Treatment of anal cancer

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INTRODUCTION

The term "anal cancer" usually refers to a squamous cell cancer (SCC) of the anal canal, which represents the majority of cancers arising in the anal region. However, SCCs can also arise in the perianal skin and in the rectum, and SCCs arising at these sites are generally treated in the same manner as anal canal SCCs. On the other hand, the treatment paradigm for anal adenocarcinomas, which are much less common than anal SCCs, is similar to that for rectal adenocarcinomas, with resection representing an important component of multimodality therapy for most patients.

This topic review will cover the treatment of all of these types of anal cancers. The classification, histology, epidemiology, clinical features and staging of anal cancers, as well as the diagnosis and management of anal intraepithelial neoplasia are presented separately. (See "Classification and epidemiology of anal cancer" and "Clinical features and staging of anal cancer" and "Anal squamous intraepithelial lesions: Epidemiology, clinical presentation, diagnosis, screening, prevention, and treatment".)

ANATOMY AND TYPES OF TUMORS

The anus consists of a glandular mucosa-lined anal canal and the epidermis-lined perianal "margin" (figure 1). The anus encompasses mucosa of three different histologic types: glandular (mucosa-lined), transitional, and squamous, proximal to distal, respectively. Distally,

the squamous mucosa (which is devoid of the epidermal appendages, hair follicles, apocrine glands, and sweat glands) merges with the hair-bearing perianal skin (true epidermis). This mucocutaneous junction has been referred to as the anal "verge" or margin. (See "Classification and epidemiology of anal cancer".)

Four distinct categories of tumors arise in the anal region:

- Tumors that develop from any of the three types of mucosa and that cannot be visualized in their entirety while gentle traction is placed on the buttocks are termed anal canal cancers [1]:

  - Tumors arising in the transitional or squamous mucosa are squamous cell cancers (SCCs) and appear to behave similarly, despite their sometimes variable morphologic appearance. By convention, most series that report outcomes of "anal cancer" refer exclusively to these tumors. The term "anal cancer" by common definition refers to SCCs arising within the mucosa of the anal canal, and the two terms will be used interchangeably throughout this review. These tumors are mainly treated with radiation therapy (RT) plus concurrent chemotherapy. (See 'Squamous cell cancer of the anal canal' below.)

    Basaloid (also termed junctional or cloacogenic) carcinoma is a variant of SCC that arises from epithelial transitional zone. However, these terms have largely been abandoned because these tumors are now recognized as nonkeratinizing types of SCC. Tumors arising within the anal canal above the dentate line are termed nonkeratinizing SCCs, while those arising within the anal canal distal to the pectinate (dentate) line are termed keratinizing SCCs.

  - Adenocarcinomas arising from glandular elements within the anal canal are rare. They appear to share a similar natural history with rectal adenocarcinomas and are treated similarly. (See 'Anal adenocarcinoma' below.)

- Tumors arising within the hair-bearing skin at or distal to the squamous mucocutaneous junction have been referred to as anal margin cancers. However, the most recent (eighth) edition of the American Joint Committee on Cancer (AJCC) cancer staging manual and the fifth edition of the World Health Organization (WHO) classification of tumors of the digestive tract specifically defines tumors that arise within the skin at or distal to the squamous mucocutaneous junction that can be seen in their entirety with gentle traction placed on the buttocks and are within 5 cm of the anus as perianal cancers [1,2]. Like most clinicians, we treat SCC lesions of the perianal skin the same as anal canal cancers, using RT and concurrent chemotherapy. (See 'Squamous cell cancer of the anal canal' below.)

Local treatment, surgery, or local RT (electrons) is used only when the lesion is very separate from the anal verge and is a discrete skin lesion. (See 'True perianal skin cancers' below.)

- Primary rectal SCCs, which are very rare, can be difficult to distinguish from anal cancers, but they are treated according to the same approach as anal cancer. (See 'Rectal squamous cell cancers' below.)

An algorithmic approach to selecting initial treatment based on the tumor location and histology is provided (algorithm 1).

TREATMENT OF LOCALIZED DISEASE

Squamous cell cancer of the anal canal — We suggest initial concurrent chemoradiotherapy rather than upfront surgery for most patients with anal canal squamous cell cancers (SCCs), even those with T1-2N0M0 tumors. Despite the absence of randomized trials directly comparing upfront chemoradiotherapy versus surgery, chemoradiotherapy has emerged as the preferred method of treatment for anal canal SCC because it can cure many patients while preserving the anal sphincter in approximately 70 to 85 percent. Local excision may be an option for carefully selected patients with very favorable, small (<1 cm) superficially invasive tumors that are completely excised and have ≤3 mm of basement membrane invasion and a maximal horizontal spread of ≤7 mm. However, local excision has never been compared with radiation therapy (RT) or chemoradiation, which are considered the standards of care in this patient population. If this approach is selected, vigilant follow-up is mandatory, with the prompt initiation of chemoradiotherapy for recurrent disease. (See 'Local excision for small T1 tumors' below.)

Initial chemoradiotherapy — We suggest concurrent use of fluorouracil (FU) plus mitomycin during RT rather than FU alone or FU plus cisplatin for most patients, including those with cT1N0 tumors. Because poor compliance to chemotherapy and RT are associated with inferior local failure-free survival and overall survival, treatment interruptions should be minimized, and overall treatment time and total dose maintained as much as possible. (See 'Management of recurrent or persistent disease' below.)

Although the original regimen, described as the "Wayne State or Nigro regimen," used infusional FU 1000 mg/m^2 on days 1 to 4 and 29 to 32 (plus mitomycin 10 to 15 mg/m^2 on day 1 only) concurrent with RT [3], consensus-based National Comprehensive Cancer Network (NCCN) guidelines suggest a modified regimen as was used in the Radiation Therapy Oncology Group (RTOG) 98-11 trial [4,5]. The chemotherapy consists of infusional FU 1000 mg/m^2 on days 1 to 4

and 29 to 32 plus mitomycin 10 mg/m^2 on days 1 and 29, maximum 20 mg per dose. European guidelines also suggest the infusional FU plus mitomycin regimen, but offer the option of utilizing mitomycin 12 mg/m^2 on day 1 only (maximum 20 mg single dose), as was used in the ACT II trial [6]. In our view, either approach is acceptable. (See 'Replacement of mitomycin by cisplatin' below.)

Evolution of sphincter-sparing treatment — In the past, abdominoperineal resection (APR) was routinely performed for tumors arising in the anal canal. This radical procedure required removal of the anorectum with creation of a permanent colostomy. In early series, the overall probability of five-year survival was 40 to 70 percent, with a perioperative mortality of 3 percent [7-12].

