

# Anal Cancer: A Multispecialty Disease, a Multispecialty Cure

## Part 2: Perianal Cancers—Multimodality Treatment

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The anal canal and perianal region are subject to a diverse group of diseases. The anatomy of this region was covered in Part 1 of this series and malignant precursors were discussed. Part 2 will examine perianal cancers. Part 3 will examine squamous cancers of the anal canal. Part 4 will look at unusual cancers of the anal canal.

### Perianal Squamous Cell Carcinoma

Squamous cell carcinomas of the perianal area are 5 times more rare than their anal canal counterparts. They are similar to other skin-based squamous cell cancers. They may be located anywhere on the perianal skin, which begins at the anal verge and extends up to 5 cm outward. Males and females are almost equally affected with an average age at presentation of between 60 and 70 years.<sup>1,2</sup> Symptoms may be similar to those of other benign perianal conditions, often lulling the patient or physician into a false sense of complacency. Misdiagnosis is common and one-third of patients are incorrectly diagnosed at their initial visit to a physician.<sup>3</sup> A late-stage presentation with a large tumor is not uncommon even though a mass, bleeding, pain, discharge, or pruritus should have alerted the patient or physician to a problem at a much earlier time.<sup>1</sup> Even large perianal squamous cancers are often diagnosed 24 months after the first appearance of symptoms.<sup>4</sup> However, diagnostic delay does not seem to worsen the prognosis,<sup>3</sup> underscoring the slow-growing nature of

these tumors. When delay is associated with nodal involvement, cure rates are poor.

These tumors are commonly keratinized and well differentiated, similar to typical skin cancers. Lymphatic spread to the inguinal and femoral nodes may occur, but usually only in larger lesions (Figure 1). Further spread occurs via the iliac nodal system.

As was discussed in Part 1 of this series, certain genotypes of human papillomavirus (HPV) are strongly associated with anal canal squamous cancers, especially those cancers proximal to the dentate line where the mucosa is commonly non-keratinized. In these cancers, HPV is thought to play a prominent role in causation. However, perianal squamous cancers are located in keratinized skin and less often have associated HPV. The etiology of perianal squamous cell cancers may be different from those found in the anal canal.

### What Do They Look Like and How Are They Diagnosed?

Not all perianal skin lesions are malignant. Symptoms of a short duration, symmetrical rashes, and local irritations that resolve with topical therapy are usually secondary to a benign condition. Once the condition has resolved, patients should be followed to ensure that resolution has been maintained. However, persistent or recurrent symptoms call for further attention and biopsy.

When clinical suspicion prompts investigation, diagnosis is usually straightforward. A visual examination may be telling. The tumor appears as a central ulcer with rolled, everted edges

(Figure 2). It may be small, less than 1 cm, or may be large, obstructing the anal opening. A digital exam will yield information about the lesion, its size, and the possible presence of tumor fixation to underlying structures. Any non-healing ulceration should be considered malignant and biopsied. Although a biopsy can be performed in the office setting, patient comfort and diagnostic precision are enhanced when patients are examined under anesthesia. It is important to differentiate anal canal lesions from perianal lesions, as prognosis and treatment programs may differ. The location of the tumor relative to the anal verge should be noted at the time of biopsy. A pelvic exam should be performed in women to search for vaginal invasion or associated genital lesions. Patients must be examined for involved lymph nodes, with careful evaluation of the inguinal nodal system. Suspicious nodes may be evaluated with fine needle aspiration. A chest x-ray should be performed looking for metastatic disease. Chest computed tomography (CT) scanning can be performed if the chest x-ray is worrisome for the spread of disease. Although perianal squamous carcinoma is not specifically associated with other colon cancers, a colon evaluation should be performed in patients who would otherwise have an examination under the present screening guidelines.

CT scanning or magnetic resonance imaging (MRI) evaluation of the abdomen and pelvis are recommended to search for liver involvement and possible nodal disease. A caveat: Scanning may be unreliable when evaluating nodal systems due to the limitations of the technology

**Table.** The TNM Staging System for Perianal Squamous Cell Cancer<sup>5</sup>

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
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 extradermal tissue(s): bone, cartilage, skeletal muscle
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastases (M)	
M0	No distant metastasis
M1	Distant metastasis
MX	Presence of distant metastasis cannot be assessed

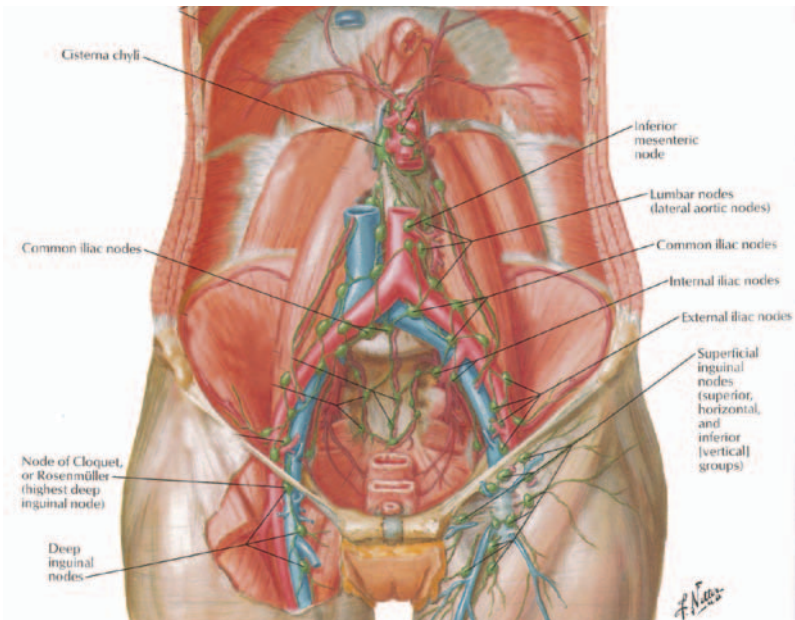
Source: American Joint Committee on Cancer. *Cancer Staging Manual*. Seventh edition, 2009.

when examining small lymph nodes, or the inability of the technology to differentiate nodes with metastatic disease from nodes with reactive hyperplasia. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, 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). Endoanal ultrasound, although useful in evaluating fistulous disease and rectal malignancies, has an ill-defined role in the evaluation of perianal cancers. It may be useful in evaluating potential sphincter involvement by a locally invasive lesion.

