequent intervals), poor quality (e.g., resulting from lack of quality control in the performance of screening tests in the laboratory), and complications of screening (e.g., colonic perforation occurring during colonoscopy); and poor followup of those who test positive. The latter may occur, for example, when those with a positive (abnormal) FIT fail to undergo colonoscopy, which is the recommended next step in the screening process (Miles and others 2004).

**Organized CRC Screening Worldwide**

The International Colorectal Cancer Screening Network (ICRCSN) is an international consortium of organized initiatives delivering screening to their populations. The ICRCSN aims to improve quality assurance and program evaluation to maximize the benefits and to minimize the risks or harms associated with screening. In 2008, the ICRCSN conducted a survey of full or pilot programs that fulfill at least four of the IARC criteria for an organized screening program (Benson and others 2012). At that time, 43 organized screening programs were identified, of which 35 programs had been collecting data for at least 12 months and were eligible for the survey. Of the 35 programs from 24 countries, 26 were full programs and nine were pilot programs. The majority of the programs were in Europe, with few from North and South America and the Western Pacific. The majority (28) used the stool-based tests as their primary
screening test: 16 used the gFOBT, nine used the FIT, and three used both tests. Wide variations were observed in the ability of the jurisdictions to report on performance indicators, such as the participation rate, the gFOBT or FIT positivity rate, and the cancer detection rate.

**Performance of Organized Screening Programs**

In general, at least 10 years is required to plan, pilot, and implement an organized CRC screening program (von Karsa and others 2010). Given that it has been less than 10 years since the launch of organized CRC screening programs, it is too early to have published results available for mortality. However, a few programs have published early results for screening participation. Ontario’s province-wide, organized screening program, ColonCancerCheck, was launched in 2008. The program is based on the gFOBT for those at average risk and colonoscopy for those at increased risk (defined by a family history of one or more first-degree relatives with the disease). The target population—men and women ages 50 to 74 years—is 3.4 million. Prior to launch of the program, gFOBT participation in 2003–04 was 15 percent; in 2010, gFOBT participation was 27 percent.

Results from the phased implementation of the United Kingdom Bowel Cancer Screening Programme (BCSP) launched in 2006 showed gFOBT participation of 52 percent in 2008 after the first 1.08 million tests (Logan and others 2011); Finland’s phased implementation with individual level randomization to screening versus control based on age and municipality reported gFOBT participation of 70.8 percent in 2004–06 with a population of 52,998 in the screening arm (Malilia and others 2008). In 2008–09, France’s national screening program reported gFOBT participation of 34.3 percent in a target population of over 9.7 million people in 46 out of 99 districts (Institut de Veille Sanitaire 2012).

The lower results for gFOBT participation in Ontario are in part explained by differences in program design. In the BCSP and the Finnish program, kits are mailed to all potential participants, removing the need for a primary care provider visit, in contrast to the Ontario program. There are also differences in the context in which these programs were launched. In Europe, very limited or virtually no prior or ongoing opportunistic CRC screening was occurring prior to organized screening; in Ontario, there was the experience with opportunistic screening colonoscopy use as the initial screening test. Moss and others (2010, p. 75) point out that “[I]n a setting where opportunistic screening (for example colonoscopy) has been taking place for some time, the uptake and performance of an organized programme may differ markedly from those in a setting where no such screening has been taking place.” However, in Ontario, when use of FS and colonoscopy are taken into account, 53 percent of the target population was up-to-date with colorectal tests in 2010. This seems a more appropriate measure of the extent of CRC screening in Ontario.

Several high-income Asian countries have begun to implement organized screening: Japan, the Republic of Korea, and Singapore). Currently, organized, population-based screening programs do not exist in the majority of low- and middle-income countries. As middle-income countries develop organized cancer screening programs, CRC screening is under consideration. There are or have been pilot studies of CRC screening conducted in several upper-middle-income countries using gFOBT, including Chile (López-Köstner and others 2012), Thailand (Lampang province: http://www.iarc.fr/en/staffdirectory/displaystaff.php?id=10114), and Uruguay (Goss and others
Shanghai is embarking on a pilot study, as is Argentina (Manzur 2013). These pilot studies are important to lay the groundwork for national programs (Goss and others 2013).

Other countries offer opportunistic screening, largely restricted to the population covered by work-based health insurance. As a high-income economy, Taiwan, China, for example, offers free screening under the national health insurance program (Ng and Wong 2013); formal sector employees and/or government employees in much of Latin America are covered for cancer screening. However, most middle-income countries do not have organized screening programs.

**International Efforts to Advance CRC Screening: The IARC**

The vision of the Early Detection and Prevention (EDP) Section of IARC is to serve as the major global resource for high-quality scientific and evidence-based information on cancer prevention and early detection interventions. The EDP evaluates and reports on early detection and prevention interventions. The findings guide the development of public health policy, with a particular focus on cancer control in low and middle income countries. The EDP’s work catalyzes the implementation of CRC prevention and early detection programs that follow the principles of organized screening as outlined, to the extent feasible.

Experience from the European Union shows that a minimum period of 10 years is required to establish a population-based cancer screening program, with any impact taking even longer (Lee and others 2013). Examples of EDP work include the European Guidelines for Quality Assurance (QA) in Colorectal Cancer Screening and Diagnosis (von Karsa, Segnan, and Patnick 2010a). In addition, a network of reference and training centers (European School of Screening Management, ESSM) has been created that is developing and piloting training courses for planning, implementation, quality assurance, and evaluation of population-based cancer screening programs. The ESSM is intended to serve as a platform to connect and facilitate collaboration among relevant personnel from high- and low-income countries. Further, EDP provides scientific and technical support to low- and middle-income countries, such as Albania and Belarus, to assist them in moving forward with population-based cancer screening programs.

