Anal Cancer: A Multispecialty Disease, a Multispecialty Cure

Part III: Anal Canal Squamous Cell Carcinoma, With an Historical Vignette

In Part I of this series, we covered anal anatomy and anal intraepithelial neoplasia. In Part II, we discussed perianal cancers and their treatment. In Part III, we will examine squamous cancers of the anal canal. Part IV will deal with unusual cancers of the anal canal.

Neoplasms of the anal canal may behave differently from those of the perianal region and therefore should be evaluated separately.

Anal Intraepithelial Neoplasia: A Malignant Precursor?

Research has focused on data pointing to the human papillomavirus (HPV) in combination with other risk factors as the etiology of many anal cancers. This may be similar to the HPV causation of cervical cancer.

HPV is a double-stranded DNA virus that infects the stratified epithelium of skin or mucous membranes. At least 20 of the more than 200 known HPV genotypes infect the anogenital area. HPV-6 and 11 are associated with anal condyloma (warts) and low-grade anal intraepithelial neoplasia (AIN). These rarely become malignant. Genotypes 16, 18, 31, 33, and 35 are associated with high-grade AIN (also called Bowen's disease, carcinoma in situ [CIS], or AIN III), as well as with invasive cancers of the anus and cervix.

AIN can be found in the anal canal as well as in the perianal region, and there is evidence that it not only behaves in a more aggressive fashion in the anal canal but that it may be a true precursor to anal carcinoma.[1] The upper anal canal transitional epithelium is composed of a columnar epithelium with an overlay of nonkeratinized squamous metaplasia. Metaplastic nonkeratinized tissue may be unusually susceptible to infection with HPV, leading to disease. HPV-16 and 18 are commonly found in anal canal carcinomas, especially proximal to the dentate line. In fact, these upper canal cancers are rarely found without HPV-16 or 18. HPV DNA almost never is found in normal anal canal tissue. It is uncommon to find HPV-16 or 18 DNA in the modified skin of the lower anal canal, with its keratinized mucosa, and HPV rarely is found in nonsquamous cell anal cancers such as adenocarcinoma.[2-4]

An abnormal anal Pap smear showing atypical squamous cells may lead to further investigation, looking for AIN or a carcinoma. A simple exam under anesthesia with acetic acid staining or Lugol's staining may reveal abnormal tissue for biopsy. Suspicious areas for targeted biopsy appear white when stained with acetic acid. AIN III appears as a tan area of anal mucosa when stained with Lugol's solution (Figure 1). Anal canal colposcopy in conjunction with aceto-whitening to highlight potential abnormal mucosal areas for biopsy may be used by those with the necessary technical experience to more closely evaluate the anal canal. High-resolution anoscopy with anal mapping, whereby a grid system is mapped onto the anal area to record precise biopsy locations looking for pathologically diagnosed occult lesions in need of treatment, may be used, although its use is less common now than in the past. The rationale behind diagnosing and treating AIN, especially AIN III or Bowen's disease, is that, in so doing, the physician may possibly halt the development of an anal canal cancer. However, it is not proven that AIN I transitions through AIN II and AIN III to an invasive squamous cancer.

Treatment of AIN I, II, and III was more completely covered in Part I of this series. It appears as if treatment is shifting toward topical therapy with imiquimod, topical 5-fluorouracil (5-FU), or targeted electrofulgeration, while reserving surgical extirpation for patients with persistent symptomatic disease or invasive carcinoma. As always, physicians should be aware of the possibility of malignant disease in other organs.

Squamous Cell Carcinoma: Many Names, Many Faces

Squamous cell carcinoma (SCC) of the anal canal is a tumor that has been given many names, such as cloacogenic carcinoma, basaloid carcinoma, transitional cell carcinoma, and keratinizing or nonkeratinizing large-cell carcinoma.