### TNM—The 2010 AJCC Staging System

The American Joint Committee on Cancer classification of malignant tumors (TNM) staging system for anal cancers is used for staging the disease<sup>5</sup> (Table).

The T-stage of an anal cancer refers to the size of the lesion at its greatest dimension. T1 tumors are 2 cm or less. T2 tumors are greater than 2 cm but less than 5 cm. T3 lesions measure greater than 5 cm, and T4 tumors are of any size with invasion into adjacent extradermal tissues such as cartilage, skeletal



**Figure 1.** Pelvic lymph node drainage. April 2011. Used with permission of Elsevier. All rights reserved.



**Figure 2.** Squamous cell carcinoma of the perianal skin.

From: Gordon PH, Nivatvongs S. Perianal neoplasms. In: Principles and Practice of Surgery for the Colon, Rectum, and Anus. New York, NY: Informa Healthcare; 2007. Reprinted with permission.



muscle, or bone. With respect to nodal status, the TNM system recognizes the absence or presence of regional nodes, with N0 representing the absence of involved nodes and N1 representing the presence of involved nodes. The system is similar with respect to metastatic disease, with M1 referencing the presence of distant metastatic disease.

The 2 most important factors affecting survival and predicting prognosis are the diameter of the lesion and the absence or presence of involved lymph nodes. These are both reflected in the TNM system. Survival rates worsen significantly as the tumor diameter increases. In the 1992 study by Papillon, 17.5% of patients presented with T1 lesions and had 100% survival; 66.6% of patients presented with T2 lesions and had a survival rate of 61%; and 15.8% of patients presented with T3 lesions, with a survival rate of 12.5%.<sup>2</sup>

The incidence of nodal involvement also increases with increasing tumor size. With nodal metastases, survival rates again decrease. In the same study, 26% of patients had inguinal nodal metastases at the time of presentation. Nodal metastases were never seen with primary tumors less than 2 cm (T1). In T2 tumors between 2 and 5 cm, nodes were involved in 23% of cases, and in tumors greater than 5 cm (T3), nodes were involved in 67% of cases.<sup>2</sup> Other important tumor factors potentially affecting survival are the depth of the tumor, specifically the possible presence of sphincter involvement, the degree of tumor differentiation, and the location of the primary tumor.

Although controversy exists regarding certain treatment aspects, it is well accepted that later-stage disease is associated with a poor response to operative intervention, and is treated best with radiation or chemoradiation.<sup>2,6,7</sup> Again, tumor size and nodal status are instrumental in determining the disease stage.

### Treatment Options

Historically, wide local excision (WLE) or abdominoperineal resection (APR) were used to treat perianal cancers. Failure rates were found to be high except in a small, select group of patients with early lesions. Present-day treatment options have evolved considerably and are tailored to the specifics of the individual stage of the disease.

Currently, available options for eradicating disease are radiation therapy, with or without chemotherapy, or surgical excision in select cases. While radiation therapy, with or without chemotherapy, is the most common form of treatment, surgical excision is appropriate and effective in a small group of perianal cancers. The use of APR for initial tumor

treatment is now of historical interest as local recurrence rates were found to range from 27% to 47% and 5-year survival rates ranged from 40% to 70%.<sup>6,8</sup> APR is reserved for those patients with persistent or recurrent disease. APR also may be used in those infrequent patients with sphincter involvement and incontinence, in those with particularly bulky disease, or in those who have failed initial nonsurgical treatment.

### Carcinoma in Situ or T1 Disease: T1 N0

Treatment commonly depends on the experience and judgment of the treating physician(s).

Cure rates approach 100% using WLE when treating carcinoma in situ or T1 lesions. Lesions must not involve the anal sphincter to a substantial degree, and should be excisable with a 1-cm margin of normal tissue.<sup>1,9,10</sup> The surgical option is an attractive one as radiation therapy is not without associated morbidity, including anal skin irritation, variable degrees of incontinence, proctitis, and bleeding. Chemotherapy is associated with well-known systemic side effects.

There are patients who cannot or will not undergo surgical extirpation. Or, it may not be possible to obtain the necessary 1-cm margin of normal tissue around the tumor without disfigurement or dysfunction. Radiation therapy is the treatment of choice in these situations.

Radiation treatment of anal cancers has been used since the close of World War I.<sup>11,12</sup> The success of this modality was offset by the severe complications suffered as a result of the irradiation. The surgical option then became the preferred mode of treatment of anal cancers. Radiation therapy experienced a resurgence in use as better equipment and administration techniques became available. Its use in treating anal canal cancers increased in the 1970s. The renewed use of radiation in the treatment of perianal cancers followed shortly thereafter.

Chemoradiation of anal canal tumors was introduced by Norman Nigro in 1972.<sup>13</sup> Subsequent to this, many physicians began using chemoradiation to treat perianal squamous cancers as well. Although not completely substantiated, it appears that chemoradiation is superior in many aspects when compared with radiation alone in the treatment of perianal squamous carcinomas.<sup>14</sup> Five-year survival rates approach 100%, similar to those rates seen with surgical extirpation.<sup>2,6,15,16</sup> The chemotherapeutic drugs used in treatment are fluorouracil (5-FU), a well-known pyrimidine analogue whose metabolites are cytotoxic when incorporated into DNA and RNA, and mitomycin C (MMC). MMC is an

alkylating agent that binds to DNA and inhibits DNA synthesis. It is a radiosensitizer that is thought to target radiation-resistant hypoxic cells, rendering them more vulnerable to the effects of the radiation.