**Other International Organizations and Networks Promoting Screening**

The International Cancer Screening Network (ICSN) is a consortium of countries that have active population-based cancer screening programs and active efforts to evaluate and improve the processes and outcomes from cancer screening in practice. These programs can be national or subnational in scope, and established or pilot-based. Administered by the Applied Research Program of the United States National Cancer Institute, the consortium includes 33 countries and holds biennial meetings; specific activities are moved forward through working groups. Participation in the ICSN is open to any country that has initiated a population-based screening program.

The World Endoscopy Organization (WEO) is a federation of national digestive endoscopy societies; its mission includes the advancement of digestive endoscopy for the diagnosis and treatment of gastrointestinal diseases in underserved areas. The WEO has an active CRC Screening Committee that holds annual meetings in the Asia and Pacific region, Europe, and the United States, in conjunction with the major regional scientific meetings of gastroenterology.
societies. The meetings provide a forum to facilitate the presentation and discussion of new knowledge related to CRC screening and sharing of best practices across the world.

The International Digestive Cancer Alliance (IDCA) promotes the screening, early detection, and primary prevention of digestive cancers worldwide. The IDCA recommended staging the approach to screening, with respect to the choice of screening test, to the resources available in a given country (Winawer 2007).

**Diagnosis**
In high-income countries, persons with CRC can present in several ways.

- First, the cancer can be detected as a result of screening. When gFOBT, FIT, or FS is used as the initial screening test, colonoscopy is undertaken as a diagnostic test to evaluate those with an abnormal screening test. During the colonoscopy, polyps are removed, and masses or other suspicious lesions are either removed or biopsied to establish a pathological diagnosis.
- Second, the cancer can be detected when an individual undergoes colonoscopy to evaluate large bowel symptoms, such as rectal bleeding, anemia, or a change in bowel habits.
- Third, some individuals may present as an emergency, such as a large bowel obstruction, in which case the cancer may be diagnosed at surgery without prior diagnostic evaluation.

**Staging**
When the cancer is diagnosed in nonemergency presentations, staging and complete visualization of the colon and rectum with colonoscopy are undertaken. Complete colonoscopy is also undertaken for the purpose of detecting synchronous cancers (present in 3 to 5 percent of cases); if not done prior to definitive treatment, it should be done within 6 to 12 months. Barium enema, a radiological test, was used to diagnose CRC prior to the widespread availability of colonoscopy in high-income countries and may still be relevant in low-income settings.

Stage I refers to colorectal cancers that are confined to the surface of the bowel. Stage II means that the cancer has invaded through the muscle layer of the bowel wall. Stage III cancers involve the local lymph nodes. These stages are usually determined by examining the tumor pathologically after surgery.

Stage IV cancers have spread (metastasized) into other organs, most commonly the liver or lungs. In high-income countries, liver and chest imaging with CT is used to detect these distant metastases (Leufkens 2011). Chest x-ray and abdominal ultrasound are less expensive alternative tests that can be used in lower income settings.
Treatment

Surgery for Colon Cancer
The cornerstone of treatment is surgical resection. For early-stage cancers, surgery alone may cure the disease. For colon cancer, the preferred procedure is a hemicolectomy (resection of either the right or the left colon) with wide (i.e., > 5 cm) margins of normal colon. This procedure can typically be performed by a general surgeon. Where available, minimally invasive (laparoscopically-assisted) techniques have been found to produce similar long-term results compared to an open procedure, but with shorter hospital stays and increased speed of recovery. Achieving these benefits requires an experienced surgeon and specialized instruments, however; even in high-income countries, the cost-effectiveness of this approach has been questioned. A minimum of 12 lymph nodes in the surgical specimen is required for adequate staging and is associated with better outcomes than a lesser dissection. In patients presenting with stage IV colon cancer where cure is not possible, if the primary (that is, the site of the original cancer) is not associated with symptoms and the metastatic disease (that is, the sites where the disease has spread) is anticipated to be controlled with chemotherapy, the primary tumor does not necessarily need to be resected.

Surgery for Rectal Cancer
Surgery for rectal cancer is much more complex. High-volume, specialized surgeons and centers have been associated with better outcomes (less likely to need an ostomy bag, lower rates of local recurrence, better overall survival).

- Mid-to-upper rectal tumors can be resected with a low anterior resection, which leave the rectal sphincter intact, thereby avoiding colostomy.
- Lower lying tumors, that is, those within 2 to 3 centimeters of the anal sphincter or levator muscles, require an abdominal perineal resection and creation of a permanent stoma requiring colostomy.
- Total meso-rectal excision: the meticulous sharp dissection of perirectal tissues with removal of the primary tumour and lymph nodes all in one piece, has been shown to decrease local relapse rates.
- To avoid a stoma, transanal excision of small early stage distal tumors with good prognostic features can be considered. (Good is defined here as T1N0, < 3 cm, < 30% circumference, not poorly differentiated, no lymphovascular or perivascular invasion).