Ideally, the diagnosis of SCC of the anus should be made early in the clinical course of the disease. However, patient or physician delay is not uncommon, and the initial presentation often may be one of late-stage disease. Symptoms of this treatable disease may have been present for months to years before a correct diagnosis is suspected. Bleeding occurs in 50% of patients.[5-7] Other symptoms include anal pain, pruritus, discharge, or a mass. Advanced tumors may present with a change in bowel habits, incontinence, an anovaginal fistula, or pelvic pain, and may represent a tumor with sphincter involvement, signifying later-stage disease. Because of the variable presentation of disease, an incorrect initial diagnosis is common, and 33% of patients may be incorrectly diagnosed as having benign disease.[6,8]

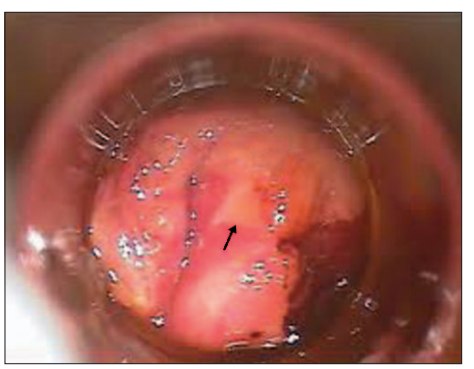

Figure 1. AIN 3 stained with Lugol's solution (arrow).

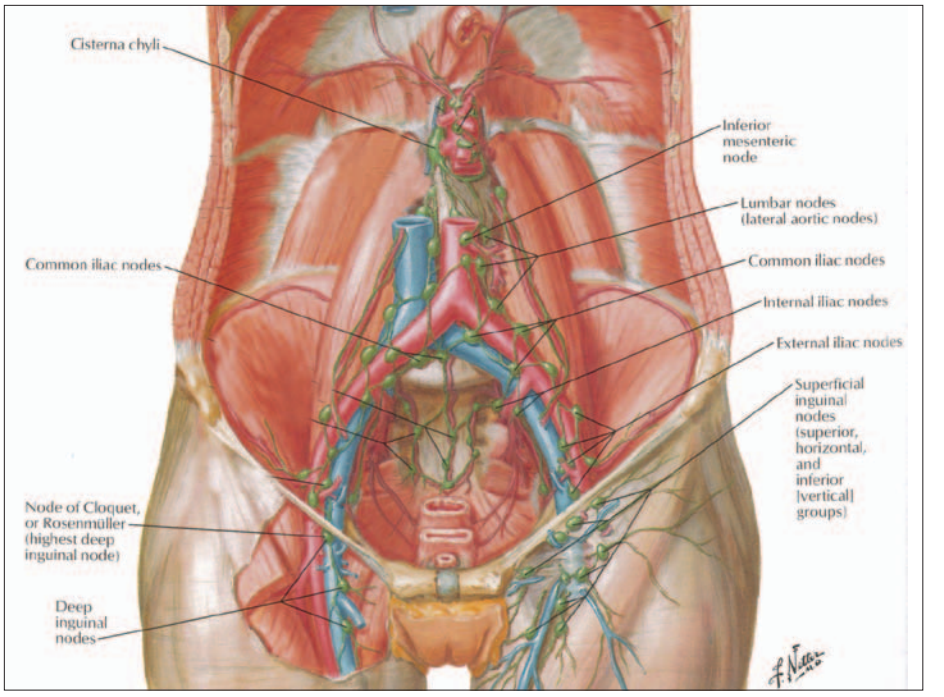

Figure 2. Pelvic lymph node drainage.

Straightforward Diagnosis … If the Physician Thinks of It

Diagnosis usually is straightforward when a patient presents with symptoms and the physician includes squamous cell carcinoma in the differential diagnosis of an otherwise benign set of symptoms. A history of an HPV or HIV infection, cervical neoplasia, or immunosuppression should alert the physician. A digital exam will reveal a mass, which may or may not be fixed. The size of the mass as well as its exact location should be noted. Attention must be given to the inguinal region, as this area is a common site of metastatic disease when the primary tumor is located distal to the dentate line. In women, a pelvic examination should be performed looking for tumor invasion into the vagina. An HIV test should be performed in high-risk patients. Highly active antiretroviral therapy (HAART) should be initiated in patients with newly diagnosed HIV. Those patients with CD4 counts less than 200 often will require modifications to the treatment protocol.[9]