### Inguinal Nodal Prophylaxis in Early Lesions

For the most part, superficial T1 tumors do not spread to the inguinal nodal basins. Persistent disease after treatment or recurrent disease is also rare. T1 lesions are almost never associated with lymph node disease,<sup>2</sup> allowing for the following conclusions: First, prophylactic surgical lymphadenectomy, a procedure associated with potential and significant morbidity in the form of lymphedema, is not needed or recommended in conjunction with WLE, unless the disease is associated with biopsy-proven nodal involvement, and even then, the disease may be treated with inguinal radiation rather than operative excision. Biopsies should be performed to differentiate lymph node metastases from nodal reactive hyperplasia. Second, routine prophylactic inguinal node irradiation, also associated with the potential for morbidity in the form of lymphedema, is not needed or recommended in conjunction with

curative perineal radiation or chemoradiation unless the disease is associated with biopsy-proven nodal metastases.<sup>1,8,9</sup> It should be noted that the treatment of clinically uninvolved inguinal regions is not standardized between institutions, and many clinicians do administer prophylactic radiation to these areas.

### Larger Lesions: T2, T3, T4, and N1

Treatment of early T2 lesions may be by WLE or radiation therapy.<sup>9</sup> Radiation is administered through perineal portals. However, many institutions add inguinal irradiation as even small T2 lesions may be associated with inguinal disease.<sup>2</sup> The definition of an "early" T2 lesion is subjective and there is a risk for missed, untreated inguinal lymph nodes with only WLE of early T2 tumors. Radiation of the perineal and inguinal fields as the initial mode of treatment may be the more prudent alternative.

Larger T2 cancers and T3 and T4 cancers are usually treated with chemoradiation. Operative intervention is reserved for salvage of persistent or recurrent disease, for patients with large, bulky tumors, or for those patients unable or unwilling to undergo chemoradiation. With these more ominous tumors, prognosis worsens as survival rates decrease.

SEE ANAL CANCER page 10

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Inguinal Nodal Prophylaxis In Larger Lesions

While the incidence of lymph node involvement for T1 tumors approaches 0%, the incidence of nodal disease rises to 23% in T2 lesions and 67% in T3 lesions,<sup>2</sup> necessitating the addition of nodal irradiation. Both the perineal and inguinal fields are treated in T2 disease.<sup>2,7</sup> With the larger T3 and T4 lesions, pelvic irradiation is added.<sup>2,9,17,18</sup>

Local control rates are variable with

radiation therapy alone. The literature reports widely differing results and often is not clear as to how patients are stratified, as many studies report results of treatment mixing patients receiving radiation alone with patients receiving chemoradiation. Local control rates range from 60% to 100% for T2 lesions and 37% to 100% in T3 lesions.<sup>2,7,15,16,18</sup> Fifty percent of irradiated patients with persistent tumor after treatment may be salvaged with further operative treatment or a radiation boost, thus raising the overall success rates of treatment.<sup>10</sup>

The overall 5-year survival rates range

from 40% to 100% with survival rates decreasing with increasing tumor size (T-stage) or with the presence of nodal disease (N1).<sup>6,9</sup> Again, caution must be used when comparing treatment results based on differing treatment modalities.

There are data showing that chemoradiation is superior to radiation alone with respect to local control rates.<sup>16</sup> Additional data come from a study comparing radiation alone versus chemoradiation in the treatment of squamous cell cancers of the anal canal and anal margin. In this UKCCCR study,<sup>19</sup> chemoradiation was found to be superior to radiation alone



Figure 3. Paget's disease of the perianal skin.

in local control rates. However, there was no improvement in overall survival. The authors noted that adding chemotherapy to the radiation treatment “increased immediate morbidity but did not add materially to long-term problems” and suggested that adding 5-FU and mitomycin C to radiation therapy should be the standard treatment protocol for perianal cancers.

Long-term follow-up is necessary in these patients as recurrences can occur as late as 11 years after the initial treatment. Patients must be educated as to the warning signs of a recurrence. Symptoms of recurrence are indolent and patients may complain of seemingly benign perineal discomfort, a lump, bleeding, or soiling.

While post-treatment scar excision looking for persistent disease is not uncommonly performed for anal canal cancers, post-treatment scar excision may also be performed for post-treatment perianal cancers if the scar looks atypical or suspicious for persistent or recurrent disease.

Patients with persistent disease who were originally treated with radiation or chemoradiation may be salvaged with WLE or an APR with a 50% salvage rate. Patients with recurrence after a disease-free interval also may be treated with attempted surgical salvage.<sup>19</sup>

Chemoradiation: A Toxic Cure

With radiation doses greater than 40 Gy, the complication rate increases. Complications may be systemic, such as dermatitis, mucositis, diarrhea, fatigue, or bone marrow suppression. Death is rare. Local complications include cystitis, small bowel obstruction, and iliac artery stenosis. Anorectal function is commonly preserved in up to 90% of patients, but there may be associated anorectal irritability with tenesmus, proctitis, diarrhea, bleeding, urgency, and incontinence. Most of these 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.

Anemia, neutropenia, or thrombocytopenia may occur in up to 64% of patients receiving MMC. This is



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WARNINGS AND PRECAUTIONS

- Potential risk of thrombosis if absorbed systemically.
- In patients with known hypersensitivity to snake proteins, there may be a potential for allergic reaction.

ADVERSE REACTIONS

The serious adverse event that occurred in ≥ 1% (n=6/583) of patients exposed to RECOTHROM in completed clinical trials was atrial fibrillation. The most common adverse events in patients exposed to RECOTHROM in clinical trials (N=583) were incision site pain (51%), procedural pain (30%), and nausea (28%).