Radiation
The availability of radiation therapy is most relevant for cancers of the rectum, as local recurrence is much more common than in colon cancer due to the inability to obtain wide margins and the lack of a serosal barrier. Radiation therapy has been shown to improve local control for persons with stage II and III rectal cancer (Hoffe and others 2010). Evidence suggests that compared with postoperative radiation, preoperative radiation is associated with improved
surgical outcomes and disease-free survival (Sebag-Montefiore and others 2009). This decision depends on determining the stage of cancer preoperatively, which requires diagnostic services such as MRI or specialized endorectal ultrasound capability. Where these are not available, postoperative delivery of radiation and chemotherapy still provides important benefits.

Most radiotherapy protocols require concurrent chemotherapy with either infusional 5-fluorouracil or its oral equivalent, capecitabine for radiosensitization. An exception is “short course” radiotherapy consisting of five fractions of high-dose radiotherapy alone followed immediately by surgery. Long-term outcomes appear to be similar; accordingly, in settings with access to radiation but difficulty obtaining or delivering chemotherapy, or where travel requirements preclude the 5.5 weeks of daily long-course radiotherapy, short-course radiotherapy may be a preferred option (Içli and others 2010).

**Chemotherapy**

Evidence-based practice guidelines recommend six months of adjuvant chemotherapy following surgery for persons with stage III colon cancer (Benson and others 2000) and stages II and III rectal cancer. FOLFOX (FOLinic acid (leucovorin), Fluorouracil, OXaliplatin) is the preferred regimen. If chemoradiotherapy is given for rectal cancer, only four months of chemotherapy are required. In addition to being able to pay for the drugs, however, systemic chemotherapy always requires the ability to monitor blood counts for safety and may require venous access devices.

**Management of Metastatic Colorectal Cancer**

Metastatic colorectal cancer is treated the same way, regardless of whether it started in the colon or rectum. Although metastatic disease is generally incurable, it is increasingly recognized that, where possible, in a minority (10 to 20 percent) of patients, aggressive resection of liver and lung metastases may lead to cure about 20 to 30 percent of the time. Such surgery requires highly specialized training and centers, even in high-income countries. Alternatives to surgical resection, such as radiofrequency ablation and stereotactic body radiotherapy can provide long-term control in these situations, but surgical resection is preferred where feasible. Perioperative chemotherapy with FOLFOX has been shown to improve disease-free survival in this setting.

For the majority of patients with metastatic CRC, however, treatment is palliative, with an expected median survival with surgery alone of six to 12 months. For patients with good performance status combination chemotherapy regimens, such as FOLFOX and FOLFIRI, combined with antiangiogenic agents such as bevacizumab in the first- and second-line setting, have been shown to prolong overall survival to a median of one to two years. For patients whose tumors do not possess a mutation of the K-RAS gene, the Epidermal Growth Factor Receptor (EGFR) inhibitors cetuximab (in combination with irinotecan) and panitumumab have also modestly prolonged survival, as has the multikinase inhibitor regorafenib. K-RAS testing requires specialized pathology resources. The absolute improvement in overall survival provided by each of these drugs is in the range of only six to eight weeks, at a cost of several thousand dollars per month of treatment (Schrag 2004).
International Partnerships for CRC Cancer Care

As with CRC screening, international partnership arrangements can support diagnosis and treatment in low and middle income countries. The American Society of Clinical Oncology (ASCO) (http://www.asco.org), established an International Affairs Committee in 2007 with a goal of reducing disparities in cancer care and maximizing chances of survival through the global exchange of oncologic knowledge. The National Comprehensive Cancer Network (NCCN) (http://www.nccn.org) provides translations of many of its guidelines into other languages such as Chinese, Japanese, and Spanish, and has published local adaptations of guidelines, for example, for countries in the Middle East and North Africa. One NCCN institution, the MD Anderson Cancer Center at the University of Texas, lists 28 sister institutions as well as affiliates in at least 18 countries, 10 of these low- and middle-income countries (http://www.mdanderson.org/education-and-research/education-and-training/schools-and-programs/global-academic-programs/sister-institutions/index.html). Similar partnerships exist with other major cancer centers.

Cost-Effectiveness of CRC Screening and Treatment

A systematic search of the literature on CRC screening and treatment was undertaken using PubMed from 2004 to 2013 to identify relevant articles for low- and middle-income countries, as well as selected high-income Asian countries that can help serve as regional models (principally Hong Kong SAR, China; the Republic of Korea; Singapore; and Taiwan, China). The parameters were medical subject heading (MESH) terms (colorectal neoplasms OR colonic neoplasms OR rectal neoplasms OR colorectal cancer OR colon cancer OR rectal cancer) AND (colonoscopy OR sigmoidoscopy) AND multiple terms related to economic evaluation, cost, cost analysis, and cost-effectiveness.

This search was supplemented by a non-systematic search using the internet for certain low- and middle-income countries. For high-income countries, a fairly recent publication (Greenberg and others 2010) was used. This is a systematic review of the cost-effectiveness literature for various cancers, primarily for industrialized countries, and has the advantage that all the costs have been standardized to those of a common year.