Extending prior observations of a radiation-potentiating effect of concomitant fluoropyrimidines in a variety of gastrointestinal malignancies, investigators at Wayne State initially devised a protocol of preoperative treatment with chemotherapy plus RT as a means of decreasing the surgical failure rate for patients with anal canal cancer [3]. The "Nigro" regimen consisted of FU (1000 mg/m^2 per day by continuous infusion days 1 through 4 and 29 through 32), mitomycin (10 to 15 mg/m^2 on day 1 only), and intermediate dose RT (30 Gy). The finding that the first three patients had complete pathologic responses led to the development of strategies that were directed at preservation of the anal sphincter.

In a follow-up series, patients with anal canal cancer were initially treated with chemoradiotherapy (same regimen) and subjected to subsequent surgery (typically an APR) only if there was residual tumor in a postradiation biopsy [13]. The majority of patients treated with chemoradiotherapy were cured (five-year overall survival 67 percent) without an APR (five-year colostomy-free survival 59 percent).

These findings were subsequently confirmed by multiple investigators using a variety of regimens. Taken together, the use of combined chemoradiotherapy results in local failure rates of 14 to 37 percent, five-year overall survival rates of 72 to 89 percent, and five-year colostomy-free survival rates of 70 to 86 percent [13-19]. As a result of these data, the use of concurrent RT with infusional FU and mitomycin has become the standard of care for patients with SCC of the anal canal, replacing surgery, even for those with T1-2N0 disease.

It should be noted that the use of local excision alone for T1N0 disease is increasing over time, especially for tumors that are <1 cm in size. Overall survival data appear to be comparable with chemoradiation, although local recurrence, colostomy-free survival, and tolerability are lacking. (See 'Local excision for small T1 tumors' below.)

Chemoradiotherapy versus radiation therapy alone — The necessity of including chemotherapy in the nonoperative treatment regimen for anal cancer has been addressed in at least two randomized trials:

- The Anal Cancer Trial Working Party of the United Kingdom Coordination Committee on Cancer Research (UKCCCR) randomly assigned 585 patients with T1 to T4 SCC of the anal canal or margin to receive either RT alone (45 Gy external beam in 20 or 25 fractions over four to five weeks plus a 15 Gy external beam or 25 Gy brachytherapy boost), or RT plus concurrent infusional FU (1000 mg/m^2 for four days or 750 mg/m^2 for five days during the first and the final weeks of RT) and mitomycin (12 mg/m^2 on day 1 only) [20]. Chemoradiotherapy was associated with significant reductions in local failure (59 versus 36 percent) and cause-related mortality (28 versus 39 percent). More acute morbidity, including six deaths, occurred with combined modality therapy; late morbidity was similar.

  Overall survival was similar between the two groups, and this was attributed to an early increase in non-anal cancer deaths in the first five years, which disappeared by year 10 [21]. Only 11 patients in the chemoradiotherapy group suffered a locoregional relapse as a first event after five years.

- In a second trial, The European Organisation for the Research and Treatment of Cancer (EORTC) randomly assigned 110 patients with locally advanced (T3-4 or N1-3) anal cancer to receive RT (45 Gy with a 15 or 30 Gy boost) with or without concurrent infusional FU (750 mg/m^2 per day on days 1 through 5 and 29 through 33) plus mitomycin (15 mg/m^2 day 1 only) [22]. Chemoradiotherapy was associated with a significantly higher pathologic complete remission rate (80 versus 54 percent), an 18 percent higher five-year locoregional control rate, a 32 percent higher colostomy-free rate, and higher event-free and progression-free survival. Overall survival was not significantly different, and in contrast to the UKCCCR trial, the incidence of acute and late side effects and treatment-related mortality did not differ between the groups.

The role of RT alone for early-stage tumors is discussed below. (See 'Elderly or extensive comorbidity' below.)

Role of mitomycin — The need for mitomycin has been questioned since it does not sensitize tumor cells to the effects of RT, has only modest antitumor activity against SCCs, and is associated with renal, pulmonary, and bone marrow toxicity [23,24]. (See "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)" and "Mitomycin pulmonary toxicity".)

The need for mitomycin in curative treatment of anal cancer was addressed in a joint trial from the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG) in which 310 patients with anal cancer of any tumor or nodal stage were randomly assigned to combined modality therapy with or without mitomycin (using the Wayne State regimen) [4]. Patients who received mitomycin had significantly better four-year colostomy-free survival (71 versus 59 percent) and disease-free survival (73 versus 51 percent), but pathologic complete response rates and overall survival were similar. Grade 4 toxicity (23 versus 7 percent) and fatal neutropenic sepsis (4 versus 1 patient) were significantly more common in the mitomycin group.

The authors concluded that, despite greater toxicity, the use of mitomycin in a definitive complete response regimen for anal cancer was justified.

Replacement of mitomycin by cisplatin — Cisplatin is more active in the treatment of SCCs in general than is mitomycin. Early uncontrolled studies suggested encouraging colostomy-free and overall survival rates with the substitution of cisplatin for mitomycin in the treatment of anal cancer [14-16,25]. This issue has been addressed in two large controlled studies, with conflicting results [26,27]:

- The substitution of cisplatin for mitomycin in the treatment of anal canal cancer was not supported by the results of the United States Intergroup trial (RTOG 98-11) [26,28]. Induction chemotherapy plus concurrent chemoradiotherapy using cisplatin and FU (with RT begun on day 57 after two courses of cisplatin and FU) was directly compared with the standard regimen of mitomycin, FU, and RT. The chemotherapy drugs in both arms were given during weeks 1 and 5 of RT. The trial enrolled 682 non-HIV-infected patients with SCC of the anal canal, 27 percent >5 cm, and 26 percent clinically node positive.

  In the latest update, there were significant differences favoring FU plus mitomycin in five-year disease-free survival (68 versus 58 percent, p = 0.006), overall survival (78 versus 71 percent, p = 0.026), and colostomy-free survival (72 versus 65 percent, p = 0.05) [28]. FU plus mitomycin was also associated with a statistically nonsignificant trend toward fewer locoregional failures (LRFs; 20 versus 26 percent) and fewer colostomies (cumulative rate of colostomy failure 12 versus 17 percent). Hematologic toxicity was worse in the mitomycin group, but nonhematologic toxicity and late RT-related toxicity were similar in the two groups.

- On the other hand, the therapeutic equivalence of cisplatin and mitomycin when used in combination with infusional FU concurrent with RT was suggested in the ACT II randomized trial of 940 non-HIV-infected patients with anal SCC (30 percent node positive,

43 percent T3/4) [29]. Treatment consisted of RT in both arms (50.4 Gy in 28 fractions) with concurrent infusional FU (1000 mg/m^2 per day on days 1 to 4 and 29 to 32) and either cisplatin (60 mg/m^2 on days 1 and 29) or mitomycin (12 mg/m^2 day 1 only). There was a second randomization to receive or not receive maintenance chemotherapy starting four weeks after chemoradiotherapy (two courses of cisplatin plus FU, administered four weeks apart).