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials have been performed with RECOTHROM applied with absorbable gelatin sponge (Phase 2, Phase 3, and Phase 3b studies) and applied with a spray applicator (Phase 2 study). Adverse events reported in clinical trials were consistent with those commonly observed in surgical patients.

• Clinical Trials of RECOTHROM Used in Conjunction with Gelatin Sponge

Among the 411 patients treated with study drug in the randomized, double-blind, Phase 3 study that compared RECOTHROM to bovine thrombin, both applied with gelatin sponge, in patients undergoing spinal surgery, hepatic resection, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access, all but 2 patients (1 patient/treatment group) reported adverse events. Most events were moderate in severity and had a similar incidence in the RECOTHROM and bovine thrombin treatment groups. The most common adverse events were incision site pain (63% for both treatment groups), procedural pain (RECOTHROM 29%; bovine thrombin 34%), and nausea (RECOTHROM 28%; bovine thrombin 35%). Serious adverse events were reported by 18% of patients treated with RECOTHROM and 22% with bovine thrombin.

Adverse events of interest were pre-specified, based on the thrombin mechanism of action, use of absorbable gelatin sponge, USP, historical reporting in association with cross-reacting antibodies to bovine thrombin product, and results from Phase 2 clinical trials of RECOTHROM applied with absorbable gelatin sponge. The incidences of these pre-specified adverse events were similar between treatment groups (see Table 1).

Table 1. Events of Interest in the RECOTHROM Phase 3 Study

AE Category*	RECOTHROM (N=205) n (%)	Thrombin-JMI† (N=206) n (%)
Patients with any event category	124 (60%)	136 (66%)
Bleeding	27 (13%)	24 (12%)
Cardiac	41 (20%)	38 (18%)
Hypersensitivity	30 (15%)	37 (18%)
Nausea + vomiting	68 (33%)	83 (40%)
Other infection	26 (13%)	31 (15%)
Post-operative wound infection	19 (9%)	22 (11%)
Thromboembolic	12 (6%)	10 (5%)

\*Adverse events were included in event categories based on a blinded review of the investigator verbatim and coded terms.

†THROMBIN-JMI® Thrombin, Topical (Bovine).

In an open-label, single-group Phase 3b study, 209 patients with documented or highly likely prior exposure to bovine thrombin within the previous 3 years were treated with RECOTHROM when undergoing surgeries (spinal or peripheral arterial bypass or arteriovenous graft formation for hemodialysis access). The most common adverse events were incision site pain (45%), procedural pain (39%), and nausea (27%). Similar to the Phase 3 study, serious adverse events were reported by 22% of patients treated with RECOTHROM.

• Clinical Trials of RECOTHROM Applied with Spray Applicator

In an open-label, single-group, Phase 2 study in burn patients, 72 patients were treated with RECOTHROM applied with a spray applicator at the burn wound excision site prior to autologous skin grafting. This study included both adults (≥ 17 years of age, n=68) and pediatric patients ≤ 16 years of age (n=4). The most common adverse events in the adult and pediatric age groups included procedural pain (35%), pruritis (25%), and constipation (19%).

• Immunogenicity

The potential development of antibodies to RECOTHROM has been evaluated in multiple clinical trials. These pre-specified evaluations were performed in order to characterize the immunogenicity of RECOTHROM and the neutralizing potential of any detected antibodies. In completed clinical studies 5 of 552 (0.9%) patients exposed to RECOTHROM with both baseline and post-treatment antibody specimens available developed specific anti-RECOTHROM product antibodies. None of these antibodies were found to neutralize native human thrombin.

In the randomized, double-blind, Phase 3 study that compared RECOTHROM to bovine thrombin, both applied with gelatin sponge, in patients undergoing spinal surgery, hepatic resection, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access, the development of specific anti-product antibodies was evaluated in both treatment groups. Blood samples were collected at baseline and at day 29 for 97% of the patients in both treatment groups. For patients randomized to RECOTHROM, the samples were analyzed by ELISA for antibodies to RECOTHROM, Chinese hamster ovary (CHO) host cell protein, and pro-thrombin activator (used in the conversion of single chain precursor to active RECOTHROM). For patients randomized to bovine thrombin, the samples were analyzed by ELISA for antibodies to bovine thrombin product.

At baseline 1.5% of patients (n=3/198) in the RECOTHROM group had positive anti-product antibody titers compared with 5% of patients in the bovine thrombin group (n=10/200). Of the patients who had detectable anti-product antibodies at baseline, 0 of 3 in the RECOTHROM group and 8 of 10 in the bovine thrombin group exhibited ≥ 1.0 titer unit (≥ 10-fold) increases in antibody levels after study treatment.

Treatment with RECOTHROM applied with absorbable gelatin sponge resulted in a statistically significantly lower incidence of specific anti-product antibody development. Three of 198 (1.5%; 95% CI, 0 to 4%) of the patients in the RECOTHROM arm developed specific anti-thrombin product antibodies (1 patient also developed anti-CHO host cell protein antibodies). No patients developed antibodies to pro-thrombin activator. Forty-three of 200 patients (22%; 95% CI, 16 to 28%) in the bovine thrombin arm developed specific antibodies to bovine thrombin product. None of the antibodies in the RECOTHROM group neutralized native human thrombin. Antibodies against bovine thrombin product were not tested for neutralization of native human thrombin. Because the study was not powered to detect a difference in clinical outcomes attributable to antibody formation, no conclusions can be drawn regarding the clinical significance of the difference in antibody formation based on the results of this study.

In the open-label, single group, Phase 3b study in patients with a high likelihood of prior bovine thrombin exposure undergoing spinal, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access, 15.6% of patients (n=32/205) had anti-bovine thrombin product antibodies at baseline prior to treatment with RECOTHROM. Following treatment, none of the 200 evaluable patients (patients for whom specimens were available for antibody testing at baseline and post-RECOTHROM treatment) developed antibodies to RECOTHROM.