An evaluation of the colon may be performed, especially for those over age 50, and an endoanal or endorectal ultrasound may be helpful in evaluating the depth of tumor invasion, as well as possible nodal disease. If an abnormality is found on chest x-ray examination, computed tomography (CT) scanning of the chest will aid in searching for metastatic disease. An abdominal and pelvic CT will be useful in searching for metastatic disease and in evaluating the inguinal regions and the pelvis. However, the sensitivity of pelvic imaging is not high.[10] It is impacted by both the limits of the technology and the inability of the technology to discriminate between malignant and benign lymph nodes. As 44% of metastatic lymph nodes may be less than 5 mm, CT scanning might not be sensitive enough to accurately predict nodal involvement.[11] Fluorodeoxyglucose–positron emission tomography (FDG-PET), which looks at the fluorine-18 fluorodeoxyglucose metabolic uptake of tissue, may have promise in identifying metastatic disease, especially when FDG-PET scanning is combined with CT scanning (PET-CT). FDG-PET scanning is dependent on tissue metabolic activity and not on nodal size. Confirmation of the usefulness of this modality will have to await trials of PET scanning with confirmatory histopathologic proof of involvement in nodes identified by PET scanning. A fine-needle aspiration, core biopsy, or an open biopsy should be performed on suspicious inguinal

see ANAL CANAL CANCER page 16

Anal Canal Cancer

Continued from page 15

disease to differentiate reactive nodal hyperplasia from carcinoma that requires treatment.

Finally, a confirmatory biopsy through an anoscope or proctoscope is diagnostic. However, an open surgical biopsy may be preferable for enhanced visualization, a more thorough anal canal inspection, and patient comfort. The relationship of the lesion to the dentate line should be documented.

Involved Lymph Nodes—Too Common

Depending on the anatomical location of the tumor, various lymph node regions may harbor metastatic disease (Figure 2). The TNM staging system is used to stage the tumor and is a relatively accurate predictor of prognosis (Table).

Tumors located proximal to the dentate line may spread along the superior rectal vascular and nodal pathway to the inferior mesenteric nodes. When located on the dentate line, the tumor also may spread laterally along the internal pudendal, hypogastric, or obturator nodes. If the tumor is located below the dentate line, the inguinal nodes are the commonest sites of spread. Of course, these patterns of spread are variable, and a thorough nodal evaluation should be performed.

The rate of lymphatic spread directly correlates with the size of the tumor. The larger the tumor, the more frequent the nodal metastatic disease. Nodal metastases also may be related to the depth of invasion and the histologic grade of the tumor, although this relationship is not as certain. Nodal disease is found in up to 20% of patients at the time of diagnosis and may become apparent later in up to 25% of patients.[12] These variables impact treatment recommendations.

With respect to tumor size, or T stage, in tumors less than 2 cm (T1), nodal spread is rare as compared with those malignancies larger than 2 cm (T2 or T3), in which spread may be encountered in up to 35% of cases.[13]

With respect to depth of invasion, with smooth muscle tumor involvement, affected nodes may be found in 30% of patients and in 60% in those with tumor spread beyond the external sphincter. In one study of 172 patients, only 17 were found to have tumors confined to only the epithelium or subepithelial connective tissue.[12]

At the time of diagnosis, 53% of patients had only local disease, whereas 38% had regional disease and 9% showed evidence of distant metastatic disease.[14] Clearly, early diagnosis might help to discover small, superficial tumors and possibly improve survival statistics.

Treatment—From Yesterday to Today

Traditionally, an abdominoperineal resection (APR) was the treatment of choice for anal squamous cell carcinoma, but was associated with local recurrence rates as high as 45%, and 5-year survival rates as low as 40%.[10,13,15-19] The presence of lymph node involvement at the time of initial diagnosis worsened survival rates even further. With the finding that wide local excision in highly selected cases yielded 5-year survival rates of 100%, and with the introduction of a curative chemoradiation protocol, APR as a primary treatment modality was abandoned except for its present-day use in those patients unable or unwilling to undergo chemoradiation. Abdominoperineal resection also may be used in patients with persistent or recurrent disease after chemoradiation, or in those patients presenting with bulky tumors or with incontinence and extensive sphincter involvement. The procedure can be performed in an open fashion or laparoscopically by those surgeons with experience in the laparoscopic technique.

