Although anal cancer has the lowest incidence rate among cancers of the lower gastrointestinal tract, statistics show that its incidence is rising. Human papillomavirus is a leading factor in the etiology of anal cancer. Other contributing factors are receptive anal intercourse, having multiple sexual partners, cigarette smoking, and HIV. The easiest and simplest method of detection is a digital rectal examination. Endoscopy, biopsy, and various imaging techniques also are used in diagnosis. Treatment for anal cancer depends on the stage at diagnosis and can include chemotherapy, radiation therapy, surgery, or a combination of treatments.

After completing this article, the reader should be able to:
- Discuss anal anatomy, physiology, and histology.
- Distinguish between anal cancer and perianal skin cancer.
- Describe risk factors for anal cancer and ways to prevent it.
- List common signs and symptoms of the disease.
- Compare diagnostic methods used for suspected anal cancer, including endoscopy, biopsy, and imaging techniques.
- Explain how anal cancer is staged.
- Specify the preferred treatments for anal cancer at each stage of the disease.
- Summarize recent clinical trials investigating new approaches to treatment.
- Outline the recommended follow-up care for anal cancer patients.

The death of pop culture icon Farrah Fawcett in 2009 helped bring anal cancer to the public light. Fawcett’s determination to publicize the disease led to Farrah’s Story, a documentary that chronicled her journey up to the point when she died from anal cancer. The film, which Fawcett narrated and coproduced, was nominated for an Emmy Award in the category of outstanding nonfiction special.

Anal cancer is responsible for only 4% of all lower gastrointestinal (GI) tract cancers and is far less common than cancers of the colon or rectum. In fact, estimates for 2014 from the American Cancer Society indicate approximately 7210 new cases of anal cancer and 950 deaths from the disease. According to the Surveillance, Epidemiology, and End Results program, new anal cancer cases rose at an average rate of 2.2% annually during the past 10 years, and the death rate increased an average of 1.7% per year during the same period.

Etiology and Epidemiology
Anal cancer is rare, accounting for only 0.4% of all new cancer cases. It is found mainly in adults, with 60 years as the average age at diagnosis. According to the Surveillance, Epidemiology, and End Results program, the number of new anal cancer cases is highest among white women, at 2.2 cases per 100 000; in the male population, black men have the highest incidence at 2.0 cases per 100 000.

The cause of anal cancer is unknown. However, men or women who have receptive anal intercourse, human papillomavirus (HPV) or HIV infection, and those with a history of...
multiple sexual partners carry a much greater risk. Other factors associated with anal cancer are genital and anal warts, genital infections, and current cigarette smoking. The rate of anal cancer is lower in people who limit their number of sexual partners, and who are not infected with any sexually transmitted diseases, and do not engage in receptive anal intercourse.

**Anal Anatomy and Physiology**

The anus is the most distal part of the large intestine. It connects the lowest region of the large intestine—the rectum—with the outside of the body. The anus allows unabsorbed food to pass out of the body as a bowel movement. The anal canal measures approximately 3 cm to 4 cm (approximately 1-2 in) long. It is directed inferiorly and posteriorly. Anatomically, the proximal region of the anal canal begins where the puborectal portion of the levator ani muscle, which makes up the pelvic floor, merges with the external anal sphincter muscle, which forms the walls of the anus.

The external anal sphincter muscles are circular muscles that help to hold the anus closed. The dentate, or pectinate, line that separates the stratified squamous epithelium distally from the rectum’s columnar epithelium proximally divides the anus. Just proximal to the dentate line are longitudinal anal folds called columns of Morgagni, an inward folding of the mucous membranes and some muscular tissue laterally. On these columns are anal papillae, raised tooth like projections that jut proximally toward the rectum. Situated between the columns of Morgagni are anal sinuses, also referred to as sinuses of Morgagni or Morgagni Crypts. The anal sinuses are tiny crevices that discharge anal mucus. They are bound together by anal valves, also called transverse or semilunar valves. The anal cushion is a mass of subepithelial tissue located in the left lateral, right posterior, and right anterior quadrants of the anal canal. This tissue seals the anal canal and maintains continence. The anal verge joins the anal canal and perianal skin (see Figure 1).

**Blood Supply and Lymphatic System**

The superior rectal artery supplies blood to the anal canal above the dentate line, while the inferior rectal arteries supply the anal canal below the dentate line. The internal rectal plexus drains into the superior rectal vein above the dentate line, and the internal rectal plexus drains to the inferior rectal veins. The middle rectal arteries and veins provide anastomoses between their respective superior and inferior rectal vessels.
Lymph drainage also differs above and below the dentate line. Above the dentate line, lymph drains into the internal iliac nodes. Inferior to the dentate line, lymph drains into the superficial inguinal nodes, which the lymph then drains to the deep inguinal nodes. Next, lymphatic fluid drains from the deep inguinal and the internal iliac nodes to the external iliac nodes. The internal iliac nodes can also drain directly to the common iliac nodes. From there the lymphatic fluid from the external and internal iliac nodes drains to the common iliac nodes, which then passes to the lumbar nodes, or para-aortic nodes, followed by drainage to the lumbar trunk. The lumbar trunk then drains into the cisterna chyli, if present, and to the thoracic duct. The lymphatic fluid from the thoracic duct enters the circulatory system at the left subclavian vein (see Figure 2).

The Nervous System

The nervous system of the rectum and anal canal includes sympathetic and parasympathetic nerves. The sympathetic nerves extending from the levels of the 11th thoracic through the 2nd lumbar vertebrae form the hypogastric nerve, which assists in relaxing the rectum and anal canal. Parasympathetic nerves from sacral levels 2, 3, and 4 of the spinal cord form the pelvis splanchnic nerve that stimulates the rectum and anus to contract, allowing bowel movements. Conversely, the internal anal sphincter is controlled by parasympathetic nerves from sacral levels 2, 3, and 4 of the spinal column, which cause the internal anal sphincter to relax while sympathetic nerves from the T11 to L2 levels of the spinal cord cause the internal anal sphincter to tighten. Internal anal sphincters cannot be controlled consciously.

Unlike the involuntary control of the internal anal sphincter, the external anal sphincter is controlled voluntarily and can be relaxed or contracted at will. The pudendal nerve, which controls the external anal sphincter, is a conjoining of spinal nerves S2 through S4 (see Figure 3).

Histology of the Anus

The anus, which is extraperitoneal, consists of 3 main histological tissue types: glandular, which is found proximally; transitional, which is located intermediate; and keratinized or nonkeratinized squamous, which is located distally. Cytokeratin is an epithelial-based protein used to help diagnose carcinomas in different areas of the body. The proteins have expression patterns that help pathologists localize tumors. The expression for anal and transitional zone epithelium patterns—cytokeratin 7 positive (CK7+) and cytokeratin 20 negative (CK20−)—differ from colorectal carcinoma. For colorectal carcinoma, the cytokeratin expression pattern is CK7− and CK20+.

Proximally, the colorectal region lies from the top of the puborectalis muscle to the dentate line. This region consists of glandular and transitional mucosa and measures...
that joins with the rectal mucosa. From there, the squamous mucosa merges with the perianal skin at the anal margin, or verge. In this region keratin is present, as well as hair and apocrine glands.  

Squamous cell carcinoma comprises approximately 80% of all anal cancers. Of these, 25% have basaloid characteristics and must be differentiated from basaloid cancers of the perianal skin. Basaloid cancers, also known as cloacogenic or junctional cancers, are alternative squamous cell carcinomas that derive from the epithelial layer of the transitional zone (see Figure 4).  

The rarest histology, adenocarcinoma, arises from the glandular epithelium within the anal canal. This type of carcinoma shares similar traits with rectal adenocarcinomas and is treated in a similar fashion; that is, it is treated as if it were a rectal cancer.  