In the randomized, double-blind, controlled Phase 2 studies of RECOTHROM compared to placebo (RECOTHROM excipients reconstituted with 0.9% sodium chloride, USP) applied in conjunction with absorbable gelatin sponge, which were performed across a range of surgical settings (spinal surgery, hepatic resection, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access), the incidence of antibody development to RECOTHROM was 1.2% in the RECOTHROM group (n=1/83) compared to 2.4% (n=1/41) in the placebo group. In the open-label, single group Phase 2 study of RECOTHROM applied with the spray applicator to excised burn wounds, 1 patient developed antibodies following treatment (1.6%, n=1/62).

The detection of antibody formation is highly dependent upon the sensitivity and specificity of the assay. The absolute immunogenicity rates reported here are difficult to compare with results from studies of other products due to differences in assay methodology, patient populations, and other underlying factors.

To report SUSPECTED ADVERSE REACTIONS, contact ZymoGenetics, Inc. at 1-888-784-7662, or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

DRUG INTERACTIONS

Drug interactions have not been formally studied.

USE IN SPECIFIC POPULATIONS

• Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with RECOTHROM. It is also not known whether RECOTHROM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RECOTHROM should be given to a pregnant woman only if clearly needed.

• Pediatric Use

Of the 72 patients undergoing burn wound excision and grafting treated with RECOTHROM applied with the spray applicator in the open-label, single group, Phase 2 study, 4 were pediatric patients. All were age 12 to 16 years. The safety and effectiveness of RECOTHROM in all pediatric age groups have not been fully established.

• Geriatric Use

Of the total number of patients in Phase 2 and Phase 3 clinical studies of RECOTHROM with absorbable gelatin sponge, 38% were 65 years old and over, while 16% were 75 years old and over.

No substantive differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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more pronounced in those receiving high doses of MMC (greater than 50 mg/m<sup>2</sup>).

In a Phase II trial evaluating chemoradiation in perianal squamous cancers, oral capecitabine was substituted for 5-FU. This decreased infusion needs and decreased hospital stays. Toxicity was found to be minimal and the regimen was well tolerated. Local control rates were found to be 70%.<sup>20</sup>

### Summary of Initial Treatment Options In Carcinoma in Situ or T1 Lesions

In patients with carcinoma in situ or T1 lesions, treatment may be initiated with either operative excision or chemoradiation. To be eligible for the surgical approach, the lesion must not involve the anal sphincter to a substantial degree, and a 1-cm margin of normal tissue should be obtained. In the case in which the anal sphincter is involved with disease, treatment with chemoradiation is associated with less anal dysfunction. Inguinal nodal basins need not be irradiated unless associated with biopsy-proven metastatic disease, or unless metachronous disease develops. However, many clinicians do routinely administer prophylactic radiation to clinically normal inguinal regions.

### Summary of Initial Treatment Options in T2, T3, and T4 Lesions

In patients with T2, T3, and T4 lesions, chemoradiation is the primary mode of treatment. Radiation is directed at the perineal and inguinal fields in T2 lesions. Radiation is directed toward the perineal, inguinal and pelvic basins in T3 and T4 tumors.

Persistent or recurrent disease is treated with surgical salvage.

### A Final Note Regarding Treatment

Active research is ongoing in an effort to further improve survival rates and decrease toxicity rates associated with treatment. For now, physicians should rely on one of the known treatment regimens administered by those with experience in this area. Long-term close follow-up is critically important.

### Paget's Disease

Perianal Paget's disease is thought to be a neoplasm arising from the apocrine glands of the perianal skin. Unlike its mammary counterpart, perianal Paget's disease may begin as a benign condition in the apocrine glands, and later transform into an invasive adenocarcinoma, spreading into the epidermis.<sup>21</sup> Another theory holds that the disease begins as an intraepithelial adenocarcinoma with a lengthy preinvasive phase,

that subsequently spreads to the deeper dermis.<sup>17,22,23</sup>

Paget's disease is exceedingly rare, with less than 200 reported cases. It affects people in the seventh decade of life and affects men and women equally.<sup>24</sup>

Pruritus is a common presenting symptom, enlarging the differential diagnosis greatly. Other presenting symptoms include an erythematous perianal skin rash with eczema, oozing or scaling, weight loss, inguinal adenopathy, or constipation. The diagnosis is often delayed because of the tumor's

similarity to many other benign anal skin conditions and because of physician unfamiliarity with the disease. The presenting lesion may be circumferential<sup>25</sup> and extend proximally to the dentate line (Figure 4). The average duration of symptoms prior to diagnosis is 3 years.<sup>26,27</sup> Anal Paget's disease may present in up to 40% of cases with an associated invasive adenocarcinoma.<sup>23,25,28</sup>

A thorough anorectal examination must be performed looking for an associated carcinoma requiring more extensive treatment. A full colon evaluation and a search for visceral carcinomatosis

are conducted. Visceral spread occurs in up to 50% of cases.<sup>22,24</sup> Common sites of spread include the gastrointestinal tract, prostate, neck, and nasopharynx.<sup>23,25-27</sup>

A biopsy of the affected area will confirm the diagnosis. Hematoxylin and eosin (H&E) staining will differentiate Paget's disease from the similar-appearing AIN and will show large, rounded cells, a large peripheral nucleus and abundant cytoplasm (Figure 4). Staining with CK7 and CK20 will differentiate Paget's disease from anorectal adenocarcinoma.