Patients receiving mitomycin had more acute grade 3 or 4 hematologic toxicity (26 versus 16 percent), but no higher rates of febrile neutropenia (3 percent in both groups) during chemoradiotherapy. Rates of grade 3 or 4 nonhematologic toxicity were similar (62 versus 68 percent). The complete response rate at six months (the primary endpoint) was 90.5 versus 89.6 percent with mitomycin and cisplatin, respectively, and the three-year colostomy-free survival rate was similar in patients treated with mitomycin or cisplatin and those treated with and without maintenance treatment (72 to 75 percent in all groups). At a median follow-up of 5.1 years, three-year progression-free survival was similar with cisplatin versus mitomycin, and overall survival was also similar (hazard ratio [HR] for death with cisplatin versus mitomycin 1.05, 95% CI 0.80-1.38). Overall survival was also comparable with and without the use of maintenance therapy (HR 1.07, 95% CI 0.81-1.41).

Taken together, these data suggest that FU plus mitomycin remains the standard of care, but that FU and cisplatin could be considered a reasonable approach as well. Both options are included in European guidelines although they state that FU plus mitomycin is generally recommended [6]. Importantly, any marginal benefit for cisplatin over mitomycin in terms of less hematologic toxicity is likely to be offset by the extra resources needed to administer cisplatin.

There appears to be no role for induction chemotherapy or a continuation of chemotherapy beyond concurrent chemoradiotherapy.

Capecitabine as an alternative to infusional fluorouracil — At least some data suggest that substituting daily oral capecitabine for infusional FU in conjunction with intravenous (IV) mitomycin during RT is well tolerated with minimal toxicity [30-32]. In a phase II trial of 31 patients, 77 percent had a complete clinical response (cCR) four weeks after completion of therapy [30]. At a median follow-up of 14 months, there were three locoregional recurrences. In our view, the combination of capecitabine and mitomycin is an acceptable substitute for infusional FU plus mitomycin for chemoradiotherapy.

Radiation therapy dose and schedule — Patients are typically treated with external beam RT using fields that initially encompass the pelvis from the S1-S2 level, inguinal lymph

nodes (even if palpably negative), and anus. Chemotherapy (typically infusional FU plus mitomycin) is administered concurrently with the first and fifth weeks of RT. Treatment interruptions should be minimized, and overall treatment time and total dose maintained as much as possible.

Compared with historical series of APR and inguinal lymph node dissection, this strategy has significantly reduced the rates of locoregional recurrence and led to markedly improved control of gross nodal disease [33-35]. Rates of inguinal node recurrence are <5 percent [34,36]; rates are higher when elective inguinal node irradiation (for those with no palpable or radiographic evidence of inguinal nodal disease) is omitted [35,37].

The optimal dose of external beam RT for the treatment of anal canal cancer is the subject of considerable debate. Total doses, including boost doses, vary considerably between countries, from 50.4 Gy as was used in the ACT II trial, to 55 to 59 Gy for T3-4 or node-positive disease (as was used in the RTOG 98-11 trial),and up to 60 Gy used in some Nordic series [26,29,38].

Even lower doses have been used. At least two retrospective studies suggest that 30 Gy of RT with concurrent chemotherapy after an excisional biopsy might be adequate for selected patients with early-stage disease [39,40]. In the larger report, the entire group of 25 patients had a five-year colostomy-free survival of 91 percent [39]. However, other retrospective reports suggest that total dose is a significant prognostic factor for both local control and survival [41-43], particularly for more advanced tumors, such as T3 or 4 or node-positive disease. As an example, in a series of 50 patients with non-metastatic anal cancer, RT doses of ≥54 Gy were associated with significantly better overall survival (84 versus 47 percent), disease-free survival (74 versus 56 percent), and local control (77 versus 61 percent) compared with lower doses [42]. Most of these patients also received concurrent FU and mitomycin. European [44] and NCCN guidelines [5] recommend a minimum dose of 45 Gy for all patients.

Two trials have evaluated the potential benefit of doses of external beam RT above 54 Gy, both of which are flawed by the use of a split-dose course of RT [45,46]:

- In an RTOG study, 47 patients with anal cancers ≥2 cm received 59.4 Gy RT in a "split dose" schedule (two-week delay after 36 Gy) plus concurrent FU and mitomycin [45], and the results compared with those of a previous RTOG trial in which patients were treated with 45 Gy in a continuous schedule plus the same chemotherapy regimen [4]. Although cross-trial comparisons such as these can be misleading, local control did not seem better with the higher RT doses, and although patients receiving 59.4 Gy had comparable toxicity, the two-year colostomy rate was much higher than expected (30 versus 9 percent in the previous trial). The split course schedule may have influenced treatment-related toxicity.

- A similar split-course schedule of RT was studied in an ECOG trial in which 19 patients received 59.4 Gy concurrent with two courses of infusional FU and cisplatin [46]. Although the response rate was 95 percent, toxicity, particularly hematologic, was prohibitive.

Radiotherapy techniques have also evolved over the past decade. Intensity-modulated RT (IMRT) is now a preferred approach over other RT techniques, including three-dimensional conformal RT (3D-CRT) [47,48]. IMRT uses three-dimensional radiation treatment planning, and there are variable, computer-controlled intensities within each RT beam, in contrast to the uniform doses within each 3D-CRT beam. Compared with most other treatment techniques, IMRT can achieve a higher degree of accuracy in conforming the radiation to the planned target while sparing normal tissue. The advantages of IMRT are particularly evident when the target volumes have complex shapes or concave regions. (See "Radiation therapy techniques in cancer treatment", section on 'Intensity-modulated radiation therapy'.)

Several retrospective reports and prospective cohort studies support the safety of IMRT in conjunction with concurrent chemotherapy for anal SCC, with promising early efficacy results [49-54] and emerging data on long-term outcomes [55]. A confirmatory phase II study was conducted by the RTOG (RTOG 0529); in the final report, outcomes with IMRT in conjunction with FU and mitomycin C were compared with those from the FU/mitomycin control arm of the RTOG 98-11 trial [56]. (See 'Replacement of mitomycin by cisplatin' above.)

The following were noted:

- The primary endpoint (reduction of grade 2+ combined acute gastrointestinal/genitourinary toxicity by at least 15 percent compared with the conventional RT/FU/mitomycin arm from RTOG 9811) was not met; the rate with IMRT (77 percent) was identical to that reported in RTOG 98-11.

- However, there were lower than expected rates of acute grade 3 or higher dermatologic (23 versus 49 percent in RTOG 98-11) and gastrointestinal (21 versus 36 percent) toxicity with IMRT, and there was also less grade 2 or higher hematologic toxicity (73 versus 83 percent).

- Importantly, 81 percent of the patients enrolled in this trial required a change in the radiation treatment plan following pretreatment central review, illustrating the learning curve for practitioners using this treatment method.

With IMRT treatment planning radiation doses are typically prescribed to PTVs (Planning Target Volumes). The dose of radiation required to control disease is extrapolated from historical studies that show excellent rates of control with concurrent radiation and chemotherapy.