**Benign Anal Tumors**  
The anal canal is susceptible to many kinds of tumor growths. Not all of these tumors are malignant, although some eventually develop into a cancer and are known as precancerous conditions. The most frequently occurring benign anal tumor is the polyp, a small, bumpy growth that develops in the mucous membrane of the anal canal. There are several types of polyps that arise in the anus, and they vary in their etiology and location. Inflammatory polyps develop in tender areas and are caused by injury or infection. Lymphoid polyps are due to an excess of lymph tissue. When anal papillae, small mucosal folds at the level of the dentate line, become swollen and form benign growths, they are called fibroepithelial polyps. Other types of benign lesions are skin tags and warts. Skin tags are small, pendulous growths made up
Romanofski

Dysplasia that occurs in the anal canal is also called anal intraepithelial neoplasia or a squamous intraepithelial lesion. These dysplasias can be divided into 2 groups: low grade and high grade, depending on histological

Table 1

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Origination</th>
</tr>
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<tbody>
<tr>
<td>Leiomyoma</td>
<td>Smooth muscle cells</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Blood vessel linings</td>
</tr>
<tr>
<td>Lipoma</td>
<td>Fat cells</td>
</tr>
<tr>
<td>Schwannoma</td>
<td>Cells that cover anal nerves</td>
</tr>
<tr>
<td>Granular cell tumor</td>
<td>Nerve cells</td>
</tr>
<tr>
<td>Adnexal tumor</td>
<td>Hair follicles or sweat glands in the perianal region</td>
</tr>
</tbody>
</table>

of connective tissue that arise in the anal canal. Skin tags are covered by squamous cells and often are mistaken for hemorrhoids. Condylomas are benign warty growths that appear below the dentate line in the distal part of the anal canal and outside of the anal canal. HPV is responsible for condylomas appearing above the dentate line, but they are unlikely to develop into anal cancer. Table 1 lists other types of benign anal tumors and where they originate.

Precancerous Anal Conditions

Changes in anal mucosa do not usually pose a cancerous threat; however, some changes can develop into anal cancer. These precancerous conditions are called dysplasia. Some condylomas, for example, contain areas of dysplasia that are precancerous.

Figure 4. Staining of anal carcinoma. A. Hematoxylin and eosin stain, low (2×) magnification. B. Hematoxylin and eosin stain, medium (10×) magnification. C. A p16 histoimmunological stain at low magnification (2×). P16 is a tumor suppressor gene product found in cases with high likelihoods of the human papillomavirus being present. Slides courtesy of Madalina Tuluc, MD, and Voichita Barad, MD, of Thomas Jefferson University Hospital, Philadelphia, PA.
appearance. Low-grade anal intraepithelial neoplasia looks very similar to normal cells; the high-grade type has a much more abnormal appearance. Low-grade anal intraepithelial neoplasia seldom develops into anal cancer and often resolves on its own.\textsuperscript{20} High-grade anal intraepithelial neoplasia necessitates much closer observation and usually requires some type of treatment. Left untreated, high-grade anal intraepithelial neoplasia is likely to develop into anal cancer.\textsuperscript{20}

**Anal Cancer vs Perianal Skin Cancer**

In determining whether a malignancy is anal cancer, the location is critical and can be problematic. There is no easily identifiable landmark distinguishing the anus from the rectum. Further complicating this issue is a vastly changing histologic appearance.

For staging, cancers are classified as rectal if their midpoint is proximally located 2 cm or more to the dentate line. If the tumor's midpoint lies 2 cm distal or less from the dentate line, it is considered an anal cancer.\textsuperscript{7}

Clinically speaking, difficulties arise when trying to discern between tumors of the anal canal and those that arise in the anal margin or perianal skin. Any tumor that arises either in the anal canal or the perianal margin and is histologically classified as a squamous cell carcinoma is treated as an anal cancer. Tumors that arise at or distal to the squamous mucocutaneous junction, other than melanomas, are termed perianal margin skin cancers and are staged, classified, and treated as skin cancers.\textsuperscript{7}

**Perianal Skin Cancers**

Most anal cancers are squamous cell carcinomas; these cancers originate from the squamous cells on the surface of the anal canal and grow deeper into the layers of the lining. In contrast, Bowen disease is a squamous cell carcinoma in situ that can occur at the perianal skin margin, but this cancer predominantly presents in skin regions that receive long-term sun exposure. Squamous cell carcinomas of the perianal skin are treated much like squamous cell carcinomas on other areas of the skin.\textsuperscript{20}

Although most anal cancers originate from squamous cells, a small number develop in the cells that line the anal canal or the glands lying just under the mucosa. These cancers are called adenocarcinomas. Paget disease is an intraepithelial adenocarcinoma that can present in one of 2 ways: as a primary malignancy of the skin in which the tumors show signs of sweat gland differentiation or as a lesion in which there is involvement because of malignancy or metastasis from an underlying adenocarcinoma of the rectum or perianal glands.\textsuperscript{20}

Melanomas are cancers that develop in the skin's pigment cells, or melanocytes. In the anal area, melanomas can develop in the skin or anal lining. These melanomas can be harmful because they often go unnoticed in the anal area, unlike other areas of the skin where the lesions can be noticed and effectively treated.\textsuperscript{20}

**Risk Factors for Anal Cancer**

In the late 1950s and early 1960s, it was believed that anal cancer developed from susceptibility associated with benign anal and perianal conditions, including hemorrhoids, fissures, and fistulae.\textsuperscript{21} Irritable bowel syndrome also was thought to be a precursor to anal cancer, but a study in Denmark disproved that theory, as did other studies involving hemorrhoids, fissures, and fistulae.\textsuperscript{21-23}

Anal cancer is uncommon, yet its incidence is increasing annually both in the United States and abroad. An increasing risk factor is HIV infection. In the early 1980s, AIDS was classified as an epidemic. At the same time, the number of anal cancer cases was estimated to be as high as 37 per 100 000 in gay men.\textsuperscript{24} Furthermore, the rate of incidence among men who were positive for HIV was nearly double that of men negative for HIV who had same-sex relationships.\textsuperscript{24}

HPV infection is the most commonly diagnosed sexually transmitted disease in the United States, and it partially supports a link between type of sexual activity and anal cancer.\textsuperscript{25} Studies show a close association between the contagions of HPV and premalignant lesions of the reproductive organs and the anorectal region.\textsuperscript{25} Although there are many types of HPV, including subtypes found in the anogenital region, only a small number have been linked to anal cancer. HPV-16 is the most frequent subtype that has been positively associated with anal malignancies.\textsuperscript{23}

The relationship among HIV, HPV, and anal cancer was established by a study that cited an increased risk of developing anal cancer in patients who were HIV positive compared with those who were HIV negative.\textsuperscript{23} In another meta-analysis of 53 studies, the presence of HPV and anal cancer was remarkably higher among
patients who were HIV positive than those who were HIV negative.23

Another risk factor for developing anal cancer includes whole-organ or partial-organ transplantation. For example, kidney transplant patients are at much higher risk of developing HPV infection—and thus an anogenital carcinoma—than the general population. In addition, long-term glucocorticoid therapy used to treat autoimmune diseases can have a predisposing effect on HPV infections.23,25

Current cigarette smokers have a higher risk of anal carcinoma compared with those who do not smoke. The risk of anal cancer increases with length of smoking history.26 In women, smoking has proved to be a high risk factor for cervical neoplasia, which in turn has been linked to anal carcinoma.25

**Preventing Anal Cancer**

Anal cancer has no definitive cause, so prevention is not possible at this time. However, protective measures include avoiding HPV and HIV infection.26

Infection with HPV might not be apparent for years after initial exposure, so the chance of spreading the virus is high. Condoms do not fully protect from HPV because the virus can be passed by direct skin-to-skin contact. Vaccines protect against some subtypes of HPV. For example, the quadrivalent HPV vaccine (HPV4; Gardasil, Merck & Co Inc) can help protect against HPV subtypes 6, 11, 16, and 18. Bivalent HPV vaccine (HPV2; Cervarix, GlaxoSmithKline) is another HPV vaccine used to help prevent infection with subtypes 16 and 18, but the U.S. Food and Drug Administration has only approved its use for cervical cancers and precancers. However, research has shown Cervarix also is useful in preventing anal cancers and associated precancers. Because smoking is a known risk factor for anal cancer, quitting smoking greatly reduces a person’s chances of getting anal cancer as well as many other serious medical conditions.26

**Signs and Symptoms of Anal Cancer**

Because of its distal location in the GI tract, anal cancer is fairly easy to diagnose. However, it is common for anal cancer to be asymptomatic. The most common sign of anal cancer is rectal bleeding. Hemorrhoids, a benign and fairly common condition in the anorectal region, occur when veins are swollen. They might or might not cause pain and can bleed. Rectal pruritus (itching) should be considered a symptom of anal cancer, but some argue that itching is a sign associated with perianal lesions. Signs and symptoms associated with anal cancer include27:

- Rectal bleeding.
- Rectal itching.
- Discomfort or pain in the anal region.
- Changes in stool caliber or dimension.
- Abnormal anal discharge.
- Swollen lymph nodes in the anal or inguinal region.