see ANAL CANCER page 12

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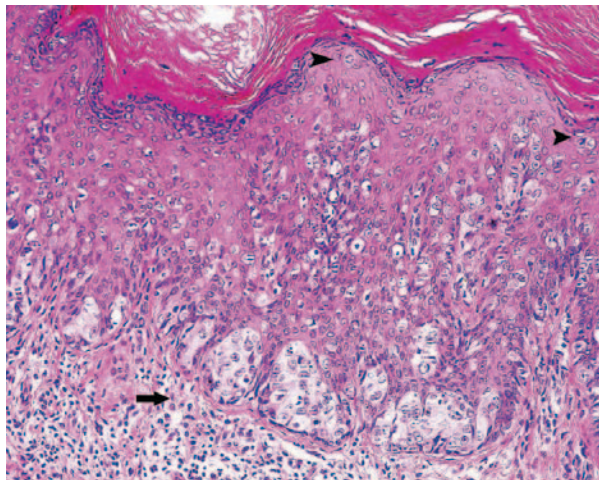
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## ANAL CANCER

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**Figure 4.** The pathology of Paget's disease. Histological examination of Paget's disease demonstrates malignant cells characterized by enlarged vesicular nuclei, prominent nucleoli and pale cytoplasm within the epidermis. The malignant cells can be arranged in nests that may "crush" the basal keratinocytes (arrow) or scattered throughout the epidermis in a "buckshot" pattern. All layers of the epidermis are affected, including the granular layer (arrowheads).

### Treatment Options for Paget's Disease

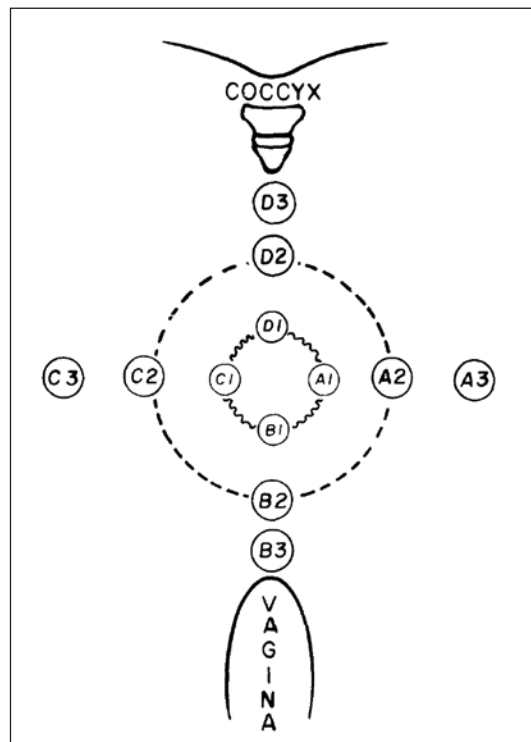
For patients who do not have an invasive cancer, WLE is the treatment of choice. Small lesions are excised and left open, or closed primarily, while large defects are covered with a rotational flap, advancement flap or split thickness skin graft. Preoperatively, dermatologic punch biopsies can be used to plan WLE margins. Once the excision is completed, intraoperative frozen sections are obtained to ensure adequate excisional margins.<sup>22</sup> Positive margins require further excision or a return to the operating room for re-excision if intraoperative frozen sections were not utilized.<sup>24</sup> The intraoperative biopsies must be taken 1 cm from the obvious edges of the tumor and in all 4 perineal quadrants, and must include both the outer skin margins and inner, anal canal margins to the dentate line<sup>29</sup> (Figure 5). If the margins are found to be clear on frozen section, a skin graft is used to cover the excision site.

With a noninvasive tumor, survival may approach 100%.<sup>29</sup>

Patients must be followed over a long period of time looking for local recurrence or invasive disease amenable to retreatment. Recurrence rates are reported ranging from 37% to 100%<sup>23,28,29</sup> and most recurrences can be treated with wide excision. The development of invasive disease is associated with a poor prognosis.

Patients initially presenting with invasive disease may be candidates for an APR with an added inguinal lymphadenectomy if documented nodal disease is present. However, at the time of presentation, these patients have a 25% incidence of metastatic spread and all patients who die of anal Paget's disease have an invasive component.<sup>23</sup> This does not rule out aggressive treatment of patients with invasive disease, nor does it mean that all patients with invasive disease require an APR. In one study, 12 patients had invasive disease and yet only 2 patients died of the disease. In this same study, however, 4 of 5 patients who had invasive disease and who underwent an APR were free of disease. Clearly, judgment is required.<sup>23</sup>

At present, the role of chemoradiation or perineal



**Figure 5.** Intraoperative biopsy sites for Paget's disease treatment.

Beck DE, Fazio VW. Perianal Paget's disease. *Dis Colon Rectum*. 1987; 30(4):263-266.

ation therapy is unclear.<sup>30</sup> However, chemoradiation may have a role in those patients unwilling or unable to undergo surgical excision.<sup>23</sup>

### Basal Cell Carcinoma

Even rarer is the perianal basal cell carcinoma. Occurring in the seventh and eighth decades of life, more commonly in men than in women, the lesion looks like other cutaneous basal cell cancers with raised, rolled edges and a central ulceration. They rarely metastasize. The etiology of basal cell carcinoma is unknown. They do not contain HPV. Up to one-third have a history of a basal cell cancer at another bodily location.<sup>31</sup> Lesions are usually smaller than 2 cm.<sup>32</sup> They may also present as papules, plaques, nodules, or ulcers. They are superficial and mobile, making wide excision straightforward. As they are of a low invasive potential, treatment is gratifying. However, recurrence is not uncommon and a re-excision is the mainstay of treatment. APR or radiotherapy may be used for large lesions with anal canal extension, although this situation occurs rarely.<sup>33</sup> In several series, no patients died of the disease after treatment. Five-year survival with adequate excision or re-excision, if necessary, is 100%.<sup>34</sup>