Typically prescribed dose varies by size of the tumor and risk of microscopic spread in elective nodal areas. One approach with "shrinking field technique" is that the low risk elective nodal PTV volume is typically prescribed to 30.6 Gy in 1.8 Gy daily fractions. The high-risk elective nodal PTV is sequentially prescribed an additional 14.4 Gy in 1.8 Gy daily fractions for a total prescribed dose of 45 Gy. Finally, for T1–2 lesions with residual disease after 45 Gy, T3–4 lesions, or N1 lesions, an additional 5.4 to 14.4 Gy in 1.8 to 2 Gy daily fractions is again sequentially prescribed to the gross disease PTV volume (total dose, 50.4 to 59.4 Gy). In RTOG-0529, the prescription parameters are different due to the use of only a single elective nodal volume and slightly different dose prescriptions depending on tumor stage. Furthermore, delivery of escalating dose to different target volumes was performed using a simultaneous integrated boost (SIB) dose painting technique with a maximum dose of 1.8 Gy per fraction to the primary tumor and large volume gross nodal involvement and 1.5 Gy per daily fraction to elective nodal areas. Table 1 outlines dose prescriptions by TNM stage according to the RTOG-0529 protocol (table 1). The SIB approach offers the convenience of developing a single treatment plan with reduced planning complexity, albeit with a lower biological dose delivered to the elective nodal areas.

Brachytherapy provides another means of dose intensification, sparing the surrounding normal structures. In several series, the addition of brachytherapy provided a complete pathologic response rate of 83 percent (range 73 to 91 percent), a local control rate of 81 percent (range 73 to 89 percent), and a five-year survival rate of 70 percent (range 60 to 84 percent) [15,16,57-62]. However, anal necrosis range developed in 2 to 76 percent [15,16,59,61], and many patients required surgical therapy (APR) for complications.

The incidence of late toxicity from RT, such as anal ulcers, stenosis, and necrosis, is also dose-dependent [57]. The development of such toxicities may necessitate a colostomy in 6 to 12 percent of patients who are otherwise free of disease [33,36,58]. In a review of late radiation complications in 144 patients with anal cancer who were treated with either RT alone or with chemotherapy, after five years, 10 percent required an APR for late treatment-related complications [57]. The serious complication rate was much higher in those patients who had at least 39 Gy of external beam RT to the pelvis before the boost to the tumor (23 versus 7 percent in those who received less than 39 Gy). (See 'Toxicity and quality of life issues' below.)

Special populations

Patients living with HIV — Anal SCC in people living with HIV (PLWH) is potentially curable with combined modality therapy, and in general these patients are treated similarly to those who do not have HIV. A low CD4 count does not necessarily predict for greater treatment-related toxicity. However, patients with active HIV/AIDS-related complications or a history of

complications (eg, opportunistic infections, other malignancies) may not tolerate full-dose therapy or may require dose adjustment. (See "Clinical features and staging of anal cancer", section on 'Pretreatment assessment for HIV infection'.)

Most data suggest that response to therapy, local control, and survival are as good in PLWH who as in non-HIV-infected patients, particularly in the era of potent antiretroviral therapy (ART; previously called highly active antiretroviral therapy) [63-71]. In some series, acute treatment-related toxicity has been worse than expected, particularly with RT doses >30 Gy [63,71,72], but this has not been a universal finding, and it does not appear to compromise long-term outcomes. Diverting colostomy or APR is required for toxicity management in 6 to 12 percent of cases [36,57].

The relationship between treatment tolerance and CD4 counts has been directly addressed only in small observational studies:

- An early report of 17 patients seen before the era of modern ART found that no patient with a pretreatment CD4 count ≥200 cells/microL required hospitalization during treatment [72]. By contrast, four of the eight with counts <200 cells/microL needed hospitalization for myelosuppression, diarrhea, or moist desquamation, and four required a colostomy for a therapy-related complication or persisting/recurrent disease. Similar findings have been noted by others [73].

- Three later series totaling 59 patients treated in the era of modern ART did not find a significant relationship between the CD4 count and treatment-related toxicity, even if the CD4 counts were <200 to 300 cells/microL [64,66,74].

In general, PLWH should be treated similarly to non-HIV positive individuals, although those with active HIV/AIDS-related complications or a history of opportunistic infections, or other HIV-related malignancies may not tolerate full-dose therapy, or may not tolerate mitomycin, and require either dose adjustment or treatment without mitomycin [75]. There is no evidence that the addition of cetuximab, which enhances the effect of RT in human papillomavirus (HPV)-related oropharyngeal SCC, improves outcomes in HIV related anal SCC when added to conventional chemoradiotherapy [76].

Patients with locally advanced disease — We approach patients with T3/4 primary tumors or N1b/c (table 2) disease similarly to those with less-advanced-stage disease (ie, using the same regimen of RT plus concomitant FU and mitomycin (table 3)). However, patients with T3, T4, or node-positive disease receive an additional RT boost of 10 to 14 Gy in 2 Gy fractions (total dose 55 to 59 Gy versus the usual 45 Gy for earlier stage disease). (See 'Radiation therapy dose and schedule' above.)

Patients with large (T3/4) primary tumors or advanced (ie, N1b or N1c (table 2)) nodal metastases have a cure rate of approximately 50 to 60 percent with standard chemoradiotherapy [77]. Several studies have attempted to escalate treatment in order to improve outcomes, with mixed results [26,78-80].

Taken together, there is no consistent demonstration of better outcomes when patients with locally advanced anal SCCs are treated with an intensified approach. We treat these patients similarly to those with earlier stage disease, an approach that is also recommended by the NCCN [5] and the European Society for Medical Oncology (ESMO) [6].

Patients with para-aortic nodal involvement — Isolated para-aortic lymph node involvement is rare and considered M1 (stage IV) disease (table 2). The optimal management of these patients is undefined. Definitive chemoradiotherapy with the inclusion of the para-aortic nodes in the radiation field is a reasonable approach; however, these patients remain at high risk for the development of additional metastatic disease.

Limited data suggest that definitive combined chemoradiotherapy is a potentially curative treatment option for these patients [81,82]. One report described outcomes in 30 patients with SCC and distant metastases limited to the para-aortic lymph nodes [82]. The primary tumor and involved nodes were treated to a median dose of 51 Gy, while uninvolved nodal regions were treated with a median dose of 45 Gy; all patients received concomitant chemotherapy. Grade 3 or 4 gastrointestinal, dermatologic, and hematologic adverse events occurred in 30, 27, and 20 percent of patients during therapy, respectively. After a median follow-up of three years, the overall and disease-free survival rates were 67 and 42 percent, respectively. Fifteen patients had experienced a recurrence at a median of 0.9 years (range 0.5 to 3.5 years), and the predominant site of recurrence was distant metastases.

While these data provide support for definitive chemoradiotherapy in the setting of isolated para-aortic nodal metastases, these patients remain at high risk for the development of additional metastatic disease. Whether additional courses of adjuvant chemotherapy might be beneficial is unknown.