Screening

Cost-effectiveness studies for CRC screening for the United States, a range of European countries, and for various high-income Asian countries/regions (Hong Kong SAR, China; the Republic of Korea; Singapore; and Taiwan, China) generally conclude that screening is cost-effective compared to no screening. The cost-effectiveness of several screening options can be considered. Guidelines generally recommend that screening should begin at age 50 (except for those with strong family history of CRC), but it can stop at different ages (such as 70, 75, 80, or 85), and tests can be undertaken in combination, such as FS combined with a sensitive gFOBT. The use of an efficiency frontier for each individual country can help to identify the most appropriate screening strategy given the budget constraints (see figure 6.6 for the United States, for example).
Studies in the United States

Cost-effectiveness studies for the United States generally have used one of a few large cancer microsimulation models. Comparative studies (for example, Pignone and others 2002, 2005) suggest that results are sensitive to the parameters used, particularly cost. The models also entail different assumptions about disease progression that also affect relative test performance (Pignone and others 2005). Since Pignone’s review (2002), three microsimulation models for CRC have become part of the United States National Cancer Institute consortium for Cancer Intervention and Surveillance Modeling Network (CISNET), a consortium of NCI-sponsored investigators that use statistical modeling to improve the understanding of cancer control interventions in prevention, screening, and treatment, and their effects on population trends in incidence and mortality. These models can be used to guide public health research and priorities. The three CISNET models for CRC are developed independently but are calibrated to the same studies, use the same population distributions and common assumptions for test sensitivity and specificity; they may vary some parameters of the underlying natural history of the adenoma-to-carcinoma sequence.

Figure 6.4 shows the results for cost-effectiveness analysis from one CISNET model, the MISCAN model (Microsimulation Screening Analysis model from Erasmus University Medical Center), for six CRC screening strategies beginning at age 50. Figure 6.4 is a modification of a larger analysis as given by Knudsen et al (2010), which assumed that subjects were 100 percent adherent to screening tests and subsequent diagnostic or treatment for those with positive tests or cancer diagnosis. Gains in life years are plotted on the y-axis and total costs are plotted on the x-axis. Each possible intervention strategy is represented by a point. The higher the point, the more effective is the screening strategy; the further to the right, the more expensive is the screening strategy (Marks 2002).

Cost effectiveness analysis does not select which strategy is economically preferred overall, but only which strategy is the most effective in terms of life-years gained for a given level of desired (or possible) expenditure. The six CRC screening strategies are ranked in order of the procedure, with the least life-years gained relative to no screening (Knudsen and others 2010). The strategies are then compared incrementally by ordering of life-years gained with respect to the life-years gained relative to the costs of each screening strategy. Those strategies that have the most life-years gained for a given level of cost are considered to be on the efficacy frontier. In this example, the lowest cost option of those options on the frontier is the less sensitive gFOBT (Hemoccult II). However, if budget available for testing increases, then a more sensitive gFOBT (Hemoccult Sensa) or FIT is the next best choice for cost relative to life-years gained with screening. The next choice would be for FS with some type of a FOBT. Colonoscopy lies just below the efficient frontier, with the rankings for life-years gained relative to costs similar to those of FS with gFOBT or FIT.

The rankings using two other models (the SimCRC model from University of Minnesota and Massachusetts General Hospital, and the CRC-SPIN model from Group Health Research Institute; see http://cisnet.cancer.gov/profiles/) were broadly similar, although the absolute cost per life-year gained differed between models. All of the strategies had average costs per life-year gained (compared to no screening) well within the threshold considered cost-effective in the United States (below US$ 50,000 per life-year gained. The lower sensitivity gFOBT (Hemoccult
II) is the least expensive CRC screening test of those considered, but it also delivers the fewest life-years gained. FS alone (without a FOBT) has life-years gained similar to that of the lower sensitivity gFOBT (Hemoccult II) test but has higher cost. The dotted line represents cost incurred for CRC without screening due to treatment of the disease in those diagnosed without screening.

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Figure 6.4. Discounted Costs and Discounted Life-Years Gained for Eight Colorectal Cancer Screening Strategies and the Efficient Frontier

Source: Zauber 2010, which uses the approach of Knudsen and others 2010.
Note: HII = Hemoccult II (FOBT); HS = Hemoccult Sensa (FOBT); FIT = Fecal Immunochemical Test; FS = flexible sigmoidoscopy; COL = colonoscopy. This analysis assumes 100 percent adherence with each strategy.

Taken together, the results from the U. S. analyses using simulation models suggest the following:

- Screening is cost-effective, and since compliance is not 100 percent, encouraging screening by any of a small group of strategies will save life-years.
- Where the total budget available is limited, the lowest cost testing strategy involves gFOBT.
The differences in cost-effectiveness of some strategies are modest and therefore susceptible to variation in assumptions. Knowledge of details of disease progression is limited (how, for example, untreated adenomas progress toward cancer; or how this progression varies by individual characteristics such as age, sex, and family history). Different assumptions regarding disease progression affect the results of the simulation model.

The evidence base for different screening methods continues to evolve. Flexible sigmoidoscopy and colonoscopy can be performed by appropriately trained nonphysicians, including nurses (Maule 1994; Wallace and others 1999). Newer generations of chemotherapy agents increase life expectancy modestly, but they considerably increase treatment costs; accordingly, most screening methods (although not colonoscopy by a narrow margin) remain cost-saving (Lansdorp-Vogelaar and others 2009).

**European Studies**

The European studies identified by Pignone and others’ (2002) systematic review (two studies of gFOBT and one of FS, for Denmark, Norway, and the United Kingdom) all supported the conclusion that screening is cost-effective (compared to no screening), and the cost per life-year saved was lower than in the United States due to the higher overall medical costs in the United States (Gyrd-Hansen and others 1998; Norum 1998; Whynes and others 1998).

**Studies of High-Income Economies in Asia**

Table 6.1 summarizes cost-effectiveness results for four studies of Asian economies, with the standardized model for the United States from Pignone and others (2005) for comparison. Observations from these results include the following:

- Screening in the four Asian economies is cost-effective, although the simpler models used in some studies may underestimate costs.
- Relative costs of procedures such as colonoscopy/FS and colonoscopy/gFOBT vary by country, which is likely to affect rankings.
- For the Republic of Korea, for example, it has been argued that colonoscopy reimbursement rates are artificially low and do not reflect cost (Park and others 2005). This is likely to affect the relative ranking of strategies for that country.