Table. The TNM Staging System for Perianal Squamous Cell Cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ (Bowen's disease, high-grade squamous intraepithelial lesion/HSIL, anal intraepithelial neoplasia/AIN II-III)
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size that invades adjacent organ(s): vagina, urethra, bladder
Note: direct invasion of the rectal wall, perirectal skin, subcutaneous tissue or sphincter is not classified as pT4	
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes or bilateral internal iliac or inguinal lymph nodes
Regional lymph nodes: perirectal (anorectal, perirectal, lateral sacral), internal iliac (hypogastric), inguinal (superficial)	
Distant metastases (M)	
M0	No distant metastasis
M1	Distant metastasis
MX	Presence of distant metastasis cannot be assessed

Source: American Joint Committee on Cancer. *AJCC Cancer Staging Manual.* Seventh edition, 2009.

Anal SCCs are quite radiosensitive, and radiation therapy with a curative intent has been used since the end of World War I as the primary mode of treatment. The radiation was administered as external beam or brachytherapy. An increasing dose of radiation was found to be associated with an improved tumor response, but doses as high as 55 Gy had to be administered.[20,21] Local control and cure rates were high, but these came at the price of increased morbidity secondary to the radiation. Additionally, with T3 and T4 lesions, or in patients with N1 disease, cure rates were seen to diminish by 50%.[20,22] Major morbidity was found to include anal necrosis or stenosis, fecal incontinence, small bowel obstruction, iliac artery stenosis, urethral stenosis, cystitis, diarrhea, or anorectal ulcerations.[23] With the loss of normal functioning of the anal canal, a colostomy was needed in up to 12% of patients. The occurrence rate of other major morbidities was found to be dose-dependent.[22,24] The only independent predictor of the need for a colostomy was the size of the primary tumor.[25] As such, radiation therapy alone as a primary treatment modality is offered rarely unless the patient is too ill for surgical therapy, refuses surgical treatment, or is unable to receive chemoradiation.

A Treatment Milestone: The Nigro Protocol

Searching for a method to improve the survival statistics associated with an abdominoperineal resection for squamous cell carcinoma, Norman Nigro, MD, in 1972, began administering preoperative chemoradiation. Dr. Nigro noted: "There are causes for the low cure rates even beyond the biologic characteristics of the neoplasm itself. The anatomic features of the anal canal are such as to promote early spread of malignant cells. The area has both a profuse blood supply and an abundant lymphatic drainage system that leads in all directions. At the same time, there is a serious limitation in the amount of tissue around the anal canal that can be removed. Lymphatic involvement occurs early to areas like the deep pelvic nodes, which are always difficult and sometimes impossible to remove." He continued, "It appears to us that surgical excision is not likely to be adequate treatment for many patients with cancer of the anal canal."[26]

The results of a 3-patient experiment were presented in a lecture to the American Proctologic Society in 1973. This 3-page report was published in 1974 in *Diseases of the Colon and Rectum*.[26] In anticipation of the performance of a curative abdominoperineal resection for anal SCC, 3 patients were given preoperative chemoradiation. Six weeks after the completion of the month-long regimen, 2 of the patients underwent the planned operation. The third patient refused operative intervention after the initial chemoradiation. All 3 patients were tumor-free between 6 and 15 months after completion of treatment.

The treatment protocol began with 30 Gy of preoperative perineal, pelvic, and inguinal nodal irradiation over a 15-day period. A 5-day course of 5-FU was given as a continuous infusion beginning on day 1 (25 mg/kg). Mitomycin C (MMC) was given as a bolus on day 1 only (0.5mg/kg). The chemotherapy was given during an inpatient hospitalization. An abdominoperineal resection was performed 6 weeks following this treatment and the 2 surgical specimens were studied. Neither specimen contained any tumor.

A follow-up "pilot study" on 10 additional patients was published as a 2-page report in 1977.[27] The chemotherapeutic regimen had been modified slightly. Nine patients underwent post-treatment APR.

Six patients, all of whom had tumors less than 4 cm in diameter, had no residual tumor in the resected specimens after an abdominoperineal resection. One patient with a 4-cm lesion refused an operation and was disease-free at 18 months post-treatment. Overall, 7 patients with tumors 4 cm or less in size remained tumor-free at 2 to 53 months postoperatively. The 3 patients with either persistent tumor or metastatic disease had cancers that were originally between 6 and 8 cm. Of note, Dr. Nigro reported that "The tissues were not grossly altered, bleeding was not excessive, and dissection presented no technical difficulty. Healing of all tissues, including the perineal wounds, was normal."