Elderly or extensive comorbidity — Concomitant chemoradiotherapy using conventional doses of FU plus mitomycin is the standard approach for most patients with localized anal SCCs (table 3). For the extremely aged population with T1N0 tumors, or those with significant comorbidities, enrollment on clinical trials testing the feasibility of lower RT and chemotherapy doses (eg,) is preferred. If protocol therapy is not available, reduction of mitomycin and FU doses during RT could be considered, although this is not a standard approach.

- **RT alone** – Randomized trials demonstrate the superiority of chemoradiotherapy over RT alone in terms of disease-free survival, local relapse, and colostomy-free survival, but whether these benefits apply to early-stage disease (T1-2N0 (table 2)) is unclear. Only one of the two randomized trials described above enrolled patients with T1 or 2 tumors, and results were not analyzed according to primary tumor stage [20].

  Several retrospective series report excellent outcomes for patients with T1-2N0M0 disease RT alone [83-85]. However, not all reports are favorable:

  - A retrospective series of 146 patients with T1-2N0M0 anal SCC treated with RT alone (n = 71) or chemoradiotherapy (n = 75) reported a twofold higher rate of LRF with RT alone (five-year locoregional control 76 versus 87 percent) [86].

  - A preliminary report of an analysis derived from the National Cancer Database (NCDB) and presented at the 2021 American Society of Clinical Oncology GI Cancer Symposium also noted inferior outcomes for patients with cT1N0 anal SCC who were treated with RT alone without multiagent chemotherapy [87]. Of the 2959 patients with cT1N0 disease reported to the NCDB from 2004 to 2016 who were treated nonoperatively who had at least two months of follow-up, 92 percent had multiagent chemotherapy, but 237 were treated without chemotherapy. Predictors of omission of chemotherapy were older age, comorbidity, Black American race, and more remote year of treatment. The use of multiagent chemotherapy was a significant predictor of survival (HR for death 0.48, 95% CI 0.38-0.62), as was female biologic sex, younger age, higher income, and private insurance. After propensity matching, overall survival at 120 months for patients treated with and without chemotherapy was 86 and 65 percent, respectively.

- **RT with reduced dose chemotherapy** – RT using lower chemotherapy doses has been used for older adult patients with anal canal SCC [40,88-92]. One report evaluated 58 patients ≥75 years of age who received RT (39.6 Gy followed by a delayed boost of 20 Gy) with or without infusional FU (median dose 600 mg/m^2 per day, days 1 through 4, and 29 through 32) plus mitomycin (median dose 9.5 mg/m^2 on day 1 only) [88]. The toxicity of this regimen was comparable with that seen in younger patients treated with higher chemotherapy doses, and efficacy was preserved (five-year survival and local control rates were 54 and 79 percent, respectively). Others note poorer outcomes than could be achieved using standard chemoradiotherapy [93].

  Notably, NCCN guidelines recommend definitive chemoradiotherapy using standard dose FU and mitomycin for all patients with anal canal SCC, even those with T1-2N0M0 tumors [5].

Local excision for small T1 tumors — Local excision is an option for patients with T1 tumors less than 1 cm in size, although this approach has never been compared with RT or chemoradiotherapy, which are considered the standards of care in this patient population. We reserve this approach for superficially invasive cancers (ie, a completely excised lesion with ≤3 mm of basement membrane invasion and a maximal horizontal spread of ≤7 mm) without lymphovascular invasion. These are the definitions for superficially invasive tumors from the Lower Anogenital Squamous Terminology (LAST) Project of the College of American Pathologists (CAP) [94]. If this approach is selected, vigilant follow-up is mandatory, with the prompt initiation of chemoradiotherapy for recurrent disease.

The use of local excision for T1 tumors has been increasing over time [95], and the available evidence suggests that it is appropriate in selected patients. Updated guidelines from the NCCN suggest that this approach be limited to superficially invasive squamous cell anal cancers, defined as a completely excised lesion with ≤3 mm of basement membrane invasion and a maximal horizontal spread of ≤7 mm, adopting the definition of the CAP [96]. In one retrospective analysis of 17 patients with completely excised T1 anal SCC treated with local excision, 7 of whom met the criteria for a superficially invasive lesion, 12 received adjuvant RT for a positive margin, and the remainder were treated with local excision alone [97]. After a median follow-up of 45 months, five-year overall survival in the entire cohort was 100 percent, and there was no difference in five-year cancer recurrence-free survival between the superficially invasive and invasive cancers.

Prognosis — The main prognostic factors are tumor diameter and nodal status, as reflected by Tumor, Node, Metastasis (TNM) stage [98]. In data derived from the United States Intergroup RTOG 98-11 trial of chemoradiotherapy for squamous cell anal cancer [99] and using the most recent 2017 American Joint Committee on Cancer (AJCC) staging system for anal cancer (table 2) [1], the following rates of five-year survival and LRF were reported:

- T2N0 – 82 percent survival; 17 percent LRF
- T3N0 – 74 percent survival; 18 percent LRF
- T4N0 – 57 percent survival; 37 percent LRF
- T2N+ – 70 percent survival; 26 percent LRF
- T3N+ – 57 percent survival; 44 percent LRF
- T4N+ – 42 percent survival; 60 percent LRF

Palpable, clinically positive lymph nodes and male sex are also poor prognostic factors for LRF and overall survival [22,98,100].

Over the past three decades, the percentage of cases with positive lymph nodes has increased significantly, largely attributed to enhanced detection with newer imaging modalities. As an example, in one analysis of 62 studies including 10,569 patients with anal SCC, the lymph node positivity proportions increased from a mean estimate of 15 percent in 1980 to 37 percent in 2012 [101].

Despite this finding, the relative differences in overall survival for node-positive versus node-negative disease have decreased over time [101,102]. The apparently reduced ability of nodal status to predict outcomes is likely related to misclassification of true disease stage, caused by the introduction of new staging technologies.

However, reclassification has also facilitated more accurate treatment with CRT, which has probably contributed to the more favorable contemporary outcomes for patients with non-metastatic anal cancer treated with chemoradiotherapy compared with historical trials (along with incremental improvements in chemoradiotherapy driven by randomized trials). In one analysis of 560 such patients treated over a 25-year period at a single large British medical institute, comparing individuals treated from 1990 to 1994 with those treated most recently (2010 to 2014), three-year locoregional failure rates declined from 33 to 16 percent, and five-year overall survival increased from 62 to 80 percent [102]. This is despite striking increases in the rate of pretreatment nodal positivity from 17 percent in 1990 to 1994 to 41 percent in 2010 to 2014.

Colostomy rates — Colostomy-free survival is a measure of anal sphincter preservation after treatment with RT or chemoradiotherapy. Multiple investigators using a variety of regimens report five-year colostomy-free survival rates of 65 to 86 percent [13-19,103]. (See 'Evolution of sphincter-sparing treatment' above.)