**Diagnosing Anal Cancer**

Anal cancer can be detected early largely because of its distal gastrointestinal location and the fact that a health care professional can observe anal abnormalities. Nevertheless, anal cancer might not manifest until it reaches a later stage; one reason for this is that the signs and symptoms often mimic other medical conditions such as hemorrhoids. One test that can detect anal cancer in an early stage is the anal Pap test or Pap smear. The anal lining is swabbed and the cells are then studied for cancerous conditions.

Anal cancer can be diagnosed in a number of ways, and with early diagnosis patients can expect a more positive outcome.27 The easiest technique is a simple digital rectal examination performed by a physician or other health care professional during a routine physical examination to diagnose a possible anal lesion. A routine hemorrhoidectomy also can uncover an abnormality. Another test used to diagnose anal cancer is an endoscopy. A physician inserts an endoscope, a long tube with a lens or small video camera on the end, into the anal canal to search for signs of anal cancer. Conversely, an anoscope is a short tube with a light on the end that the physician inserts it into the anal canal to view the anus and lower rectum. This procedure is usually painless.27 To conduct a rigid proctosigmoidoscopy, a physician inserts a tube longer than the one used in anoscopy into the anal canal to visualize up to and including the distal sigmoid colon. This procedure requires patient preparation with either an enema or laxative.27 If during any of these procedures the physician notices anything suspicious, a biopsy is performed to further evaluate and confirm abnormal findings.27 If the growth is suspicious, the physician might try to excise the entire
mass. However, if extension to surrounding structures is detected, further biopsies might be necessary to determine the full extent of the disease and any metastasis.  

A fine-needle aspiration biopsy is performed to sample surrounding lymph nodes in the groin or anal region to detect anal cancer spread. During this procedure, a very thin needle is inserted into surrounding lymph vessels and nodes, and small samples of fluid or tissue are removed and submitted for pathological evaluation. If the lymph samples are positive for anal cancer, surgery might be necessary to remove the cancerous lymph nodes.  

Another test that can be performed is a sentinel node biopsy. This test is used to help diagnose cancer that has spread into surrounding lymph nodes. It involves injecting the cancerous tumor and surrounding areas with a low-level radioactive tracer and a blue dye. The lymph nodes are scanned to trace the path of the radioactive dye. The physician then removes any radioactive or blue-dye–stained lymph nodes and sends them for pathological analysis.  

**Diagnostic Imaging Studies**

Ultrasoundography is useful for diagnosing anal cancer that might have spread into surrounding structures. A transducer is placed rectally and high-frequency sound waves produce images that help radiologists diagnose metastatic disease (see **Figure 5**).  

Chest radiographs can reveal metastatic disease in the lungs, and computed tomography (CT) helps physicians diagnose anal cancer that might have spread to other locations, such as the liver. Patients might be required to drink an oral barium sulfate suspension to coat the lining of the GI tract. Patients might also receive an intravenous injection of an iodine-based viscous solution that lines the arterial and venous walls and helps distinguish abnormalities. CT’s ability to display millimeter-thin slices of the body helps the medical team further diagnose tumor size, nodal involvement, and distant metastatic spread (see **Figure 6**).  

Magnetic resonance (MR) imaging also is diagnostically useful for anal cancers and, unlike CT, uses no radiation. However, MR has certain limitations, including long scanning times and claustrophobia in some patients because of the narrow, tube-like design of many MR scanners. Nevertheless, MR yields more detailed images than CT scans, and anal tumors can be better distinguished from surrounding structures (see **Figure 7**).  

Positron emission tomography is a specialized nuclear imaging test using fludeoxyglucose F 18 as a radioactive tracer. Cancer cells are highly metabolically active, and PET imaging allows physicians to see increased metabolic activity anywhere in the body, helping to diagnose metastatic changes caused by anal cancer.  

**Staging Anal Cancer**

Anal cancer is staged according to the tumor, node, metastasis (TNM) classification system developed by the American Joint Committee on Cancer and the Union for International Cancer Control. Pierre Denoix, MD, developed the TNM system between 1943 and
1952 at the institute of Gustave–Roussy in France. In 1953, a journal article detailed the staging of cancers, and in 1987 the Union for International Cancer Control and the American Joint Committee on Cancer unified classifications of malignant tumors. Tumor staging involves describing the size of the primary tumor in centimeters. Nodal staging is used to describe the extent of cancer's spread to nearby or local lymph nodes. Metastatic spread involves cancer spreading to any other organs in the body. The various TNM stages can be classified in groups, designated 0, I, II, III, IV, and recurrent.

According to the American Cancer Society, there are 2 predominant types of anal cancer staging: clinical and pathological. Clinical staging relies on several types of tests and examinations to arrive at an estimate of the cancer's extent. These tests can include blood tests,
biopsies, imaging examinations, and clinical examination. Clinical staging is used both to select the preferred treatment for a particular patient and as a baseline for assessing the effectiveness of treatment.14

Pathological, or surgical, staging uses information obtained during surgery, often a dissection to remove cancerous tissue, nearby lymph nodes, or both. In some instances, however, surgery is performed simply to assess the cancer and take samples of diseased tissue. It is possible for clinical and pathological staging to differ. For example, surgical staging sometimes reveals that a cancer is more advanced than clinical staging suggested. Pathological staging is considered more precise than clinical staging and provides more reliable information about a patient’s prognosis and his or her likely response to treatment.14

CT Simulation for Anal Cancer Treatment

After anal cancer is diagnosed and staged, a treatment plan is recommended. Treatment plans are designed from among the best possible options for each patient and can include chemotherapy, radiation therapy, surgery, or a combination of these options.19 In addition, the specifics of each patient’s diagnosis, along with other factors, are evaluated to determine whether the patient is a suitable candidate for a research protocol or clinical trial. Once a course of treatment is selected, if radiation therapy is prescribed, the patient will meet with a radiation oncologist to discuss how treatment will be delivered and what the patient can expect.30–32

The first step for the patient is to have a simulation. During the simulation, several steps occur: the patient’s treatment position is determined, all positioning aids and immobilization devices are placed, information used to design the treatment is collected, the patient receives markings that will be used for daily alignment, and he or she receives information about what to expect from the treatments.31,32 For example, patients should be instructed to maintain a low-fiber diet throughout their treatment (see Box 1).

The patient might be placed in a prone, supine, decubitus, or lithotomy position. Setup aids and immobilization devices can include an alpha cradle (Vac-Lok) or a bellyboard.32,34–37 The setup position and immobilization devices needed largely depend on the patient. For instance, if a patient has had previous anorectal surgery, he or she might be equipped with a colostomy bag, making it difficult for the patient to lie prone and necessitating alternate positioning, such as supine or decubitus.

Once the patient is in position, radiopaque markers and wires might be placed in specific areas to assist the radiation oncologist and medical dosimetrist during treatment planning. These markers can be placed at the level of the anal verge, the perianal area, and the inguinal nodal regions to delineate the anatomy. Other areas that might require markers include the vaginal dilator,
used for female patients who wish to reduce or avoid vaginal stenosis. If the disease is more advanced, the patient's buttocks might be taped apart and delimited by wire. Taping the buttocks brings the treatment dose closer to the surface of the anus through application of wet gauze or bolus material.