It was at this time that it was suggested that an APR might not be necessary in those patients whose tumors were smaller than 4 cm and who showed no residual tumor in the resected scar after the completion of chemoradiation. Thus began the era of "less is more" for treatment of SCC of the anal canal.

In 1984, Dr. Nigro presented his 4-page follow-up on 104 patients.[28] Eighty-two patients were alive and disease-free at between 2 and 11 years post-treatment (22 having undergone APR and 60 having undergone only chemoradiation). Of note, 7 patients underwent

see Anal Canal Cancer page 18

Anal Canal Cancer

Continued from page 16

a delayed APR for recurrent disease after initially having been found to be disease-free following chemoradiation and with normal post-treatment biopsies showing no residual tumor. Four of these patients were alive and without disease after salvage APR ("two for three years and two for four years"). The conclusions were simple: "This experience with chemoradiation therapy for squamous cell cancer of the anal canal has convinced us that it is as effective as abdominoperineal resection of the rectum in the majority of patients."

All of this was presented over 12 years in 3 articles that occupied a total of only 9 pages.

Present-Day Treatment Protocols

Chemoradiation has been found to be superior to operation alone or radiation alone with respect to colostomy-free rates, local failure rates, and cancer-specific survival rates.[29-31] During the years following Dr. Nigro's introduction of chemoradiation for anal cancer, changes have been made to the chemotherapeutic regimens and variations in the treatment protocols have been studied. The Nigro protocol, however, remains the model for treatment.

Importantly, before beginning treatment, patients with anal canal cancer must be evaluated appropriately for other malignancies. Although radiotherapy has not been found to be associated with an excess of new, radiation-induced cancers,[32] a pretreatment baseline evaluation should be performed.

Treatment Choices

Carcinoma in Situ and T1 Lesions

Chemoradiation is widely accepted to be the initial treatment choice for T1 lesions. Results equal those after wide local excision. The administration of prophylactic inguinal radiation is not standard in T1 disease. Arguments against prophylactic inguinal radiation include the development of lymphedema and the onset of debilitating anorectal dysfunction, albeit at a rare rate of occurrence. However, the rate of severe morbidity associated with inguinal radiation is minimal and recurrence rates seem to be higher in those patients who have not undergone prophylactic inguinal irradiation. Many centers do administer prophylactic inguinal radiation.

As in treatment for squamous cell carcinoma of the perianal skin, wide local excision in selected cases can achieve a cure while preserving anorectal functioning. In a highly selected, small group of patients, survival rates have been found to approach 100%.[13,17,18] The key to success seems to be in patient selection. The tumors

should be mobile, less than 2 cm in size, well differentiated, and demonstrate invasion no deeper than the submucosa. If local excision fails and there is persistent disease or a local recurrence, salvage chemoradiation or APR may be curative.

T2, T3, T4 Lesions

In those patients requiring anything other than wide local excision, chemoradiation with 5-FU with MMC is currently the initial treatment modality. Treatment regimens differ, but most authors accept that a standard treatment includes 40 to 54 Gy administered to the perineum and inguinal nodal basins over 25 days in those with T2 lesions. In patients with T3 and T4 tumors, pelvic irradiation is added.

Chemotherapy includes cycles of 5-FU during weeks 1 and 5 and a single dose of MMC on day 1. Many centers repeat MMC on day 29. With T3 and T4 tumors, radiation boosts can be given for a total of 55 Gy. To treat with radiation alone in those patients unable to undergo chemotherapy, 70 Gy can be used.

Radiation Therapy and Chemotherapy: Toxic Cures

After receiving radiation therapy, relatively normal anorectal functioning is preserved in up to 90% of patients. However, with radiation doses greater than 40 Gy, the rate of complications increases as well. The complications may be systemic, such as dermatitis, mucositis, fatigue, or bone marrow suppression. Death is rare. There may be associated anorectal irritability with tenesmus, proctitis, diarrhea, bleeding, urgency, and incontinence. Most of these symptoms can be controlled with medication, but a proximal ostomy may become necessary. Far from causing further disability, an ostomy may be a welcome relief from symptoms caused by disease treatment.[24] Pelvic complications include urethral stenosis, cystitis, small bowel obstruction, and arterial stenosis.