### Verrucous Carcinoma

Associated with HPV-6 and 11, verrucous carcinoma or Buschke-Lowenstein tumor is a huge, soft, fleshy, cauliflower-like cancer that is painful and slow-growing (Figure 6). It affects men almost 3 times more often than women in the fifth decade of life. Symptoms include pain, abscesses, pruritus, bleeding, a malodorous smell, and altered bowel habits. Located on the perianal skin or in the distal anal canal or rectum, these lesions are relentless in their growth. Although benign when viewed under the microscope, they must be considered malignant in their behavior, with the potential for local erosion, invasion into the ischioanal fossa and perirectal tissue. CT scanning will define the extent of invasion. Microscopically, verrucous carcinoma looks like condyloma acuminata. It does not metastasize.<sup>21,33</sup>

WLE is the treatment of choice, with APR performed in unusual cases of late-stage disease with



**Figure 6.** Perianal verrucous carcinoma.

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sphincter invasion. Radical excision may be necessary in order to achieve a cure. Reports of radiotherapy, imiquimod treatment and CO<sub>2</sub> laser treatment are available, but wide excision with postoperative vigilance looking for recurrences is the mainstay of therapy.

Moving in the proximal direction, the next review (Part 3) will focus on squamous cell carcinoma of the anal canal.

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TEFLARO™ (ceftaroline fosamil) injection for intravenous (IV) use  
Brief Summary of Full Prescribing Information  
Initial U.S. Approval: 2010

**INDICATIONS AND USAGE:** Teflaro™ (ceftaroline fosamil) is indicated for the treatment of patients with the following infections caused by susceptible isolates of the designated microorganisms. **Acute Bacterial Skin and Skin Structure Infections** - Teflaro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Klebsiella oxytoca*. **Community-Acquired Bacterial Pneumonia** - Teflaro is indicated for the treatment of community-acquired bacterial pneumonia (CAP) caused by susceptible isolates of the following Gram-positive and Gram-negative microorganisms: *Streptococcus pneumoniae* (including cases with concurrent bacteremia), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Escherichia coli*. **Usage** - To reduce the development of drug-resistant bacteria and maintain the effectiveness of Teflaro and other antibacterial drugs, Teflaro should be used to treat only ABSSSI or CAP that are proven or strongly suspected to be caused by susceptible bacteria. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to ceftaroline. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

**CONTRAINDICATIONS:** Teflaro is contraindicated in patients with known serious hypersensitivity to ceftaroline or other members of the cephalosporin class. Anaphylaxis and anaphylactoid reactions have been reported with ceftaroline.

**WARNINGS AND PRECAUTIONS: Hypersensitivity Reactions** - Serious and occasionally fatal hypersensitivity (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterials. Before therapy with Teflaro is instituted, careful inquiry about previous hypersensitivity reactions to other cephalosporins, penicillins, or carbapenems should be made. If this product is to be given to a penicillin- or other beta-lactam-allergic patient, caution should be exercised because cross sensitivity among beta-lactam antibacterial agents has been clearly established. If an allergic reaction to Teflaro occurs, the drug should be discontinued. Serious acute hypersensitivity (anaphylactic) reactions require emergency treatment with epinephrine and other emergency measures, that may include airway management, oxygen, intravenous fluids, antihistamines, corticosteroids, and vasopressors as clinically indicated. **Clostridium difficile-associated Diarrhea** - *Clostridium difficile*-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents, including Teflaro, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur more than 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated [see *Adverse Reactions*]. **Direct Coombs' Test Seroconversion** - Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving Teflaro and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. In the pooled Phase 3 CABP trials, 51/520 (9.8%) of Teflaro-treated patients compared to 24/534 (4.5%) of ceftriaxone-treated patients seroconverted from a negative to a positive direct Coombs' test result. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after treatment with Teflaro, drug-induced hemolytic anemia should be considered. Diagnostic studies including a direct Coombs' test, should be performed. If drug-induced hemolytic anemia is suspected, discontinuation of Teflaro should be considered and supportive care should be administered to the patient (i.e. transfusion) if clinically indicated. **Development of Drug-Resistant Bacteria** - Prescribing Teflaro in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

**ADVERSE REACTIONS:** The following serious events are described in greater detail in the Warnings and Precautions section: Hypersensitivity reactions; *Clostridium difficile*-associated diarrhea; Direct Coombs' test seroconversion. **Adverse Reactions from Clinical Trials** - Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be compared directly to rates from clinical trials of another drug and may not reflect rates observed in practice. Teflaro was evaluated in four controlled comparative Phase 3 clinical trials (two in ABSSSI and two in CAP) which included 1300 adult patients treated with Teflaro (600 mg administered by IV over 1 hour every 12h) and 1297 patients treated with comparator (vancomycin plus aztreonam or ceftriaxone) for a treatment period up to 21 days. The median age of patients treated with Teflaro was 54 years, ranging between 18 and 99 years old. Patients treated with Teflaro were predominantly male (63%) and Caucasian (82%). **Serious Adverse Events and Adverse Events Leading to Discontinuation** - In the four pooled Phase 3 clinical trials, serious adverse events occurred in 98/1300 (7.5%) of patients receiving Teflaro and 100/1297 (7.7%) of patients receiving comparator drugs. The most common SAEs in both the Teflaro and comparator treatment groups were in the respiratory and infection system organ classes (SOC). Treatment discontinuation due to adverse events occurred in 35/1300 (2.7%) of patients receiving Teflaro and 48/1297 (3.7%) of patients receiving comparator drugs with the most common adverse events leading to discontinuation being hypersensitivity for both treatment groups at a rate of 0.3% in the Teflaro group and 0.5% in comparator group. **Most Common Adverse Reactions** - No adverse reactions occurred in greater than 5% of patients receiving Teflaro. The most common adverse