To spare as much of the small bowel as possible during treatment, it might be necessary to instruct the patient to have a full bladder on the day of the simulation and for every treatment. Oral or IV contrast media might be requested by the physician before the simulation to enhance the visibility of the small and large bowel for treatment planning purposes.

**Treatment Planning for Radiation Therapy**

Once the simulation has been completed, the medical dosimetrist takes the information gathered during the simulation and creates a radiation treatment plan that fits the parameters designated by the radiation oncologist. The medical dosimetrist begins treatment planning by identifying and contouring the critical structures and treatment site. Identification of the treatment volume and critical structures can change the approach to treatment. For instance, if the treatment volume is more proximal, a rectal treatment approach might be necessary. A rectal treatment approach would require a change in the focus and volumes of treatment.

Several studies support a multidisciplinary approach to treating anal cancer. Patients commonly receive one of the following approaches to their radiation treatments: 3-D conformal radiation therapy, intensity-modulated radiation therapy (IMRT), or volumetric-modulated arc therapy.

If a conventional plan is the best method for administering radiation therapy to a patient, then a plan similar to the protocol used in the Radiation Therapy Oncology Group (RTOG) trial 9811 might be used. This plan targets the primary tumor; any inflamed lymph nodes; and the external, internal, and inguinal lymph nodes. An initial anteroposterior/posteroanterior parallel-opposed field is used with treatment energies of 6 MV or higher to achieve a dose of 30.6 Gy delivered at 1.8 Gy per fraction. The borders should extend superiorly to the L5/S1 junction. Inferiorly, the border should extend to include a 2.5 cm margin below the anus and tumor. The anteroposterior field should include the lateral inguinal lymph nodes. The posteroanterior field should extend laterally to the greater sciatic notch and should not include or diverge into the lateral inguinal lymph nodes. An accompanying posterior radiation therapy regimen should be delivered to the inguinal lymph nodes, and an anterior electron field should be delivered to match the exiting posterior field.

A boost, shrinking field, or coned-down field should be delivered by decreasing the superior border to the level of the inferior sacroiliac joints and treating to an additional 14.4 Gy at 1.8 Gy per fraction to bring the total radiation delivered to 45 Gy. If the patient has been staged at N0, the lateral field treatment should stop at 36 Gy.

Also, according to RTOG 9811, an additional accompanying field should be planned if the patient is staged at T3-T4, has any positive lymph nodes, or if a patient with stage T2 anal cancer has residual presenting cancer after 45 Gy. A boost field should be treated, including the original tumor plus a 2 cm to 2.5 cm margin of 10 Gy to 14 Gy at 2.0 Gy per fraction for a total of 55 Gy to 59 Gy using a multifield approach, lateral fields, or treatment to the perineal field using either photons or electrons. Any pelvic lymph nodes should be treated with electrons if the patient's small bowel can be spared.

If IMRT is prescribed, one approach to treating the patient might be based on RTOG 0529. This protocol treats all planning target volumes (PTVs) concurrently. The PTVs should receive 50.4 Gy in 28 fractions at 1.8 Gy per day. The surrounding lymph node regions should receive 42 Gy in 28 fractions at 1.5 Gy per day. For patients who have been staged at T3-T4, N0, the PTV should receive 54 Gy in 30 fractions at 1.8 Gy per day. The surrounding lymph node region should receive 45 Gy in 30 fractions at 1.5 Gy per day. Patients who have been staged with any nodal involvement should receive 54 Gy in 30 fractions at 1.8 Gy per day to their primary tumor site. Any uninvolved lymph nodes should receive 45 Gy in 30 fractions at 1.5 Gy per day. Patients with lymph node involvement less than or equal to 3 cm should receive 50.4 Gy in 30 fractions at 1.68 Gy per day. A patient who has been shown to have lymph node involvement of greater than 3 cm should receive 54 Gy in 30 fractions at 1.8 Gy per day.

Dosimetrists also need to account for surrounding structures and organs when developing a treatment plan.
cm margin of normal tissue was possible with normal primary closure. However, immediate local recurrence rates were as high as 50%. In these cases, a second surgical procedure was performed to excise the recurrent cancer, and the survival rate increased to more than 80% for tumors smaller than 2 cm.7

In 1974, Norman Nigro, MD, published a landmark study in which 3 of his patients were treated with preoperative chemotherapy and radiation therapy. By the time of surgery, all patients were shown to have had a complete response to his regimen.48

According to the National Comprehensive Cancer Network (NCCN) Guidelines, version 2.2013 for anal carcinoma, once anal cancer is suspected and a biopsy returns a positive result for squamous cell carcinoma, a category 2A recommendation is indicated unless otherwise noted. Category 2A is based on lower-level evidence and has unanimous agreement of the NCCN that intervention is appropriate.49

The NCCN defines anal cancer as regionalized if it is bounded by:

- The palpable upper border of the anal sphincter and the puborectalis muscles of the anorectal ring measuring 3 to 5 cm in length, and the inferior border starts at the anal verge, the lowermost edge of the sphincter muscles, corresponding to the introitus of the anal orifice.49

The NCCN further recommends that a work-up for all stages of anal cancer should include a digital rectal examination and an inguinal lymph node biopsy if nodes appear questionable. A chest CT scan also is recommended, as well as MR imaging of the abdomen and pelvis, anoscopy, and HIV testing. For women, a gynecologic examination should include screening for cervical cancer. A PET-CT scan might be recommended, based on further physician validation.49

Treatment Options

In the early 1980s, anal cancer was most commonly treated with abdominoperineal resection. This treatment involved removal of the anorectal region, and a permanent colostomy bag was inserted. Subsequent research soon showed that the 5-year survival rate ranged from 40% to 70%.44 Further research showed that a permanent colostomy was not necessary under most conditions. Instead, a wide local excision with a 1 cm margin of normal tissue was possible with normal primary closure. However, immediate local recurrence rates were as high as 50%. In these cases, a second surgical procedure was performed to excise the recurrent cancer, and the survival rate increased to more than 80% for tumors smaller than 2 cm.7

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### Treatment by Stage

#### Early-Stage Cancers

The primary treatment for T1-T2, N0, localized anal cancer, according to the NCCN, is a regimen of 5-fluorouracil (5-FU) plus a regimen of mitomycin (MMC) and a round of radiation therapy.44

On days 1 through 4 and days 29 through 32, 5-FU should be infused continuously at 1000 mg/m²/d
intravenously (IV). MMC should be infused only on days 1 and 29 at a rate of 10 mg/m$^2$/d IV (see Figure 8).

The consensus of the NCCN is to use an IMRT multifield technique as opposed to a 3-D conformal technique. Along with the multifield technique, energies greater than 6 MV should be used to deliver a dose of at least 45 Gy in 1.8 Gy per fraction over 5 weeks for a total of 25 fractions to the primary site or location. The initial radiation fields should include the pelvis, anus, and perineum. The superior border should include the level of L5/S1 junction and reach inferiorly to include the anus with a 2.5 cm margin beyond or below the anus and its tumor. The lateral borders should include the lateral inguinal lymph nodes. A minimum dose to the femoral heads is recommended.

After 2.5 weeks of radiation therapy, or a cumulative dose of 30.6 Gy, a boost or shrinking field technique should be implemented by lowering the superior field to the level of the inferior border of the sacroiliac joints. After another 3 fractions, if the lateral nodes are negative for the presence of cancer, then a lateral shrinking field to include the inguinal nodes should be used for the remainder of the protocol.

If a parallel-opposed field technique is being used, the NCCN recommends that the lateral inguinal fields should be treated to a minimum dose of 36 Gy with the use of an anterior electron boost matched to the posterocentral exit field.

Late-Stage Cancers

The NCCN recommends additional radiation therapy for patients with more advanced anal cancer, T3-T4, N0, or any T with positive nodes. After the “bookend” regimen of chemotherapy with MMC and 5-FU as in Figure 5, plus the 45 Gy in 25 fractions over 5 weeks, an additional boost of 9 to 14 Gy should be delivered in 1.8 to 2.0 Gy fractions to the original primary tumor site plus the involved lymph nodes with a margin of 2.0 to 2.5 cm. Thus, the total delivery of radiation to the anal region is 54 to 59 Gy delivered in 30 to 32 fractions over 6 to 7.5 weeks. A 4-field box pelvis technique, or the patient lying in a lithotomy position receiving photons or electrons, also is acceptable.