Hematologic toxicity, specifically anemia, neutropenia, and thrombocytopenia, may occur in up to 64% of patients receiving MMC, but the use of MMC has been found to further decrease colostomy rates, increase colostomy-free rates, and increase disease-free survival rates. However, overall survival rates at 4 years have been shown to be no different with or without MMC.[33]

Suggestions have been made that cisplatin might be substituted for MMC in an attempt to decrease hematologic toxicity. Cisplatin, although less toxic than MMC, also is myelosuppressive, with pancytopenia occurring in 25% to 30% of patients. This is more pronounced in those receiving high doses of cisplatin (>50 mg/m^2). Patients also may experience hemolytic anemia. Results of trials have not substantiated a survival benefit and there is a statistically significant higher colostomy rate when using cisplatin in place of MMC (19% vs 10%, respectively). There were more study-related deaths in the cisplatin group, although it was not implied that cisplatin was the cause of death. As expected, there was less severe acute hematologic toxicity in the cisplatin group compared with the MMC group (61% vs 42%, respectively).[34,35] Cisplatin has not replaced MMC in the standard chemoradiation protocol for squamous cell carcinoma of the anus.

Capecitabine (Xeloda, Roche) is an oral chemotherapeutic agent that is enzymatically converted to 5-FU in tumor tissue. If it proves efficacious, capecitabine might be substituted for 5-FU in order to avoid prolonged IV infusion.

Results of Treatment: Size Matters

Over the years since Dr. Nigro's seminal work, numerous studies have shown that, on average, with varying doses of radiation and various chemotherapeutic protocols, complete responses occur in up to 87% of cases, local control occurs in up to 86%, and 5-year survival rates are between 66% and 92%.[36] When stratified by T stage, without lymph node metastatic disease, T1 tumors show a long-term survival rate of 93%. In T2 disease, long-term survival is 84%. Survival drops to 60% in T3 disease and to 37% in T4 disease (with or without involved lymph nodes).[37] Tumors larger than 5 cm are more problematic, with 50% requiring a salvage abdominoperineal

see Anal Canal Cancer page 20

Anal Canal Cancer

Continued from page 19

resection. However, if patients with these larger tumors are disease-free at the conclusion of the initial chemoradiation, only 25% will require a salvage APR.[36]

Treating Uninvolved Inguinal Lymph Nodes At Diagnosis: Wait or Don't Wait?

In the absence of involved inguinal nodes at the time of initial diagnosis in T1 lesions, it is not clear as to whether prophylactic inguinal radiation has a place in the standard treatment of newly diagnosed squamous cell carcinoma. Two common approaches include a wait-and-see approach and a prophylactic irradiation strategy. In one study of 24 patients without inguinal lymph nodes at the time of diagnosis, 2 developed nodal involvement, 1 in an irradiated inguinal field and 1 in a nonirradiated field.[38] Three studies showed the late nodal recurrence rate to be between 15% and 25% when inguinal fields were not routinely included in the radiation treatment.[13,39,40]

Wait

The rationale underlying the wait-and-see approach is that up to 90% of patients will need no therapy to the inguinal region. This would avoid the potential morbidity associated with inguinal radiation. However, 10% to 15% will develop metachronous disease, but this can be controlled in 50% of those affected.[22,41-43] Acute toxicity, sometimes leading to mortality, also can occur, albeit rarely, in 2% of cases.[30,33] This seems to occur in elderly or frail patients.

Don't Wait

Prophylactic bilateral radiation of initially uninvolved inguinal regions is associated with the appearance of inguinal disease in less than 5% of patients so treated.[24,30,33] In an effort to reduce the volume of radiation and associated complications, some institutions will irradiate only one inguinal and iliac nodal region if the tumor is clearly located on the homolateral side of the anal canal. Standard doses of 45 to 55 Gy are used.[13,22,43] Several institutions use a lower dose of radiation when combining treatment with chemotherapy.[24,33,34] This approach lowers the risk for and morbidity associated with radiation toxicity, while also controlling the disease. Iliac recurrences are difficult to control and prophylactic radiation may circumvent the development of iliac disease.[44]

Presently, most protocols do include prophylactic inguinal irradiation.[45]

Prophylactic inguinal dissection does not increase 5-year survival and carries a high morbidity rate. It is not used routinely.[6,7]

Synchronous Inguinal Nodes

Synchronous inguinal lymph node involvement is reported in 10% to 25% of cases.[6,10,13,18,45] The rate of inguinal metastases increases as the tumor size increases. The overall survival in patients with synchronous inguinal node disease is 48% (30%-60%). Large nodes (>2 cm) in larger tumors (T3 or T4) decrease the survival rate even further, to approximately 30%.