Failure to control anal cancer and complications of treatment are alternative indications for a colostomy, but in most cases, colostomy is required for recurrent tumor:

- In a review of 235 patients diagnosed with anal cancer between 1995 and 2003 and treated with curative-intent RT or chemoradiotherapy at four different Danish centers, the five-year cumulative incidences of tumor-related and treatment-related colostomy were 26 and 8 percent, respectively [104]. Large tumor size (>6 cm) was associated with a higher risk of tumor-related colostomy, while a history of prior excision was a risk factor for therapy-related colostomy.

- Similarly, in an analysis of data from RTOG trial 98-11 (discussed above), five-year colostomy rates among patients treated initially with chemoradiotherapy were 9 percent for those with node-positive disease, and 19 percent for tumors >5 cm in diameter,

regardless of nodal status [105]. Overall, 78 percent of the colostomies were performed for persistent or recurrent disease. (See 'Management of recurrent or persistent disease' below.)

Toxicity and quality of life issues

- **Early toxicity** – In the two trials comparing conventional RT with and without chemotherapy described above, significant acute gastrointestinal toxicity occurred in 33 to 45 of patients treated with chemoradiotherapy, while 49 to 76 percent of patients had significant acute dermatologic toxicity, and rates of grade 3 or 4 hematologic toxicity were as high as 50 percent [20,22]. Modern RT techniques such as IMRT have been associated with lower rates of acute toxicities during CRT, including grade ≥3 hematologic (range 20 to 40 percent), dermatologic (range 10 to 40 percent), gastrointestinal (range 7 to 21 percent), and genitourinary (range 0 to 7 percent) toxicities [52,53,56]. The majority of patients report anorectal discomfort which tends to be worse at the end of treatment and improves thereafter [53]. Rates of hematologic toxicity tend to be lower with a single rather than two cycles of mitomycin. (See 'Role of mitomycin' above.)

  Managing hematologic toxicity during therapy is paramount to avoid life-threatening infections and treatment delays.

- **Late toxicity** – Pelvic RT can cause late toxicity, including altered bowel, urinary, and sexual function, potentially impacting quality of life (QOL) [106-112]. The following data are available on long-term QOL in patients undergoing chemoradiotherapy for invasive anal cancer:

  - In a national cohort of 199 anal cancer survivors treated with curative chemoradiotherapy between 2000 and 2007, 128 returned questionnaires addressing symptoms and QOL; the same questionnaires were answered by an age- and sex-matched reference group of volunteers (n = 269) not treated for pelvic cancer [110]. The median time since diagnosis was 66 months. Global QOL was significantly reduced among survivors (difference 15 points, $p < 0.001$). Survivors had markedly worse scores for fatigue, dyspnea, insomnia, and diarrhea; significantly increased stool frequency; more buttock pain, flatulence, fecal incontinence, impotence (males), dyspareunia, and reduced sexual interest (females). In a later analysis of this same cohort compared with an expanded group of 1211 volunteers, stool incontinence of any degree was reported in 43 versus 5 percent of the survivors and volunteers, respectively, while rates of rectal urgency were 64 versus 6 percent [111].

- Sexual dysfunction may occur in both men and women. The majority of male survivors report inability to achieve or sustain an erection, difficulty with climaxing, lack of interest in sex, and less energy [107]. A trial of a phosphodiesterase type 5 (PDE5) inhibitor such as sildenafil is reasonable, although the data on efficacy of these drugs in men with erectile dysfunction due to pelvic chemoradiotherapy are only anecdotal.

  A large proportion of women report dyspareunia (which may be related to vaginal stenosis [113]), fatigue, loss of sexual desire, and/or emotional changes that affect sexual functioning. These findings are consistent with other reports noting late effects of RT for other pelvic malignancies. For women, proactive approaches, including early and ongoing use of dilators, moisturizers, and lubricants, should be encouraged. Unless contraindicated, topical estrogen (one to three times weekly) applied in the first six months following radiation may reduce dyspareunia and improve vaginal caliber. (See "Overview of sexual dysfunction in female cancer survivors", section on 'Vaginal stenosis' and "Treatment-related toxicity from the use of radiation therapy for gynecologic malignancies", section on 'Vaginal stenosis' and "Management of intra-abdominal, pelvic, and genitourinary complications of colorectal surgery", section on 'Genitourinary complications'.)

Post-treatment surveillance and assessing the local response to primary chemoradiotherapy — SCCs regress slowly and continue to decrease in size for up to 26 weeks following therapy. We perform a clinical assessment of response by physical examination (digital rectal examination [DRE], palpation of the inguinal regions) from 8 to 12 weeks following the completion of therapy. For patients with a clinical complete response, re-evaluation at three- to six-month intervals with DRE, anoscopy, and inguinal node palpation is recommended for five years, with contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis or contrast-enhanced magnetic resonance imaging (MRI) performed annually for three years.

Patients with clinical suspicion for persistent disease on the initial post-treatment physical examination can be watched for up to six months following completion of RT and chemotherapy as long as there is no progressive disease during this period of follow-up. Progression of disease at any time or a clinical suspicion for persisting disease six months or more after completion of chemoradiotherapy should prompt a biopsy, with salvage therapy (typically APR) offered to those with biopsy-proven disease persistence/recurrence.

There are no prospective trials to guide the post-treatment surveillance strategy for patients treated for anal cancer. In general, LRFs predominate after primary chemoradiotherapy, and early identification of those with persistent or recurrent locoregional disease who need salvage therapy (typically an abdominoperineal resection) is an important goal of the post-treatment

surveillance strategy. The majority of recurrences develop within three years [114], providing justification for more intensive surveillance during this period.

The first post-treatment assessment by physical examination is typically carried out at 8 to 12 weeks after the completion of all treatments. Early assessment of response by MRI is unhelpful and not recommended [115].

Clinical suspicion of persistent disease at this early time point should not necessarily prompt a biopsy or referral for APR. SCCs regress slowly and continue to decrease in size for up to 26 weeks following therapy [33,116]. This was shown in an analysis of data from the ACT II trial, in which 940 patients were randomly assigned to FU plus either mitomycin or cisplatin during concurrent RT, and then were further randomized to receive or not receive maintenance chemotherapy [116]. (See 'Replacement of mitomycin by cisplatin' above.)

The protocol required three response assessments at 11 and 18 weeks (with DRE, with or without examination under anesthesia) and at 26 weeks (DRE, examination under anesthesia, abdomen and pelvis CT, and chest radiograph). Biopsies were not routinely performed. The cCR rate increased over time in both chemoradiotherapy groups (52, 71, and 78 percent at 11, 18, and 26 weeks, respectively). Importantly, 72 percent of those not in a cCR at 11 weeks achieved it at 26 weeks. Furthermore, the greatest separation in outcomes between complete responders and those who did not achieve a cCR occurred when the assessment took place at 26 weeks (progression-free survival 80 versus 33 percent, HR for progression 0.16, 95% CI 0.12-0.21; overall survival 87 versus 46 percent, HR for death 0.17, 95% CI 0.12-0.23). These data support the view that anal SCCs continue to regress for up to 26 weeks after the completion of chemoradiotherapy and that the decision to pursue APR for persisting disease is best deferred until at least 26 weeks.

