

## Treatment of Anal Cancer

### How Chemotherapy and Radiation are Given

When patients are diagnosed with invasive anal cancer that cannot be treated by simple surgery, they are referred for treatment with radiation and chemotherapy. Patients are referred to a physician who specializes in delivering radiation to patients to treat their cancers, also known as a radiation oncologist. Patients will also see a medical oncologist, a doctor who specializes in treating cancer patients and administering chemotherapy.

1. The radiation oncologist will perform a history and physical examination paying particular attention to where the cancer is located and assessing the inguinal lymph nodes. The physician will assess the patient's overall health status for conditions that may affect the treatment, such as HIV infection. He or she will explain the course of therapy and the expected side effects and likely outcome based on the examination and review of the CAT scans.
2. Radiation therapy means using energy called ionizing radiation or X-rays to kill cancer cells and shrink tumors. Radiation only destroys cells that are targeted by the x-ray beam. It destroys cells in the area being treated by damaging their genetic material. When damaged, the cells can no longer divide and multiply. Although radiation damages both cancer cells and normal cells, most normal cells are able to recover and function normally. The goal of radiation therapy is to carefully target the abnormal tissue, sparing or limiting damage to the neighboring tissue as much as possible. The radiation is delivered externally similar to the way a regular X-ray is taken, except that the energy is much higher than a regular X-ray.
3. Once a plan is devised as to how much radiation will need to be given and to what areas of the body, then treatment planning and simulation occur. During this process the patient lies very still on an examining table while the radiation therapist uses a special X-ray machine to define the treatment port or field, which is the exact place where the radiation will be aimed. Often CAT scans are used for part of this process so the X-rays can be aimed as precisely as possible at the tumor and limit the damage to healthy tissue. The patient lies on the table often in molds or forms to limit mobility. Then small tattoos are placed on the skin so that the X-ray beam can be aligned properly and in the same way every time. Sometimes shields are made of lead to protect the normal tissues.
4. A prescription is designed to provide a total dose of radiation and then the amount that will be given per day. This dose previously was measured in rads in which 1 rad equals 1 centiGray (cGy) and doses are also reported in Gray (Gy). Patients are usually treated with a dose of 1.8 Gy per day for 5 days in a row for a total dose of 45 Gy delivered in 25 fractions over 5 to 6 1/2 weeks. Patients with T3, T4, or nodal involvement or T2 tumors with residual disease at the end of 45 Gy are treated with an additional 10 to 14 Gy to a reduced field at 2 Gy per day fractions.
5. The radiation is given once a day for 5 to 6 weeks. The treatment itself takes less than a minute once the patient is properly positioned and the beam aligned. Patients are examined weekly to assess how they are tolerating the treatment. Patients receive

supportive care in the terms of anti-nausea and pain medications and attention to good skin care around the anus to limit the severity of the reaction to normal skin.

6. Typical side effects include fatigue that tends to be cumulative meaning that it gets somewhat worse towards the end of therapy, mild nausea, loss of appetite, irritation of the rectum and anal area, diarrhea, increased frequency of urination, loss of pubic hair, redness, drying, irritation, burning, and occasionally blistering and weeping of the skin around the anus. Long-term side effects which are uncommon include ulcers, obstruction of the bowel, obstruction of the ureters, and the development of fistulas or abnormal connections or tracts between the pelvic tissues.
7. Chemotherapy is given during the first few days of the radiation and in the middle of treatment. The chemotherapy is given during the radiation because it acts as a radiation sensitizer, which means that the chemotherapy enhances the effect of the radiation.
8. Usually a special intravenous catheter is inserted to facilitate the delivery of the chemotherapy, which is usually arranged by the medical oncologist. One type is called a PICC line and refers to a long catheter that is threaded through a vein in the arm into the large veins near the heart. It is covered with a special dressing and can stay in place for several weeks and then is removed at the end of therapy.
9. The medical oncologist will also review all of the medical records, CAT scans, and perform a history and physical examination prior to starting the chemotherapy. The medical oncologist works together with the radiation oncologist to ensure that the treatment is given as safely and effectively as possible. Together they will monitor blood counts carefully and may adjust the second cycle of chemotherapy if there are excessive side effects or toxicity with the first cycle.
10. One of the most common types of chemotherapy used is a medication known as mitomycin given at a dose of  $10\text{mg}/\text{m}^2$ , which is a method used to calculate chemotherapy doses based on body surface area that is calculated as  $\text{m}^2$  (square meters) of body surface area with most adults being between 1.5 and  $2\text{ m}^2$ . The chemotherapy is given as a single intravenous injection of the first day of the radiation and then again on the 29<sup>th</sup> day of therapy. It is given with another chemotherapy drug called 5-FU or 5-fluorouracil, which is given at a dose of  $1,000\text{ mg}/\text{m}^2$  as an infusion that is given continuously for the first 4 days of therapy and then repeated on the 29<sup>th</sup> day. The 5-FU is usually delivered using a pump, which can be like a small elastic balloon or like a small tape recorder. The treatment is usually given as an outpatient.
11. Side effects of the chemotherapy may include nausea, vomiting, hair loss, mouth sores, diarrhea, and low blood counts including low white cells, red cells and/or platelets, which can be severe enough to cause bleeding, need for transfusion and to place the patient at risk for a potentially life-threatening infection and rarely death. Rarely mitomycin has been associated with kidney damage and a disorder of the blood called hemolytic anemia in which some of the red cells burst and small clots can form in blood vessels, a condition known as microangiopathic hemolytic anemia or hemolytic uremia syndrome.
12. Most people get through the therapy fairly well and only rarely have all of the side effects mentioned. The good news is that the treatment usually works very well, many people are cured, and it only lasts for 6 weeks and then is finished.
13. Once therapy is finished, the side effects begin to dissipate and energy levels and appetite and blood counts return to normal and the skin heals. Close follow up is important. Patients are usually seen every 3 months for the first year, then every 6 months for the second year, and then every year. If there is a recurrence, it tends to occur in the first 2 years.