These four Asian economies do not all have published cost-effectiveness thresholds used for public decision making. However, using the WHO Commission on Health (WHO 2001), health interventions costing up to three times per capita GDP per disability-adjusted life-year saved should be considered. By this criterion, all the methods of CRC screening considered here (gFOBT, FS, colonoscopy) would be acceptable in these four economies.

Another study for Hong Kong SAR, China, for women only (Woo and others 2007) concluded that CRC screening had higher costs than for men per DALY (disability-adjusted life-year) saved and would not be cost-effective (CRC incidence rates in women are lower than in men).
Studies for Low- and Middle-Income Countries

Two global cost-effectiveness models report estimates of cost-effectiveness of interventions for various world regions. Ginsberg and others (2010) conclude that expanding treatment in low-income countries is a higher priority than screening. Ginsberg and others (2012) come to a similar conclusion when focusing on Southeast Asia and Sub-Saharan Africa, and they conclude that screening colonoscopy is cost-effective in Sub-Saharan Africa. However, the feasibility of implementing this approach in light of resource availability and health system infrastructure limitations was not addressed.

No other studies of cost-effectiveness of screening were identified for low- and middle-income countries from a systematic search. One other study was found from an unsystematic search using the internet for the Islamic Republic of Iran (Barouni and others 2012). From the results presented, it is possible to conclude that colonoscopy every 10 years is cost-effective (but not very cost-effective) in the Islamic Republic of Iran, but that gFOBT screening is not. There are problems with the calculation of the incremental cost-effectiveness ratios in this study, but enough information is given to permit the reader to recalculate them.

We anticipate that CRC screening would be equally cost-effective in urban areas of other upper-middle-income countries (for example, Argentina, the Russian Federation, and Uruguay) where incidence rates approach levels similar to high-income countries (30 or more per 100,000 in men, age-standardized rates). Lambert and others (2009) conclude that population screening for CRC is not the highest priority in most low- and middle-income countries, but that it deserves to be developed “in limited regions of large emerging countries where there is a shift to Western lifestyle and an aging population,” (p255) and they point to Mumbai; Hong Kong SAR, China; and Sao Paulo as examples.

Treatment

No literature on cost-effectiveness of treatment for CRC was found for low- and middle-income countries. Chapter 14 summarizes the evidence of cost-effectiveness of treatment from high-income countries, making the assumption that treatments that are “very cost-effective” in high-income countries are the first candidates for consideration in middle-income countries, while treatments which are “not cost-effective” in high-income countries are unlikely to be so in low- and middle-income countries. This is likely to be a better guide if relative costs and “standard care”— the alternative to which a particular treatment is compared—are reasonably similar.

Recommendations

Country income level does not have to dictate the availability of screening, diagnosis and treatment. Countries can help overcome resource constraints by accessing technical assistance from IARC and international networks, or from partnerships with cancer centers or cancer agencies in other countries. Local champions are essential for moving CRC screening and treatment forward as a priority.

Tables 6.2-6.7 summarize the authors’ recommendations on how screening, diagnosis, and treatment for CRC might be implemented in four different resource environments: low-income countries, rural areas of middle-income countries, urban areas of middle-income countries, and high-income countries. These correspond approximately to the basic, limited, enhanced, and
maximal resource environments for a similar exercise undertaken for breast cancer by the Global Breast Health Initiative and discussed in chapter 3. These recommendations provide initial guidance only and need to be validated by a larger international expert group.

**Low-Income Countries**

In low-income countries, the incidence of CRC is relatively low; other diseases—including other cancers—are a higher priority for screening and treatment. Laying the foundation for cancer screening and treatment is important. This process includes investing in public health and primary health care where screening is initiated, in the hospital systems, and in a cancer registry. Investments in health require not only medical personnel, but also good systems for monitoring and evaluation and quality control. Smaller countries lacking specific resources such as radiation facilities and specialized laboratories may need to rely on other countries in the same region.

Even in low-income countries, surgery for colon cancer at a good district hospital is possible to save lives and improve the quality of remaining life. Even if colonoscopy is unavailable as a diagnostic tool, barium enema may be an option. Radiation therapy is available only in limited volumes, if at all, and laboratory services required for chemotherapy are not likely to be available. Pain management for late-stage cancers is an ethical imperative, since ability to treat effectively is extremely limited.

**Middle-Income Countries**

In middle-income countries, there is an increase (more pronounced initially in urban areas) in both CRC incidence and the ability to intervene. Opportunistic screening increases for those covered by health insurance. Those countries that have already begun organized screening for other cancers (including Latin America and the Caribbean and upper-middle-income Asia: see chapter 13) may decide to implement screening initially as a pilot study in selected urban regions. Other regions that are beginning organized screening for other cancers may decide to incorporate screening as well, for example, by developing programs in the large Asian cities.

Priority countries are those where CRC incidence rates in men are close to 30 per 100,000 (for example, Poland, the Russian Federation, and other countries in Eastern Europe), in addition to those economies with existing pilot programs, such as Argentina; Hong Kong SAR, China; Taiwan, China; and Uruguay. Countries where CRC incidence rates in men approach 20 per 100,000 may need to begin planning (for example countries such as Jordan, Kazakhstan, and Malaysia). Data are not available using Globocan for individual cities, but similar CRC incidence thresholds could be used to consider when to begin to take action on CRC screening.