In keeping with these data, updated NCCN guidelines recommend post-treatment re-evaluation with DRE examination at 8 to 12 weeks after chemoradiotherapy, with the response classified clinically as a complete response, persistent disease, or progressive disease [5]:

- For patients with a cCR, re-evaluation every three to six months with DRE, anoscopy, and inguinal node palpation is recommended for five years. In addition, contrast-enhanced CT of the chest abdomen and pelvis or contrast-enhanced MRI is recommended annually for three years.

- Patients with clinical suspicion for persistent disease can be watched for up to six months following completion of RT and chemotherapy as long as there is no progressive disease during this period of follow-up.

- Patients who appear to have progressive disease require histologic confirmation.

European guidelines for management of anal canal cancer also suggest 26 weeks may be the optimal time to assess complete response to chemoradiotherapy if surgical salvage is being discussed [6].

Consensus-based guidelines from ESMO are comparable [6]:

- Clinical examination including DRE and palpation of the inguinal nodes every three to six months for two years, then every 6 to 12 months until year 5.
- Suspicious lesions should be assessed by MRI and/or PET, and biopsied, if possible.
- Once tumor regression is confirmed at 3 and 6 months, annual CT scans for surveillance at 12, 24, and 36 months are recommended. Given the very low relapse rate (<1 percent after three year as in the ACT-II study), extended imaging surveillance after this time is not warranted.

Role of FDG/PET — There is insufficient evidence to recommend integrated fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT in the assessment of treatment response or follow-up of treated anal canal [117-119]. Its ability to impact earlier salvage compared with clinical evaluation remains inconclusive. Consistent with guidelines from the NCCN, ESMO, and the American Society of Colon and Rectal Surgeons, we do not routinely order it, unless there is an equivocal finding on cross-sectional imaging [5,6,120].

Management of recurrent or persistent disease

Risk factors — Risk factors for disease recurrence/persistence include primary tumor size >5 cm and nodal-positivity [99]. In addition, poor treatment adherence, unnecessary chemotherapy dose reductions, and treatment delays also increase the risk for locoregional failure [121].

Persistent or locally recurrent disease following chemoradiotherapy can be successfully salvaged with surgery (typically APR); however, locally recurrent anal SCC can be a difficult clinical problem that is associated with profound morbidity and long-term disease control in only approximately 25 to 40 percent of cases.

Abdominoperineal resection — APR is the treatment of choice for locally recurrent anal cancer following chemoradiotherapy; long-term disease control is achieved in 25 to 40 percent of cases [43,122-129]. Outcomes of locally recurrent anal cancer can be illustrated by a series of 185 consecutive patients with anal cancer treated with either RT alone or chemoradiotherapy, in

which 42 developed local failure requiring salvage therapy [126]. Twenty-six patients (62 percent) underwent potentially curative surgery, including 23 APRs and 3 local excisions. The five-year rates of overall survival, secondary local control, and locoregional control were 45, 53, and 43 percent, respectively.

APR is also the treatment of choice for patients who have persisting disease after completion of combined modality therapy, as noted above; based on data from the ACT II trial, patients with clinical suspicion for persistent disease on the initial post-treatment physical examination at 8 to 12 weeks can be watched for up to six months following completion of RT and chemotherapy as long as there is no progressive disease during this period of follow-up. Progression of disease at any time or a clinical suspicion for persisting disease six months or more after completion of chemoradiotherapy should prompt a biopsy, with salvage therapy (typically APR) offered to those with biopsy-proven disease persistence/recurrence. (See 'Post-treatment surveillance and assessing the local response to primary chemoradiotherapy' above.)

The results of surgical salvage for persistent anal cancer are similar to those for patients with locally recurrent disease. This was shown in a series of 111 patients with anal cancer who were treated with chemoradiotherapy or RT alone, followed by APR for persistent (n = 61) or recurrent (n = 50) disease [124]. The estimated five-year survival rate disease free was 30 percent. In univariate analysis, outcomes were similar for patients with persistent versus recurrent disease. In multivariate analysis, only three factors significantly influenced prognosis: the status of the surgical margin, perineural and/or lymphatic invasion, and whether or not the nodes in the resected specimen were involved with tumor.

Sphincter-sparing salvage therapy — The relative efficacy of nonsurgical salvage in patients with persistent disease is not known. However, at least some of these patients may be successfully salvaged with further sphincter-sparing therapy. As an example, the RTOG/ECOG treated 22 patients who had persistent disease following primary chemoradiotherapy; they received FU, cisplatin, and RT (9 Gy boost) as a salvage regimen [4]. Twelve (55 percent) were rendered disease free after chemoradiotherapy; among these, four required subsequent APR and are free of disease, four died (three with recurrent disease), and four remain disease free. Of the 10 patients who had unsuccessful nonoperative salvage therapy, nine underwent APR. After four years, three were alive without disease and seven had died, six with recurrent disease. However, it is important to note that this trial mandated a post-treatment biopsy at 60 to 74 days after completing treatment, and if the biopsy was positive, the patient received further RT plus chemotherapy. Modern treatment plans emphasize the continued regression up to 26 weeks. (See 'Post-treatment surveillance and assessing the local response to primary chemoradiotherapy' above.)

In our view, the decision to pursue sphincter saving treatment for persistent/recurrent disease is a difficult one, and should entail a multidisciplinary discussion and consideration of the biopsy results and clinical course of the individual lesion.

Anal adenocarcinoma — For patients with adenocarcinoma of the anal canal, we suggest treatment according to a rectal cancer paradigm rather than initial FU and mitomycin-containing chemoradiotherapy, as is used for anal SCCs. For most patients this will include surgery (typically APR) and either preoperative or postoperative fluoropyrimidine-based chemoradiotherapy. The selection of patients for neoadjuvant chemoradiotherapy rather than initial resection followed by adjuvant therapy is discussed elsewhere. (See "Neoadjuvant therapy for rectal adenocarcinoma".)

Primary adenocarcinoma of the anal canal is rare (representing 5 to 19 percent of anal canal cancers [130-132]), and many of these tumors represent rectal cancer with downward spread. Determination of the anatomic site of origin of carcinomas that overlap the anorectal junction can be problematic. For staging purposes, such tumors are classified as rectal cancers if their epicenter is located more than 2 cm proximal to the dentate line or proximal to the anorectal ring on digital examination, and as anal canal cancers if their epicenter is 2 cm or less from the dentate line [8].

Prognosis of anal adenocarcinomas is worse than it is with either anal squamous cell cancer or distal rectal adenocarcinoma [133-136]. (See 'Prognosis' above and "Overview of the management of rectal adenocarcinoma", section on 'Prognosis'.)