Metastatic Disease

For metastatic anal cancer, the NCCN recommends using the aforementioned radiation therapy technique for local control, plus a regimen of chemotherapy with cisplatin (CDDP). The CDDP-based technique calls for continuous delivery of 5-FU on days 1 through 5 at a rate of 1000 mg/m$^2$/d intravenously. The CDDP chemotherapy should be infused on day 2 at a rate of 100 mg/m$^2$/d intravenously and repeated every 4 weeks (see Figure 9). It should be noted that if the CDDP regimen has no positive effects, there are no better alternatives, according to the NCCN. However, if at 6 months no regression is observed or if disease progresses, then more intensive treatment options should be investigated.

Anal Margin Lesions

If a biopsy reveals squamous cell carcinoma in the anal margins, the workup should include a digital rectal examination, a biopsy of the inguinal lymph nodes if

<table>
<thead>
<tr>
<th>Medication</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
</tr>
<tr>
<td>MMC</td>
<td>IV bolus 10 mg/m$^2$/d</td>
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<table>
<thead>
<tr>
<th>Medication</th>
<th>Day 29</th>
<th>Day 30</th>
<th>Day 31</th>
<th>Day 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-FU</td>
<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
</tr>
<tr>
<td>MMC</td>
<td>IV bolus 10 mg/m$^2$/d</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Figure 8. Dose and administration of chemotherapy combination treatment for 32-day cycle for localized cancers. Note the 5-fluorouracil is administered as a continuous intravenous infusion over the course of 4 days. Abbreviations: 5-FU, 5-fluorouracil; IV, intravenous; MMC, mitomycin.
 nodsal involvement is suspected, chest CT, anoscopy, a CT scan or MR imaging of the abdominopelvic region, HIV testing, and a cervical examination for women.

If the pathology report indicates clinical stage T1, N0, well-differentiated anal cancer, then a local excision is recommended. If the surgical margins prove adequate, the only necessary follow-up is close observation. If the margins are insufficient, a repeat excision is recommended or local radiation therapy and 5-FU-based chemotherapy should be considered. The radiation and chemotherapy regimens are the same as those previously described for anal canal cancer.

For clinical stages T2-T4, N0, or any T, N+, the primary treatment according to the NCCN is the same chemotherapy regimen as previously described plus observation. A National Cancer Research Institute study, ACT II, showed no difference in overall survival or progression-free survival, meaning that patients may show positive results for up to 6 months following combined chemotherapy and radiation therapy.

If an anal margin lesion is shown to be positive for metastatic disease, then CDDP-based chemotherapy and radiation therapy should be administered.

Managing Sexual and Reproductive Effects of Radiation Therapy

Before proceeding with radiation therapy, women should be instructed and educated about vaginal stenosis, the possibility of using a vaginal dilator, and banking their oocytes, or eggs. Men should be instructed about storing sperm in a fertility clinic bank. Both sexes should be informed about infertility uncertainties.

Chemotherapy’s Role in Treating Anal Cancer

Each patient with anal cancer can react differently to chemotherapy drugs and should be monitored closely for any acute changes (see Box 3). The chemotherapy drugs used most often to treat anal cancer are MMC, 5-FU, and CDDP. The recommended protocol is to infuse CDDP on day 1 and day 29, and the 5-FU is to be infused continuously over the course of days 1 through 4 and days 29 through 32 (see Figure 10). Radiation therapy also is started on day 1 and usually runs continuously for 5 weeks.

Nausea and vomiting are the main adverse effects of chemotherapy. The 3 main types of chemotherapy-induced vomiting are presented in Box 4. In addition, MMC has irritant or vesicant (ie, blister-causing)

<table>
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<tr>
<th>Medication</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
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<tr>
<td>5-FU</td>
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<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
</tr>
<tr>
<td>CDDP</td>
<td></td>
<td>IV 100 mg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 9. Dose and administration of chemotherapy combination treatment to be repeated every 4 weeks for metastatic disease. If at 6 months no regression is observed or if disease progresses, more intensive treatment options should be investigated. The 5-FU is administered as a continuous IV infusion over 5 days. Abbreviation: CDDP, cisplatin.
Hydration is essential to establish a urine flow of at least 100 mL per hour for at least 2 hours prior to and after the administration of CDDP. Depending on the facility where the chemotherapy is administered, the fluids might or might not include electrolytes. The amount and timing of fluid administration preinfusion and postinfusion also can vary.

Toxicity and Anal Cancer
The RTOG has developed an acute radiation morbidity scoring system to facilitate reporting adverse radiation effects from anal cancer treatment. Scoring is based on a 0 to 5 scale, with 5 representing the most serious grade (see Table 2). Ben-Josef et al combined data from the RTOG 8704 and 9811 trials and used the scoring system to report radiation toxicity in a study of properties and can cause ulcerations, necrosis, cellulitis, and tissue sloughing. Consequently, extravasation must be avoided. S-fluorouracil also can cause irritation. Even more significant problems occur if a large bolus of the drug is extravasated, which can lead to severe tissue necrosis. Patients who have hepatic or renal insufficiencies might need smaller doses than other patients when starting a chemotherapy regimen to avoid toxicity.

<table>
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<tr>
<th>Medication</th>
<th>Day 1</th>
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<th>Day 3</th>
<th>Day 4</th>
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</thead>
<tbody>
<tr>
<td>S-FU</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
</tr>
<tr>
<td>CDDP</td>
<td>IV 75 mg/m²</td>
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**Day 5 to Day 28**

<table>
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<th>Day 30</th>
<th>Day 31</th>
<th>Day 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-FU</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
<td>IV 1000 mg/m²/d</td>
</tr>
<tr>
<td>CDDP</td>
<td>IV 75 mg/m²</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

**Figure 10.** Dose and administration of chemotherapy combination treatment. The S-FU is administered as a continuous IV infusion over 4 days.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No changes</td>
</tr>
<tr>
<td>1</td>
<td>Increase in frequency, change in bowel habits or rectal discomfort that does not require medication or an analgesic</td>
</tr>
<tr>
<td>2</td>
<td>Diarrhea requiring a parasympatholytic drug, mucus discharge not requiring sanitary pads, or abdominal pain requiring analgesic</td>
</tr>
<tr>
<td>3</td>
<td>Diarrhea requiring parenteral support, severe mucus or bloody discharge requiring sanitary pads, or abdominal distension</td>
</tr>
<tr>
<td>4</td>
<td>Obstruction, fistula, or perforation; GI bleeding requiring transfusion; or abdominal pain or tenesmus requiring tube decompression; or bowel diversion</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
</tr>
</tbody>
</table>

Table 2
RTOG Radiation Morbidity Scoring Criteria

Abbreviations: GI, gastrointestinal; RTOG, Radiation Therapy Oncology Group.

<table>
<thead>
<tr>
<th>Type of Toxic Effect</th>
<th>Grade 2 (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>Unknown Grade (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>54.7</td>
<td>37.7</td>
<td>0</td>
<td>3.8</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>56.6</td>
<td>15.1</td>
<td>0</td>
<td>3.8</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>11.3</td>
<td>0</td>
<td>0</td>
<td>3.8</td>
</tr>
<tr>
<td>All hematologic</td>
<td>20.8</td>
<td>18.9</td>
<td>39.6</td>
<td>–</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>22.6</td>
<td>22.6</td>
<td>30.2</td>
<td>–</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.9</td>
<td>15.1</td>
<td>34.0</td>
<td>–</td>
</tr>
<tr>
<td>Anemia</td>
<td>39.6</td>
<td>9.4</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9.4</td>
<td>15.1</td>
<td>13.2</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 3
Radiation Toxicity by Grade and Type

Abbreviations: GI, gastrointestinal; RTOG, Radiation Therapy Oncology Group.
Clinical Trials and Research

Chemotherapy Plus Radiation Therapy vs Radiation Therapy Alone

The United Kingdom Co-ordinating Committee on Cancer Research Anal Cancer Trial (ACT 1) was a randomized trial conducted in the United Kingdom in 1996. It analyzed nonsurgical management of epidermoid anal cancer with either radiation therapy alone or combination therapy. A total of 585 patients received a regimen of 45 Gy radiation therapy plus a boost of either 15 Gy from external-beam radiation therapy or a 25 Gy boost of brachytherapy. In addition, 290 of the 585 patients received 1000 mg/m² for 4 days or 750 mg/m² for 5 days of 5-FU and 12 mg/m² of MMC on day 1 followed by a 6-week break.