For CRC screening, the gFOBT is inexpensive; however, additional investments are needed to implement all the components of organized screening. Middle-income countries initiating organized CRC screening may be advised to use FIT rather than gFOBT, and doing so may become more attractive if a larger demand for such tests results in a decrease in the unit costs of the kits. Singapore and the Republic of Korea, which started their screening programs more recently than the European countries, have opted to use FIT.

Middle-income countries also have more resources for treatment and can extend this to a larger proportion of the population. As cancers are detected earlier, the goal of treatment shifts from...
palliation to cure. Middle-income countries can be active participants in international networks and local centers of excellence and can provide support for other countries in their region.

**High-Income Countries**

In high-income countries, cost-effectiveness considerations suggest that FIT, FS accompanied by a sensitive gFOBT or FIT, or colonoscopy, are options for screening. Adherence to screening varies; although each test has its advocates, the best test is the one that gets done, and done well. A wider range of treatment options are also feasible in these countries, which typically have higher cost-effectiveness thresholds.

**Conclusion**

Screening for, and treatment of, CRC is becoming a larger priority in an increasing number of countries as health resources are enhanced and changes in lifestyles and risk factors lead to a rise in incidence. Research on the cost-effectiveness of options in these countries is needed, ideally adapting currently available well-constructed models to these environments. Development of regional CRC screening guidelines would be helpful, and it is hoped that the resource-based recommendations outlined in this chapter may be useful in that process.
Table 6.1. Selected Costs and Cost-Effectiveness of Screening, and GNP and CRC Incidence for Four High-Income Asian Economies Compared to the United States

<table>
<thead>
<tr>
<th>Item cost or value (US$)</th>
<th>United States 2005&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Republic of Korea 2004&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Taiwan, China 2004&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Hong Kong SAR, China 2003&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Singapore 2004&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>gFOBT</td>
<td>10</td>
<td>1.91</td>
<td>0.6</td>
<td>4</td>
<td>5.6</td>
</tr>
<tr>
<td>Colonoscopy (diagnostic)</td>
<td>625</td>
<td>43.8</td>
<td>66.2</td>
<td>450</td>
<td>368.7</td>
</tr>
<tr>
<td>Colonoscopy (polyp removal)</td>
<td>900</td>
<td>—</td>
<td>—</td>
<td>830</td>
<td>446.9</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>200</td>
<td>22.2</td>
<td>35.3</td>
<td>244</td>
<td>134</td>
</tr>
<tr>
<td>Treat CRC, local</td>
<td>24,000</td>
<td>4,292</td>
<td>3,117.6</td>
<td>16,552</td>
<td>11,173.2</td>
</tr>
<tr>
<td>Treat CRC, regional</td>
<td>31,000</td>
<td>—</td>
<td>7,705.9</td>
<td>27,321</td>
<td>19,553</td>
</tr>
<tr>
<td>Treat CRC, distant</td>
<td>40,000</td>
<td>8,583</td>
<td>7,647.1</td>
<td>71,751</td>
<td>—</td>
</tr>
<tr>
<td>Colon perforation</td>
<td>24,000</td>
<td>2,500</td>
<td>1617.6</td>
<td>10,790</td>
<td>4863.7</td>
</tr>
<tr>
<td>Cost-effectiveness versus no screening US$/LYS</td>
<td>gFOBT 9,676, COL 21,000 median all 5, standardized assumptions</td>
<td>COL (5 years) 1142; others dominated</td>
<td>FOBT 70 SIG 594 COL 407</td>
<td>FOBT 6222 SIG 8044 COL 7211</td>
<td>FOBT 91 SIG 190 COL 225</td>
</tr>
<tr>
<td>Per capita GDP&lt;sup&gt;6&lt;/sup&gt; US$</td>
<td>46,760</td>
<td>19,028</td>
<td>17,461</td>
<td>31,426</td>
<td>34,466</td>
</tr>
<tr>
<td>CRC incidence&lt;sup&gt;7&lt;/sup&gt; /100,000 (age-standardized to world population)</td>
<td>34.1 men 25.0 women</td>
<td>46.9 men 25.6 women</td>
<td>40.2 men 29.7 women (Taiwan, China)</td>
<td>50.1 (crude, men and women combined)</td>
<td>34.1 men 25.0 women</td>
</tr>
</tbody>
</table>

<sup>1</sup>Pignone and others 2005
<sup>2</sup>Park and others 2005
<sup>3</sup>Wu and others 2006
<sup>4</sup>Tsoi and others 2008
<sup>5</sup>Wong and others 2004
<sup>6</sup>World Bank 2013, except Taiwan, China, which is http://www.indexmundi.com
<sup>7</sup>Bray and others 2013, except Hong Kong SAR, China, which is Tsoi and others 2008
Table 6.2 Proposed Strategies for Colorectal Cancer Screening and Diagnosis, by Country Resource Levels