There is not one standard protocol for treating synchronous inguinal node disease and various centers use inguinal radiation alone, chemoradiation, or selective groin dissection with follow-up radiation or chemoradiation. The most common approach for treating synchronous nodal disease is chemoradiation. Local control rates are reported as high as 90%.[24,47] Radiation alone results in inferior local control rates of 65%.[38] A radical groin dissection is rarely successful in extending survival and is associated with morbid complications.[10]

Complications occur with radiation and are not insignificant.[45] Although higher doses of radiation help to eradicate disease,[21] the complication rate begins to rise. Split-course radiation may help to minimize complications,[24] but also may be associated with a decrease in survival rates.[32]

Results of Synchronous Node Treatment: The Statistics

In patients treated with chemoradiation, those with synchronous nodal disease had an overall 5-year survival of 54% compared with 74% in patients without synchronous disease. Those with synchronous nodes larger than 2 cm or those with T3 or T4 tumors also had poor survival rates of 30%.[45]

Metachronous Nodes

Metachronous nodes are reported to occur in 5% to 25% of cases.[6,10] These nodes usually appear within 6 months of initial treatment. In one study looking at the treatment of synchronous and metachronous inguinal node metastases, it was stressed that pathologic confirmation was obtained prior to the recommended treatment of limited groin dissection with removal of all macroscopic disease followed by irradiation when the surgical wound had healed. The average time to recurrence after initial treatment was 16 months. The risk for recurrence was higher in T3 and T4 primary lesions. Again it was observed that in patients with tumors clearly located on either side of the anal canal, the metachronous nodal recurrence was in the ipsilateral inguinal region.[45]

Results of Metachronous Node Treatment: The Statistics

In this same study, 8% of 270 patients were found to have metachronous nodal involvement. Using inguinal dissection followed by irradiation, local control of the inguinal region was obtained in 68% but the 5-year survival rate was only 41%.[45] Others have recommend only chemoradiation for metachronous nodal disease. Five-year survival in patients with metachronous nodal disease is approximately 62% when treated with chemoradiation and this appears to be the treatment of choice for metachronous nodal disease. Adding a surgical lymphadenectomy may be useful if chemoradiation fails to eradicate the disease.[10]

HIV-Positive Patients

As squamous cell carcinoma of the anal canal is associated with anoreceptive intercourse, it is useful to look at disease treatment in HIV-positive patients.

In those with CD4 counts as low as 105 cells/mL, especially in those who are not taking HAART, local excision of superficial lesions is associated with excellent results. Patients tend to succumb to HIV rather than anal disease.[48]

Currently, in HIV-positive patients with invasive anal cancer and CD4 levels greater than 200 cells/mL, treatment is similar to that in uninfected patients. In those with lower CD4 counts, treatment remains individualized. Cisplatin has been substituted for MMC and prophylactic inguinal irradiation has been omitted in an effort to reduce toxicity in this group of immunocompromised patients.[49] HAART is important, especially during treatment for SCCs of the anus. Studies have shown that in patients with all stages of anal disease and with widely differing CD4 counts, chemoradiation can be given with low toxicity. Most patients can receive the total planned dose of radiation, but the chemotherapy doses may need to be reduced in 66% of patients and 50% may experience nonfatal hematologic or skin toxicity unrelated to the CD4 counts. Opportunistic infections are rare. Three-year survival rates are high in HIV-positive patients treated with HAART.[48,50]

Treatment Failure: Persistent or Recurrent Disease

Up to 35% of patients may have persistent disease at the conclusion of chemoradiation or recurrent disease more than 6 months post-treatment. When failure occurs in the form of recurrent disease, the disease may appear in the pelvis, regional nodes, or in the anal area. Attempts should be made to distinguish a bona fide recurrence from radiation-induced reactive disease. PET scanning may help in this regard.