Results showed that combination therapy improved the 3-year local control rate: 59% of the combined-therapy patients demonstrated local control at 3 years vs 36% of the radiation therapy-only group. However, the 3-year overall survival rates were similar for the 2 groups (65% for the patients who received combination therapy compared with 58% for the radiation-only patients). Some speculated that the improved results for the combination therapy group were attributable to the 6-week break in the chemotherapy regimen.

In 1997, the European Organization for Research and Treatment of Cancer conducted a study of 110 patients with stage T3-T4 and N0-N3 or T1-T2 and N1-N3 anal carcinoma. The patients were prescribed radiation therapy delivered at a rate of 45 Gy over 5 weeks, with a daily dose of 1.8 Gy. After a 6-week rest period, a boost of 15 to 20 Gy was prescribed. The prescribed chemotherapeutic regimen, which coincides to begin on the first day of radiation therapy, was to deliver a single dose of 15 mg/m² of MMC on day 1 only and a continuous infusion of 750 mg/m² 5-FU on days 1 to 5 and again on days 29 to 33 (see Figure 11).

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RTOG 8704, a study from 1996, consisted of 291 patients who were given 45 Gy of radiation therapy. Of the 291 patients receiving radiation therapy, 145 also received a continuous IV of 1000 mg/m$^2$/d of 5-FU for days 1 to 4 and days 28 to 31. The other 146 patients also received the same 5-FU delivery plus an IV bolus of 10 mg/m$^2$ MMC on days 1 and 28. A biopsy was performed between 4 and 6 weeks posttreatment; if a residual tumor was present, an additional 9 Gy boost was delivered over 5 fractions, plus an infusion of 1000 mg/m$^2$/d over 4 days, to coincide with the start of the 9 Gy boost treatments; if a residual tumor was present, an additional 9 Gy boost was delivered over 5 fractions, plus an infusion of 1000 mg/m$^2$/d of 5-FU over 4 days, to coincide with the start of the 9 Gy boost treatments; if a residual tumor was present, an additional 9 Gy boost was delivered over 5 fractions, plus an infusion of 1000 mg/m$^2$/d of 5-FU over 4 days. Of the combination therapy patients, posttreatment biopsies were negative in 92% of those receiving both 5-FU and MMC vs 85% for the 5-FU only group. At 4 years post-treatment the disease-free survival rates were 73% for the 5-FU plus MMC group and 51% for the 5-FU only group. Of 24 patients that received boost treatments, 50% were found to be disease free.a

**The Role of Cisplatin**

The United Kingdom Co-ordinating Committee on Cancer Research Anal Cancer Trial II was the largest trial conducted to study anal cancer. It included 940 patients and was conducted from 2001 to 2008. It set out to test 2 hypotheses:
- Whether replacing MMC with CDDP improves complete response rate.
- Whether 2 cycles of maintenance chemotherapy after concurrent chemoradiation therapy improved survival rates.

**Figure 11.** Dose and administration of chemotherapy combination treatment for patients with stage T3-T4 and N0-N3 or T1-T2 and N1-N3 anal carcinoma included in the 1997 European Organization for Research and Treatment of Cancer study. The 5-FU is administered as a continuous IV infusion over 5 days.

**Figure 12.** Dose and administration of chemotherapy combination treatment during the 1996 RTOG 8704 study. A. Chemotherapy protocol for study patients receiving radiation therapy and 5-FU only. B. Chemotherapy protocol for study patients receiving radiation therapy and 5-FU plus MMC. C. Chemotherapy protocol for study patients subsequently receiving boost radiation therapy along with 5-FU and CDDP. The 5-FU is administered as a continuous IV infusion over 4 days.
RADIATION THERAPIST, Fall 2014, Volume 23, Number 2

CE
Directed Reading

Anal Cancer

In the RTOG 9811 study, patients in arm 1 received combination therapy consisting of 55 to 59 Gy delivered over 5 to 6.5 weeks at 1.8 Gy per fraction initially, followed by 2.0 Gy per fraction of a reduced field. These patients also received 5-FU delivered at 1000 mg/m$^2$ by continuous infusion on days 1 through 4 and days 29 through 32. Arm 1 patients additionally received MMC delivered at a rate of 10 mg/m$^2$ on days 1 and 29 by IV bolus. Patients in arm 2 received the same radiation therapy treatments but did not start until day 57. In addition, arm 2 patients received 1000 mg/m$^2$ of 5-FU by continuous IV infusion over days 1 through 4, 29 through 32, 57 through 60, and 85 through 88. In lieu of MMC, arm 2 patients received CDDP (75 mg/m$^2$ infused over 1 hour on days 1 and 29 and then repeated on days 57 and 85) (see Figure 13).

Results showed an overall recurrence-free survival rate at 3 years of 74% for the patients who received the maintenance chemotherapy and 73% for those who did not. There was marginal difference in the 3-year progression-free survival rates between the patients who received MMC (74%) or CDDP (73%) with maintenance chemotherapy and those who received MMC (73%) or CDDP (72%) without the maintenance chemotherapy. The researchers concluded that 5-FU with MMC plus radiation therapy is the standard of care for treating anal cancer.  

**Neoadjuvant Chemotherapy**

In the RTOG 9811 study, patients in arm 1 received combination therapy consisting of 55 to 59 Gy delivered over 5 to 6.5 weeks at 1.8 Gy per fraction initially, followed by 2.0 Gy per fraction of a reduced field. These patients also received 5-FU delivered at 1000 mg/m$^2$ by continuous infusion on days 1 through 4 and days 29 through 32. Arm 1 patients additionally received MMC delivered at a rate of 10 mg/m$^2$ on days 1 and 29 by IV bolus. Patients in arm 2 received the same radiation therapy treatments but did not start until day 57. In addition, arm 2 patients received 1000 mg/m$^2$ of 5-FU by continuous IV infusion over days 1 through 4, 29 through 32, 57 through 60, and 85 through 88. In lieu of MMC, arm 2 patients received CDDP (75 mg/m$^2$ infused over 1 hour on days 1 and 29 and then repeated on days 57 and 85) (see Figure 13). The trial results were presented in 2006 and showed a disease-free survival rate of 59% for the patients in arm 1 vs 53% for the patients in arm 2.

As recently as November 2012, a study update was published online in the *Journal of Clinical Oncology*. The protocol’s lead author, Leonard Gunderson, MD, of the Mayo Clinic in Scottsdale, Arizona, explained,

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<th>Day 1</th>
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<tr>
<td>S-FU</td>
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<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
</tr>
<tr>
<td>MMC</td>
<td>IV bolus 12 mg/m$^2$</td>
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<tbody>
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<td>S-FU</td>
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<td>IV 1000 mg/m$^2$/d</td>
<td>IV 1000 mg/m$^2$/d</td>
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Figure 13. Dose and administration of chemotherapy combination treatment during the UKCCCR ACT II trial. A. Chemotherapy schedule for patients receiving S-FU and MMC protocol. B. Chemotherapy schedule for patients receiving S-FU and CDDP protocol.
did not show significant survival differences between the two treatment regimens. However, the results of this longer-term patient follow-up clearly demonstrate the superiority of radiation therapy plus 5-FU/MMC for both delaying the time when a patient may experience a cancer relapse and for extending patient survival.