<table>
<thead>
<tr>
<th>Level of Resources</th>
<th>General</th>
<th>Detection and Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Basic</strong></td>
<td>Build capacity: human, physical (for example, radiation capacity), cancer registry</td>
<td>Barium enema if colonoscopy not available; in emergency situations, may be diagnosed at surgery</td>
</tr>
<tr>
<td><strong>Limited</strong></td>
<td>Establish capacity for colonoscopy (needed for diagnosis)</td>
<td>Opportunistic screening for those covered by health insurance</td>
</tr>
<tr>
<td></td>
<td>Partnership arrangements with cancer centres to build capacity</td>
<td>Diagnostic colonoscopy (or barium enema) for those with symptoms</td>
</tr>
<tr>
<td></td>
<td>Establish national guidelines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Build quality assurance for lab testing</td>
<td></td>
</tr>
<tr>
<td><strong>Enhanced</strong></td>
<td>Join international screening networks</td>
<td>Establish organized screening in high-incidence cities/regions: use sensitive gFOBT (or FIT), or combined FS and sensitive gFOBT (or FIT)</td>
</tr>
<tr>
<td></td>
<td>Provide support to less-well-resourced countries in region</td>
<td></td>
</tr>
<tr>
<td><strong>Maximal</strong></td>
<td></td>
<td>National (or jurisdiction-wide) organized screening: use sensitive gFOBT (or FIT), or combined FS and sensitive gFOBT (or FIT) starting at age 50 in average risk; in cases of increased risk because of family history, consider colonoscopy</td>
</tr>
</tbody>
</table>

*Note:* Since no international consensus-setting exercise has occurred, this categorization represents a basis for further discussion and work, and not a definitive analysis. Basic resource level is assumed to correspond to low-income countries (limited or no access to radiation, and likely insufficient support for blood chemistry to undertake chemotherapy). Limited resource level corresponds to rural areas of middle-income countries, where distances to radiation and chemotherapy resources make use in treatment difficult. In urban areas of middle-income countries (enhanced level), radiation therapy is available, as are many chemotherapy drugs no longer under patent. The maximal level corresponds to resource availability in high-income countries. See [chapter 14](#) for more detailed discussion of resource levels.
Table 6.3 Treatment Resource Allocation: Stage I and II Colon Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation</td>
</tr>
<tr>
<td><strong>Basic</strong></td>
<td>Hemicolecotomy and regional lymph node dissection</td>
<td></td>
</tr>
<tr>
<td><strong>Limited</strong></td>
<td>Hemicolecotomy and regional lymph node dissection</td>
<td></td>
</tr>
<tr>
<td><strong>Enhanced</strong></td>
<td>Hemicolecotomy with en bloc removal of at least 12 regional lymph nodes</td>
<td></td>
</tr>
</tbody>
</table>
| **Maximal**        | Polypectomy for selected stage I cancers with good prognostic features\(^1\)  
Hemicolecotomy with en bloc removal of at least 12 regional lymph nodes. May be laparoscopically-assisted | Consider adjuvant 5-fluorouracil or capecitabine in high-risk stage II\(^2\) | |

**Note:**

1 Edunculated polyp that is not high grade, not removed piecemeal, not invading the stalk, clear margins, no lymphovascular or perineural invasion.

2 Obstruction, perforation, T4, lymphovascular or perineural invasion, less than 12 lymph nodes removed.

Since no international consensus-setting exercise has occurred, this categorization represents a basis for further discussion and work, and not a definitive analysis. Basic resource level is assumed to correspond to low-income countries (limited or no access to radiation, and likely insufficient support for blood chemistry to undertake chemotherapy). Limited resource level corresponds to rural areas of middle-income countries, where distances to radiation and chemotherapy resources make use in treatment difficult. In urban areas of middle-income countries (enhanced level), radiation therapy is available, as are many chemotherapy drugs no longer under patent. The maximal level corresponds to resource availability in high-income countries. See chapter 14 for more detailed discussion of resource levels. The recommendations
are cumulative: any intervention which is feasible at a lower resource level is also an option in facilities with higher resource levels. Blank cells indicate that no additional options of a particular type of treatment are available at the particular resource level considered.

Table 6.4 Treatment Resource Allocation: Stage I Rectal Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation</td>
</tr>
<tr>
<td>Basic</td>
<td>Abdominal-perineal resection or low-anterior resection for proximal tumors, with lymph node dissection</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Abdominal-perineal resection or low-anterior resection for proximal tumors, with lymph node dissection</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Total mesorectal excision. Trans-anal excision possible in some low-lying T1N0 tumors with good prognostic features&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Total mesorectal excision. Trans-anal excision possible in some low-lying T1N0 tumors with good prognostic features&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

Note:

<sup>1</sup> T1N0, < 3 cm, < 30% circumference, not poorly differentiated, no lymphovascular or perivascular invasion.

Since no international consensus-setting exercise has occurred, this categorization represents a basis for further discussion and work, and not a definitive analysis. Basic resource level is assumed to correspond to low-income countries (limited or no access to radiation, and likely insufficient support for blood chemistry to undertake chemotherapy). Limited resource level corresponds to rural areas of middle-income countries, where distances to radiation and chemotherapy resources make use in treatment difficult. In urban areas of middle-income countries (enhanced level), radiation therapy is available, as are many chemotherapy drugs no longer under patent. The maximal level corresponds to resource availability in high-income countries. See chapter 14 for more detailed discussion of resource levels. The recommendations are cumulative: any intervention which is feasible at a lower resource level is also an option in facilities with higher resource levels. Blank cells indicate that no additional options of a particular type of treatment are available at the particular resource level considered.
Table 6.5 Treatment Resource Allocation: Stage III Colon Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation</td>
</tr>
<tr>
<td>Basic</td>
<td>Hemicolecotomy and regional lymph node dissection</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Hemicolecotomy and regional lymph node dissection</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Hemicolecotomy with en bloc removal of at least 12 regional lymph nodes</td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Hemicolecotomy with en bloc removal of at least 12 regional lymph nodes. May be laparoscopically-assisted</td>
<td></td>
</tr>
</tbody>
</table>