Treatment for failed chemoradiation with a pelvic recurrence or with locally recurrent disease, is with a salvage APR with or without a radiation boost.[24] There is a significant rate of wound-healing problems that might require coverage with flaps or grafts. The original T stage is not predictive of survival after salvage attempts, but it appears that node positivity does correlate with mortality rates.[25,32,51] Overall, results of salvage APR show widely discrepant survival rates in the literature. However, this should not preclude salvage therapy. Abdominoperineal resection is contraindicated if there is sidewall fixation precluding curative resection with clear margins.[52] Adjacent organ involvement is not a contraindication to APR as long as tumor-free margins can be obtained.[52]

Treatment Results in Persistent or Recurrent Disease: The Statistics

After salvage attempts, 5-year survival ranges between 24% and 58%.[51-53] If the local recurrence is mobile, median survival is 40 months.[51] Nodal disease at salvage is associated with an 11% 5-year survival.[52] Those with pelvic sidewall fixation after initial treatment, experience an average 8-month survival, with no patient surviving beyond 2 years.[51]

Distant Metastases: Ominous

Distant metastases occur in 10% to 17% of patients,[30,31] and are commonly found in the liver, lung, bone, and subcutaneous tissue. Twenty percent of patients with recurrent disease die from distant metastases.[54] Studies now under way are looking at different combinations of drugs with or without irradiation in the treatment of metastatic disease. When the metastatic disease is isolated and the primary focus of disease has been controlled, metastatic resection may play a role in salvage.

Follow Up: Don't Stop

Follow-up examinations should be performed 6 to 12 weeks after the conclusion of treatment. Regular exams should be conducted every 3 to 6 months for several years as there may be a late recurrence. Examination should include a visual inspection of the operative site, the inguinal region and any other body part of concern to the patient. A digital anorectal exam should be performed and if there is a suspicion

see Anal Canal Cancer page 22

Anal Canal Cancer

Continued from page 20

of persistent or recurrent disease, an open biopsy under sedation should be done. Anoscopy is useful in obtaining a visual inspection of the anorectum. Although no longer used commonly, post-treatment scar excision may be performed in an effort to find and treat any persistent disease.

Summary of Treatment Options

In patients with T1 lesions measuring less than 2 cm in greatest dimension and without sphincter involvement, either local excision or chemoradiation is an acceptable mode of treatment. Chemoradiation is the more common form of primary treatment. The chemotherapeutic agents are 5-FU and MMC. Higher doses of radiation enhance survival, but this may come at the cost of increased morbidity. There should be no treatment breaks if possible.

Synchronous lymph node involvement is rare in T1 lesions. However, it is common to irradiate at least the ipsilateral inguinal field if the lesion is clearly unilateral, or both inguinal fields for less clearly defined laterality. Histopathologic confirmation of apparently involved nodes should be obtained prior to treatment.

In T2, T3, and T4 lesions, treatment is with chemoradiation. Using radiation, the perineal and inguinal fields are irradiated in T2 lesions, as the rate of synchronous nodal involvement increases in these lesions. Pelvic irradiation is added for T3 and T4 lesions.

In those patients developing biopsy-proven metachronous inguinal nodes, chemoradiation may be administered and a surgical lymphadenectomy may be performed for resistant disease.

With persistent or recurrent disease, a salvage APR is performed. Invasion into other pelvic organs (T4) is not a contraindication to resection for cure. However, an APR for salvage should not be performed in patients with pelvic disease if tumor-free margins cannot be obtained.

In patients with recurrence after surgical salvage or in any patients with distant metastases, chemotherapy may have a role to play in treatment. Various chemotherapeutic protocols are available.

In the HIV-positive patient, treatment is as for all other patients, if the CD4 count is greater than 200 cells/mL. HAART therapy should be given concomitantly (unless contraindicated). For those with lower CD4 counts, treatment is individualized with close monitoring for toxicity.

Although squamous cell malignancies are the most common anal and perianal tumors, there is a final group of anal canal tumors that must be considered in any differential diagnosis of a common set of symptoms. This group of rare tumors will be reviewed in the final part of this series. The best that can be said of them is that they are rare.

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