“Promising results of early-phase trials prompted the investigation of whether radiation therapy plus 5-FU/CDDP would provide better cancer control and lessen the incidence of colostomy for patients with anal cancer.” He continued:

Our initial results of patient outcomes reported at a median follow-up of 2.5 years post study enrollment

**Figure 14.** Data continued from Figure 13. C. Chemotherapy schedule for patients receiving 5-FU and MMC protocol plus maintenance chemotherapy. D. Chemotherapy schedule for patients receiving 5-FU and CDDP protocol plus maintenance chemotherapy. The 5-FU is administered as a continuous IV infusion over 4 days.
through 32 continuously over 96 hours, plus 10 mg/m² of MMC delivered as a bolus on day 1. These patients were then studied for nearly 7 years (81 months).

Results showed that 4 patients were alive and free of anal carcinoma. Four patients died of AIDS complications but were free of anal carcinoma. Thus, the combination therapy proved to be effective for patients who were positive for HIV. In addition, the regimen proved reasonable and valid by avoiding abdominoperineal resection for the patients. However, more studies should be done to learn how to help patients who have both AIDS and anal cancer.

The postanalysis of this study showed remarkable results at 5 years postprotocol enrollment. Disease-free survival was 67.8% for arm 1 (the MMC patients) vs 57.8% for arm 2 (the CDDP patients). Overall survival rates were 78.3% for arm 1 and 70.7% for arm 2.88

**Treatment for Patients Who Are HIV Positive**

Paddada et al reported that between 1987 and 1995, 8 patients with anal cancer who were HIV-positive, 4 of whom also had AIDS, received combination therapy in the form of 30 Gy over 3 weeks (2.0 Gy/day) and 1000 mg/m² of 5-FU delivered on days 1 through 4 and 29 through 32 continuously over 96 hours. The CDDP was infused over the course of an hour each time. The 5-FU is administered as a continuous IV infusion over 4 days.

**Figure 15.** Dose and administration of chemotherapy combination treatment during the RTOG 9811 study. A. Chemotherapy schedule for patients treated under arm 1 protocol. B. Chemotherapy schedule for patients treated under arm 2 protocol. The CDDP was infused over the course of an hour each time. The 5-FU is administered as a continuous IV infusion over 4 days.
Another study, reported in 1999 by Hoffman et al, involved 17 patients who were HIV positive and sought to determine whether their pretreatment CD4 cell counts (a type of white blood cell that helps fight infection) had any effect on anal cancer outcomes. These patients were either given combination therapy or radiation therapy alone. Results showed that anal cancer in 9 patients with a CD4 count greater than or equal to 200 was controlled with combination therapy and did not require colostomies or hospitalization.

Of the 8 patients with CD4 counts less than 200, 4 experienced a decrease in their CD4 count, irritable diarrhea, or moist desquamation that required medical attention. In addition, 4 of the 8 patients required colostomies because of therapeutic complications or for recovery purposes. Even so, anal cancer was controlled in “6/7” of these patients. This study demonstrated positive anal cancer outcomes for most patients, regardless of CD4 counts. However, morbidity was more common among those with anal cancer and CD4 counts less than 200.

**Chemotherapy, Radiation Therapy, and IMRT**

A study performed by Salama et al from October 2000 to June 2006 involved 53 participants who received IMRT of 45 Gy on average to primary sites and involved nodes, with a boost to an average of 51.5 Gy. Three different chemotherapy regimens were administered: 48 patients received a combination of 5-FU and MMC, 1 received 5-FU and CDDP, and 4 received 5-FU alone.

The follow-up time ranged from 5.2 months to 102.8 months, with an 18-month colostomy-free survival rate of 83.7%. Overall survival was 93.4%, freedom from local failure was 83.9%, and freedom from distant failure was 83.7%. Initial results showed that combination therapy with IMRT is effective and well tolerated.

RTOG 0529 is a closed study that examined the ability of dose-painted IMRT to reduce certain adverse effects compared with a similar treatment regimen that used conventional radiation therapy. Specifically, this study investigated grade 2+ acute adverse events affecting both the GI and genitourinary systems. The chemotherapy used for the study was 5-FU and MMC. The researchers were seeking a reduction in adverse events of at least 15%.

Of 63 patients, only 52 could be used for evaluation. The primary endpoint was a “literal tie,” with both protocols showing 77% of patients experiencing grade 2+ GI/genitourinary acute adverse events. Other interesting results were found in the secondary endpoints (see Table 6). Researchers noted that 81% of the dose-painted IMRT patients needed replanning on initial review. After the final review, only 3 cases (5.7%) needed major tissue deviations. The final conclusion was that despite the primary endpoint not being met, toxicity levels of the GI, hematologic, and dermatologic systems were substantially reduced. The authors cited a need to consider IMRT as an excellent choice for treating anal carcinomas.

**Follow-up Care for Anal Cancer Patients**

Patients who have completed anal cancer treatment might have mixed emotions, including excitement about completing a rigorous course of treatment and anxiety about whether the cancer might return. Others might have to accept the fact that they will always have some form of cancer in their lives.

The American Cancer Society has some helpful suggestions concerning anal cancer patients’ follow-up care. It stresses the importance of attending all physician appointments after treatment so a complete record can be maintained and any changes or issues can be addressed immediately. Follow-up visits might require patients to answer numerous questions and undergo examinations, laboratory tests, or diagnostic imaging studies to monitor the patient for signs of adverse effects or recurrence. Patients who received chemotherapy can expect follow-up visits for up to 2 years. Patients who had colostomies need special care to maintain the integrity of their colostomy.

An evaluation 8 to 12 weeks after treatment is recommended, with a digital rectal examination as the primary

<table>
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<th>Table 6</th>
<th>Comparison of RTOG 0529 and RTOG 9811 Secondary Endpoints</th>
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<tr>
<td>Secondary Endpoints</td>
<td>RTOG 9811 (%)</td>
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<tr>
<td>Grade 2+ Hematologic</td>
<td>85</td>
</tr>
<tr>
<td>Grade 3+ Gastrointestinal</td>
<td>36</td>
</tr>
<tr>
<td>Grade 3+ Dermatological</td>
<td>49</td>
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postwork-up study. If there is progressive recurrence, a waiting period of up to 6 months might demonstrate that the patient has entered a persistent state of disease or remission. If not, and a biopsy confirms recurrence, then a clinical restaging might be necessary. If the restaging shows only local recurrence, an abdominoperineal resection should be considered, with nodal observation every 3 to 6 months for 5 years and chest, abdomen, and pelvic imaging annually for 3 years. If the clinical restaging shows metastatic disease, then the previously described CDDP and radiation therapy regimen should be instituted.

If after the initial 8 to 12 weeks of recovery the patient presents to his or her physician with persistent disease, an additional 4-week observation period should take place. If after this additional month re-evaluation shows no regression or remission, then a battery of examinations must be performed, including a new biopsy. If a "wait and see" approach is taken, continued surveillance should include a digital rectal examination, anoscopy, and nodal observation every 3 to 6 months for 5 years, along with imaging of the chest, abdomen, and pelvis annually for 3 years.

If the patient presents in complete remission, follow up should include a digital rectal examination, anoscopy, and an inguinal node evaluation every 3 to 6 months for 5 years. If the patient's initial staging was T3-T4, annual chest, abdomen, and pelvic imaging should be considered for 3 years. If at any point the patient presents with local recurrence, an abdominoperineal resection should be performed with nodal dissection if the nodes are positive. If cancer recurs in the inguinal nodes, the nodes should be excised and a combination of chemotherapy and radiation therapy should be considered, assuming it was not used previously. If distant metastasis is present, CDDP-based chemotherapy should be prescribed, or the patient might be advised to enter a clinical trial.

If curative treatment is not possible, a palliative prescription might be used to relieve the symptoms of anal cancer. If the cancer progresses or returns after one kind of therapy, there are other possibilities for the patient; if radiation alone was prescribed, a boost of additional photons or electrons might help, or a regimen of chemotherapy might be considered. Surgery might also relieve the patient's posttreatment symptoms. It is imperative to help the patient live as normal a life as possible.

At some point, treatment might no longer be helpful for either curative or palliative purposes. Hospice care might then be considered. According to the American Cancer Society, "hospice care treats the patient, not the disease." Often, this care can be provided at home or in a facility that specializes in hospice care. Patients in hospice care should be encouraged to refocus their lives on what is most important to them and make choices that allow them to enjoy their remaining time as much as possible.