## Chemotherapy and Radiation are Not Always Necessary

The standard of care for treatment of invasive anal cancer is radiation and chemotherapy. There are several situations, however, when combined modality therapy may not be necessary.

1. The most obvious is when invasive cancer is not present. A diagnosis of carcinoma in situ is not invasive cancer. A number of patients and some health care providers have misunderstood this concept and patients have been unnecessarily treated with radiation and chemotherapy. This is one reason why we prefer the more accurate terms high-grade squamous intraepithelial lesion (HSIL), or anal intraepithelial neoplasia (AIN) 3, or severe dysplasia [1] to carcinoma in situ. Patients with a diagnosis of AIN 3 must be examined carefully and biopsies of any areas suspicious for cancer biopsied, but if there is no evidence of invasive cancer then these patients could be treated using electrocautery, laser, or infrared coagulation to destroy the areas of HSIL [2] and then followed closely.
2. Anal margin cancers or cancers of the perianal skin may not require CMT. These types of cancers are often managed in a similar way to other skin cancers, which is by cutting them out and cauterizing the base underneath the lesion. Small T1 and T2 tumors that are not deeply invasive into the sphincter muscle and that can be completely excised with negative margins may be treated with simple excision and electrocautery. Patients should be referred to clinicians experienced in managing anorectal conditions, preferably using high-resolution anoscopy (HRA [3]) if it is available, for careful examinations to treat any other areas of precancerous lesions that may be present. Many patients with anal margin tumors will also have co-existent internal anal HSIL [2] that should be treated. It is important to evaluate the inguinal lymph nodes located in the groin area as anal margin cancers may spread to this region. Larger T3 tumors which invade into the external sphincter muscle or that impinge on the verge or anal canal are better treated with radiation and chemotherapy.
3. Tumors that are superficially invasive that are small may also be managed with simple excision and cautery. These tumors are referred to as superficially invasive squamous cell carcinoma (SISCCA). Superficially invasive refers to cancers that invade only a short distance beyond the basement membrane less than several millimeters. For a cancer to meet the criteria of SISCCA the invasive component must have a depth of invasion of  $\leq 3$  mm and horizontal spread of  $\leq 7$  mm. This category of superficial invasion has not been rigorously studied or clearly defined in the medical literature for anal cancer. Often patients with anal HSIL will have involvement of large parts of the anal canal and perianal area, which is referred to as a field effect. This means that the entire anogenital skin or epithelium is susceptible to HPV [4] infection and may develop precancerous lesions or HSIL. For that reason, patients diagnosed with SISCCA must be examined carefully for other lesions [5] and they must continue to be followed on a regular basis because they are at higher risk of developing recurrences either of HSIL or other cancers. A study that is currently underway is exploring the possibility that if SISCCA is removed and all HSIL treated that chemotherapy and radiation may not be needed.
4. Surgical excision may be appropriate for small T1 intra-anal cancers if they involve only a small part of the circumference and do not deeply invade into the internal anal sphincter muscle. This is a controversial approach, which in a small group of patients was shown to effectively eliminate the cancer. If excising the cancer would require

removing a portion of the internal sphincter muscle then this method should be avoided because incontinence is likely. One of the great benefits of radiation and chemotherapy is preservation of the anal sphincter and often avoiding a colostomy, so CMT is the preferred method of treatment except in highly selected patients who can be very carefully followed.

5. If patients are quite ill as a result of other medical conditions and not expected to live for more than a few months, then it may not be necessary to try to treat their anal cancers. This is a very difficult decision that should be made after consultation with the patient's primary care provider, family and friends. If a choice is made not to treat, then patients should have excellent control of pain, if it is present. Often this would be a situation where hospice care would be considered and be appropriate.

### **When Other Treatments Are Not Effective**

Prior to the 1970s, the standard treatment for anal cancer was an APR with colostomy, which is a large operation known as an abdominoperineal resection (APR). During an APR the anus and lower rectum and the skin around the anus is surgically removed. The lower end of the colon is brought out through a hole in the lower abdominal wall to create a permanent colostomy. This may be necessary for those whose chemotherapy and radiation treatment is not effective in treating their anal cancer. In 1974, Nigro published preliminary results, which showed that when patients were treated prior to surgery with chemotherapy consisting of mitomycin and 5-fluorouracil (5-FU) combined with a relatively low dose of radiation of 30 Gray (Gy and 1 Gy=100 rad) that the tumor was effectively eliminated in most surgical specimens. Additional studies confirmed the success of this approach of using combined modality therapy with higher doses of radiation and without surgery.

Several general principles emerge. Higher doses of radiation may achieve better control. It is better to treat patients continuously for 6 to 8 weeks than to take a break in the middle of therapy. Combining chemotherapy and radiation produces a better outcome than radiation alone. Overall survival is similar, perhaps due to the ability of APR to render those patients who recur after combined modality therapy disease-free. Combination chemotherapy with mitomycin and 5-FU produces better results than 5-FU alone and patients treated with the combination had a complete response of 74-90%, local control in 54-73%, colostomy-free survival in 66-70%, disease-free survival in 53-77%, and 58-89% overall survival. There is another chemotherapy drug known as cisplatin, which is being investigated in combination with 5-FU and radiation to see if it is better than mitomycin.

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