Note:

\(^1\) FOLinic acid (leucovorin), Fluorouracil, OXaliplatin

Since no international consensus-setting exercise has occurred, this categorization represents a basis for further discussion and work, and not a definitive analysis. Basic resource level is assumed to correspond to low-income countries (limited or no access to radiation, and likely insufficient support for blood chemistry to undertake chemotherapy). Limited resource level corresponds to rural areas of middle-income countries, where distances to radiation and chemotherapy resources make use in treatment difficult. In urban areas of middle-income countries (enhanced level), radiation therapy is available, as are many chemotherapy drugs no longer under patent. The maximal level corresponds to resource availability in high-income countries. See chapter 14 for more detailed discussion of resource levels. The recommendations are cumulative: any intervention which is feasible at a lower resource level is also an option in facilities with higher resource levels. Blank cells indicate that no additional options of a particular type of treatment are available at the particular resource level considered.
Table 6.6 Treatment Resource Allocation: Stages II and III Rectal Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation</td>
</tr>
<tr>
<td>Basic</td>
<td>Abdominal-perineal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>resection, or low-anterior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>resection for proximal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tumors, with lymph node</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dissection</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Abdominal-perineal</td>
<td>Preoperative short-</td>
</tr>
<tr>
<td></td>
<td>resection or low-anterior</td>
<td>course radiotherapy</td>
</tr>
<tr>
<td></td>
<td>resection for proximal</td>
<td>alone</td>
</tr>
<tr>
<td></td>
<td>tumors, with lymph node</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dissection</td>
<td></td>
</tr>
<tr>
<td>Enhanced</td>
<td>Total mesorectal excision</td>
<td>Preoperative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>chemo-radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal</td>
<td>Total mesorectal</td>
<td>Preoperative</td>
</tr>
<tr>
<td></td>
<td>excision</td>
<td>chemo-radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Authors.

Note:
\(^1\) FOLinic acid (leucovorin), Fluorouracil, OXaliplatin.

Since no international consensus-setting exercise has occurred, this categorization represents a basis for further discussion and work, and not a definitive analysis. Basic resource level is assumed to correspond to low-income countries (limited or no access to radiation, and likely insufficient support for blood chemistry to undertake chemotherapy). Limited resource level corresponds to rural areas of middle-income countries, where distances to radiation and chemotherapy resources make use in treatment difficult. In urban areas of middle-income countries (enhanced level), radiation therapy is available, as are many chemotherapy drugs no longer under patent. The maximal level corresponds to resource availability in high-income countries. See chapter 14 for more detailed discussion of resource levels. The recommendations are cumulative: any intervention which is feasible at a lower resource level is also an option in facilities with higher resource levels. Blank cells indicate that no additional options of a particular type of treatment are available at the particular resource level considered.
Table 6.7 Treatment Resource Allocation: Stage IV Colorectal Cancer

<table>
<thead>
<tr>
<th>Level of resources</th>
<th>Local-regional treatment</th>
<th>Systemic treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Surgery</td>
<td>Radiation</td>
</tr>
<tr>
<td>Basic</td>
<td>If symptomatic, palliative resection of the primary</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>If symptomatic, palliative resection of the primary</td>
<td>Palliative 5-fluorouracil</td>
</tr>
<tr>
<td>Enhanced</td>
<td>If symptomatic, palliative resection of the primary. Consider aggressive resection of liver and lung metastases for cure</td>
<td>For palliation if necessary</td>
</tr>
<tr>
<td>Maximal</td>
<td>If symptomatic, palliative resection of the primary. Consider aggressive resection of liver and lung metastases for cure</td>
<td>For palliation if necessary. Consider pseudoadjuvant radiation to the pelvis if resecting rectal cancer metastases for cure</td>
</tr>
</tbody>
</table>

Source: Authors.

Note:
¹ FOLinic acid (leucovorin), Fluorouracil, OXaliplatin.
² FOLinic acid (leucovorin), Fluorouracil, IRInotecan.

Since no international consensus-setting exercise has occurred, this categorization represents a basis for further discussion and work, and not a definitive analysis. Basic resource level is assumed to correspond to low-income countries (limited or no access to radiation, and likely insufficient support for blood chemistry to undertake chemotherapy). Limited resource level corresponds to rural areas of middle-income countries, where distances to radiation and chemotherapy resources make use in treatment difficult. In urban areas of middle-income countries (enhanced level), radiation therapy is available, as are many chemotherapy drugs no longer under patent. The maximal level corresponds to resource availability in high-income countries. See chapter 14 for more detailed discussion of resource levels. The recommendations are cumulative: any intervention which is feasible at a lower resource level is also an option in facilities with higher resource levels. Blank cells indicate that no additional options of a particular type of treatment are available at the particular resource level considered.
References


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Map 6.1 Global Colorectal Cancer Incidence in Men, 2008

Note: ASR = age-standardized rate per 100,000 men

Source: Bray 2013 from GLOBOCAN 2008 - TO BE UPDATED

Note: ASR = age-standardized rate per 100,000 women

Source: Bray 2013 from GLOBOCAN 2008 - TO BE UPDATED
Figure 6.3. Global Weighted Mean Age-Standardized Incidence and Mortality Rates per 100,000 Population by Income Level and Sex, 2008

Age-Standardized CRC Incidence and Mortality Rates, per 100,000

Source: From GLOBOCAN 2008