Patients who see a new physician after anal cancer treatment should be reminded to provide the following information, according to the American Cancer Society:

- A copy of the pathology report(s) from any biopsies or surgeries.
- A copy of the operative report(s), if surgery was performed.
- A copy of the hospital discharge summary, if the patient was hospitalized.
- A copy of the radiation therapy treatment summary, for those treated with radiation.
- A drug list with doses and dates taken, for patients treated with chemotherapeutic agents or other drugs.
- Copies of radiographs and other imaging examinations on a digital video disk.

Patients should be advised to keep copies of this information for their own records, in addition to providing copies for their care providers.

Conclusion

Anal cancer has the lowest incidence rate among cancers of the colon and rectum. It can be diagnosed and treated if found early. However, depending on its location, anal cancer can mimic other diseases and progress if not diagnosed properly.

Risk factors for anal cancer include multiple sexual partners, receptive anal intercourse, and infection with HPV or HIV. Although there is no known cause for anal cancer, steps can be taken to avoid HPV and HIV infections.

Radiation therapy is important in the treatment of anal cancer and the use of the complex delivery methods...
is helping to improve patient outcomes. With the growing number of clinical trials and research studies using both chemotherapy and radiation therapy, patients’ chances of fighting and overcoming this disease are improving.

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References


1. Estimates for 2014 from the American Cancer Society indicated approximately ______ new cases of anal cancer.
   a. 4510
   b. 6548
   c. 7210
   d. 8145

2. Anal cancer is rare, accounting for only ______ % of all new cancer cases.
   a. 0.4
   b. 2.5
   c. 3.6
   d. 5.8

3. Risk factors for anal cancer include:
   1. history of multiple sexual partners.
   2. human papillomavirus (HPV) infection.
   3. current cigarette smoking.
   a. 1 and 2
   b. 1 and 3
   c. 2 and 3
   d. 1, 2, and 3

4. The anus connects the lowest region of the large intestine—the _______—with the outside of the body.
   a. sigmoid
   b. cecum
   c. rectum
   d. descending colon

* Your answer sheet for this Directed Reading must be received in the ASRT office on or before this date. Some quizzes are renewed and the expiration date extended. Check online at asrt.org/drquiz or call Member Services at 800-444-2778.
5. The ______ line that separates the stratified squamous epithelium distally from the rectum’s columnar epithelium proximally dividing the anus.
   a. dentate  
   b. Morgagni  
   c. puborectal  
   d. levator

6. The anal cushion is a mass of subepithelial tissue located in which of the following quadrants of the anal canal?
   1. left lateral  
   2. right posterior  
   3. right anterior
   a. 1 and 2  
   b. 1 and 3  
   c. 2 and 3  
   d. 1, 2, and 3

7. Which nerve controls the external anal sphincter?
   a. perineal  
   b. inferior anal  
   c. pudendal  
   d. anterior anal

8. The anus consists of ______ tissue.
   1. glandular  
   2. squamous  
   3. endothelial
   a. 1 and 2  
   b. 1 and 3  
   c. 2 and 3  
   d. 1, 2, and 3

9. What is the most frequently occurring benign anal tumor?
   a. leiomyoma  
   b. polyp  
   c. hemangioma  
   d. adnexal tumor

10. Left untreated, ______-grade anal intraepithelial neoplasia is likely to develop into anal cancer.
    a. zero  
    b. low  
    c. intermediate  
    d. high

11. If the tumor’s midpoint lies 2 cm distal or less from the ______ line, it is considered an anal cancer.
    a. dentate  
    b. Morgagni  
    c. dentin  
    d. puborectal

12. Which of the following infectious agents is associated with anal cancer?
    1. Helicobacter pylori  
    2. HPV  
    3. HIV
    a. 1 and 2  
    b. 1 and 3  
    c. 2 and 3  
    d. 1, 2, and 3

13. What is the most common sign or symptom of anal cancer?
    a. pruritis  
    b. rectal bleeding  
    c. hemorrhoids  
    d. discharge

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14. According to the article, which procedure is the easiest method for diagnosing anal cancer?
   a. hemorrhoidectomy
   b. anoscopy
   c. rigid proctosigmoidoscopy
   d. digital rectal examination

15. Which of the following is true regarding imaging and anal cancer?
   a. Computed tomography (CT) is not useful for detecting anal cancer metastasis.
   b. Ultrasonography is useful for diagnosing anal cancer that might have spread into surrounding structures.
   c. The only limitation of magnetic resonance (MR) imaging is cost.
   d. Positron emission tomography is useful for initial diagnosis.

16. ______ staging (also called surgical staging) uses information obtained during surgery.
   a. Anatomical
   b. Morphological
   c. Pathological
   d. Final

17. To spare as much of the small bowel as possible during treatment, it might be necessary to instruct the patient to have a full bladder on the day of the simulation and for every treatment.
   a. true
   b. false

18. According to the Radiation Therapy Oncology Group (RTOG) trial 9811, which lymph nodes should be included on the anteroposterior field and excluded on the posteroanterior field?
   a. external iliac
   b. internal iliac
   c. lateral inguinal
   d. all pelvic nodes

19. According to the RTOG 9811, if a patient has been staged at N0, the lateral field treatment should stop at ______ Gy.
   a. 14
   b. 18
   c. 34
   d. 36

20. According to RTOG 0529, the organs at risk consist of the large and small bowel, the femoral heads, iliac crests, stomach, and bladder.
   a. true
   b. false

21. In the early 1980s, the most common method used to treat anal cancer was:
   a. radiation therapy alone.
   b. chemotherapy alone.
   c. combined chemotherapy and radiation therapy.
   d. abdominoperineal resection.

22. In a 1974 landmark study in which 3 patients were treated with preoperative chemotherapy and radiation therapy, ______ patient(s) was/were shown to have had a complete response to the regimen by the time of surgery.
   a. all
   b. 1
   c. 2
   d. no

23. The primary treatment for ______ localized anal cancer, according to the National Comprehensive Cancer Network (NCCN), is a regimen of 5-fluorouracil (5-FU) plus mitomycin (MMC) and a round of radiation therapy.
   a. T0, N1
   b. T1-T2, N1
   c. T1-T2, N0
   d. none of the above

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24. Which chemotherapy agents does the NCCN recommend for treating metastatic anal cancer?
   a. MMC
   b. 5-FU
   c. cisplatin (CDDP)
   d. 1 and 2
   e. 1 and 3
   f. 2 and 3
   g. 1, 2, and 3

25. If a biopsy reveals squamous cell carcinoma in the anal margins, the workup should include which of the following?
   a. chest CT
   b. CT or MR imaging of the abdominopelvic region
   c. anoscopy
   d. 1 and 2
   e. 1 and 3
   f. 2 and 3
   g. 1, 2, and 3

26. Which of the following is not required for patients receiving chemotherapy for anal cancer?
   a. assessment of electrolytes as well as hepatic and renal functions
   b. monitoring of neurologic function
   c. checking for diarrhea, mouth sores, and skin reactions
   d. a signed document confirming enrollment in a clinical trial

27. According to the RTOG, which toxicity grade represents diarrhea requiring parenteral support, severe mucus or bloody discharge needing sanitary pads, or abdominal distention?
   a. Grade 4
   b. Grade 3
   c. Grade 2
   d. Grade 1

28. In what percentage or less of T1 and T2 tumors is lymph node involvement present?
   a. 5
   b. 10
   c. 20
   d. 30

29. The United Kingdom Co-ordinating Committee on Cancer Research Anal Cancer Trial II tested whether replacing MMC with CDDP improves complete response rate and whether 2 cycles of maintenance chemotherapy after concurrent chemoradiation therapy improved survival rates.
   a. true
   b. false

30. RTOG 0529 showed that dose-painted intensity-modulated radiation therapy helped reduce toxicity levels in which systems?
   a. gastrointestinal
   b. hematologic
   c. dermatologic
   d. 1 and 2
   e. 1 and 3
   f. 2 and 3
   g. 1, 2, and 3