reactions occurring in > 2% of patients receiving Teflaro in the pooled phase 3 clinical trials were diarrhea, nausea, and rash. Table 4 in the full prescribing information lists adverse reactions occurring in ≥ 2% of patients receiving Teflaro in the pooled Phase 3 clinical trials (two in ABSSSI and two in CAP). The first value displays the percentage of patients in the pooled Teflaro trials (N=1300) and the second shows the percentage in the Pooled Comparators<sup>a</sup> trials (N=1297). **Gastrointestinal disorders:** Diarrhea (5%, 3%), Nausea (4%, 4%), Constipation (2%, 2%), Vomiting (2%, 2%); **Investigations:** Increased transaminases (2%, 3%); **Metabolism and nutrition disorders:** Hypokalemia (2%, 3%); **Skin and subcutaneous tissue disorders:** Rash (3%, 2%); **Vascular disorders:** Phlebitis (2%, 1%) <sup>a</sup> Comparators included vancomycin 1 gram IV every 12h plus aztreonam 1 gram IV every 12h in the Phase 3 ABSSSI trials, and ceftriaxone 1 gram IV every 24h in the Phase 3 CAP trials. **Other Adverse Reactions Observed During Clinical Trials of Teflaro** - Following is a list of additional adverse reactions reported by the 1740 patients who received Teflaro in any clinical trial with incidences less than 2%. Events are categorized by System Organ Class. **Blood and lymphatic system disorders** - Anemia, Eosinophilia, Neutropenia, Thrombocytopenia; **Cardiac disorders** - Bradycardia, Palpitations; **Gastrointestinal disorders** - Abdominal pain; **General disorders and administration site conditions** - Pyrexia; **Hepatobiliary disorders** - Hepatitis; **Immune system disorders** - Hypersensitivity, Anaphylaxis; **Infections and infestations** - *Clostridium difficile* colitis; **Metabolism and nutrition disorders** - Hyperglycemia, Hyperkalemia; **Nervous system disorders** - Dizziness, Convulsion; **Renal and urinary disorders** - Renal failure; **Skin and subcutaneous tissue disorders** - Urticaria.

**DRUG INTERACTIONS:** No clinical drug-drug interaction studies have been conducted with Teflaro. There is minimal potential for drug-drug interactions between Teflaro and CYP450 substrates, inhibitors, or inducers; drugs known to undergo active renal secretion; and drugs that may alter renal blood flow [see *Clinical Pharmacology*].

**USE IN SPECIFIC POPULATIONS: Pregnancy Category B** - Developmental toxicity studies performed with ceftaroline fosamil in rats at IV doses up to 300 mg/kg demonstrated no maternal toxicity and no effects on the fetus. A separate toxicokinetic study showed that ceftaroline exposure in rats (based on AUC) at this dose level was approximately 8 times the exposure in humans given 600 mg every 12 hours. There were no drug-induced malformations in the offspring of rabbits given IV doses of 25, 50, and 100 mg/kg, despite maternal toxicity. Signs of maternal toxicity appeared secondary to the sensitivity of the rabbit gastrointestinal system to broad-spectrum antibacterials and included changes in fecal output in all groups and dose-related reductions in body weight gain and food consumption at ≥ 50 mg/kg; these were associated with an increase in spontaneous abortion at 50 and 100 mg/kg. The highest dose was also associated with maternal morbidity and mortality. An increased incidence of a common rabbit skeletal variation, angulated hyoid alae, was also observed at the maternally toxic doses of 50 and 100 mg/kg. A separate toxicokinetic study showed that ceftaroline exposure in rabbits (based on AUC) was approximately 0.8 times the exposure in humans given 600 mg every 12 hours at 25 mg/kg and 1.5 times the human exposure at 50 mg/kg. Ceftaroline fosamil did not affect the postnatal development or reproductive performance of the offspring of rats given IV doses up to 450 mg/kg/day. Results from a toxicokinetic study conducted in pregnant rats with doses up to 300 mg/kg suggest that exposure was ≥ 8 times the exposure in humans given 600 mg every 12 hours. There are no adequate and well-controlled trials in pregnant women. Teflaro should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** - It is not known whether ceftaroline is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Teflaro is administered to a nursing woman. **Pediatric Use** - Safety and effectiveness in pediatric patients have not been established. **Geriatric Use** - Of the 1300 patients treated with Teflaro in the Phase 3 ABSSSI and CAP trials, 397 (30.5%) were ≥ 65 years of age. The clinical cure rates in the Teflaro group (Clinically Evaluable [CE] Population) were similar in patients ≥ 65 years of age compared with patients < 65 years of age in both the ABSSSI and CAP trials. The adverse event profiles in patients ≥ 65 years of age and in patients < 65 years of age were similar. The percentage of patients in the Teflaro group who had at least one adverse event was 52.4% in patients ≥ 65 years of age and 42.8% in patients < 65 years of age for the two indications combined. Ceftaroline is excreted primarily by the kidney, and the risk of adverse reactions may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this age group and it may be useful to monitor renal function. Elderly subjects had greater ceftaroline exposure relative to non-elderly subjects when administered the same single dose of Teflaro. However, higher exposure in elderly subjects was mainly attributed to age-related changes in renal function. Dosage adjustment for elderly patients should be based on renal function [see *Dosage and Administration and Clinical Pharmacology*]. **Patients with Renal Impairment** - Dosage adjustment is required in patients with moderate (CrCl > 30 to ≤ 50 mL/min) or severe (CrCl ≤ 15 to ≤ 30 mL/min) renal impairment and in patients with end-stage renal disease (ESRD – defined as CrCl < 15 mL/min), including patients on hemodialysis (HD) [see *Dosage and Administration and Clinical Pharmacology*].

**OVERDOSAGE:** In the event of overdose, Teflaro should be discontinued and general supportive treatment given. Ceftaroline can be removed by hemodialysis. In subjects with ESRD administered 400 mg of Teflaro, the mean total recovery of ceftaroline in the dialysate following a 4-hour hemodialysis session started 4 hours after dosing was 76.5 mg (21.6% of the dose). However, no information is available on the use of hemodialysis to treat overdosage [see *Clinical Pharmacology*].

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