There are scarce data to guide management recommendations for anal adenocarcinomas. There are no randomized trials. However, treatment using the same chemoradiotherapy regimens as are used for anal SCC has been associated with high rates of both local and distant failure [137,138], and in many (but not all [139]) retrospective series, survival rates are better in patients receiving multimodality management akin to that used for rectal cancer, that includes radical surgery, with chemotherapy and RT given as preoperative or postoperative therapy to improve local and systemic control [131,134,140-144].

The primary importance of resection in the initial management of adenocarcinomas arising in the anal canal can be illustrated by the following reports:

- A National Cancer Database (NCDB) series of 1747 anal adenocarcinomas diagnosed in 2004 to 2015 included 1005 who received surgery as a component of treatment; the remainder had chemoradiotherapy alone [131]. At a median follow-up of 3.5 years, the five-year survival in those who received surgery as a component of initial therapy was 61 percent, compared with 40 percent for those receiving chemoradiotherapy alone.

Predictors of receipt of surgery were age <65, having private insurance, overlapping involvement of the anus and rectum, clinical node-negative disease, and RT dose ≥40 Gy. However, the survival benefit of surgical treatment persisted when the analysis was restricted to a propensity score-matched cohort.

- The importance of radical surgery rather than just local excision is illustrated by a series of 28 patients with anal adenocarcinoma who were treated with curative intent at MD Anderson Cancer Center between 1983 and 2004, including 13 who had only local excision followed by either chemoradiotherapy or RT, and 15 who had radical resection and either preoperative or postoperative chemoradiotherapy [144]. At a median follow-up of 37 months, five-year overall survival for those who had local excision was 43 percent, compared with 63 percent of those treated with radical surgery.

Given these data, the management of adenocarcinomas arising in the anal canal should follow the same principles as those applied to the treatment of rectal cancer. For most patients this will include resection and either preoperative or postoperative fluoropyrimidine-based chemoradiotherapy. This recommendation is consistent with guidelines from the NCCN [5]. There are no European guidelines that are specific to management of anal adenocarcinoma [6]. Others prefer an approach that includes preoperative chemoradiotherapy plus 12 to 16 weeks of oxaliplatin-based chemotherapy prior to surgery, which is termed "total neoadjuvant therapy" [145]. The principles of preoperative staging and management of rectal adenocarcinoma, including a discussion of the merits of total neoadjuvant therapy are discussed in detail elsewhere. (See "Overview of the management of rectal adenocarcinoma" and "Pretreatment local staging evaluation for rectal cancer" and "Neoadjuvant therapy for rectal adenocarcinoma" and "Neoadjuvant therapy for rectal adenocarcinoma", section on 'Total neoadjuvant therapy for locally advanced tumors' and "Adjuvant therapy for resected rectal adenocarcinoma in patients not receiving neoadjuvant therapy" and "Radical resection of rectal cancer".)

True perianal skin cancers — For the rare patient with a T1N0 well-differentiated cancer of the perianal skin that forms a discrete skin lesion that is clearly separate from the anal canal, wide local excision alone is adequate if negative margins can be achieved without compromise of the sphincter muscles. For patients with high-risk histologic features (eg, poorly differentiated histology, perineural invasion), postoperative RT is an option. For T2 or higher disease, if sphincter function could be compromised by surgery, if there is evidence of nodal involvement, or if it is not clear where the tumor originated, we suggest chemoradiotherapy, with surgery reserved for persistent or recurrent disease.

SCC of the perianal skin is relatively rare, occurring three to five times less frequently than anal canal SCC. These tumors differ in natural history from cancers of the anal canal and usually have a more favorable outcome. The main prognostic factors are histologic differentiation, T stage, and lymph node involvement at diagnosis [146,147]. (See "Clinical features and staging of anal cancer", section on 'Anal canal versus perianal skin cancers'.)

There is a lack of prospective data regarding optimal treatment of true perianal skin cancers. For a localized lesion, surgery is often performed as long as sphincteric muscles are not compromised. The role of sentinel lymph node biopsy in this setting is unclear [148,149]. After excision of a perianal skin cancer with high-risk histologic features (eg, poorly differentiated histology, perineural invasion), postoperative RT is often pursued, but there are no trials proving benefit.

If sphincter function could be compromised by surgery, if there is evidence of nodal involvement, or for more extensive primary lesions, chemoradiation is a more effective alternative [147,150,151].

Rectal squamous cell cancers — For patients with primary rectal squamous cell cancer, we suggest chemoradiotherapy using FU and mitomycin as is used for SCC of the anal canal rather than treatment according to a rectal cancer paradigm.

Primary rectal SCC, which are very rare (0.3 percent of all rectal cancers [152]), can be difficult to distinguish from anal cancers, and they should be staged [153] according to the same approach as anal SCC. The majority represent anal SCCs with extension into the rectum, although primary SCCs of rectal origin are described [154].

The optimal treatment for rectal SCC is not well established due to its rarity. Historically, these patients were treated like rectal adenocarcinoma, and the main treatment was surgical resection. However, more recently, several retrospective single institutional cases series demonstrate that good results can be obtained using definitive chemoradiotherapy is used for anal canal SCC [153,155-163]. In the largest single institution series of 23 patients, five-year overall survival was 86 percent, local control was achieved in 83 percent, and the five-year colostomy-free survival rate was 65 percent [162].

The optimal chemotherapy regimen to be used during concurrent chemoradiotherapy is not established. Most series have utilized a combination of a fluoropyrimidine with either mitomycin or cisplatin. We prefer fluoropyrimidine plus mitomycin in this setting.

TREATMENT OF METASTATIC ANAL SQUAMOUS CELL CANCER

Systemic therapy is the usual approach for treatment of metastatic anal squamous cell cancer (SCC). There may be a small subset of patients with isolated hepatic metastases who stand to benefit from resection, but selection criteria are undefined.

The liver is the most frequent site of distant metastases [11,18,164]. However, the development of distant metastases has been infrequent overall in patients with SCC of the anal canal [20,22,29]:

- In the United Kingdom Coordination Committee on Cancer Research (UKCCCR) and the European Organisation for the Research and Treatment of Cancer (EORTC) trials described above, for example, distant metastases developed following combined modality therapy in 10 and 17 percent, respectively [20,22]. (See 'Chemoradiotherapy versus radiation therapy alone' above.)

- In the ACT II trial, only 22 percent of the 209 patients who relapsed had distant metastases [29]. (See 'Replacement of mitomycin by cisplatin' above.)

This may be changing. Epidemiologic data suggest that at least in the United States, the incidence of distant-stage SCC tripled between 2001 and 2015, with an average annual percentage change of 8.6 percent in men and 7.5 percent in women [165]. (See "Classification and epidemiology of anal cancer", section on 'Epidemiology and risk factors'.)

Systemic chemotherapy — For most patients with metastatic anal canal SCC, we recommend paclitaxel plus carboplatin, rather than cisplatin plus fluorouracil (FU), as our preferred regimen for first-line therapy. This recommendation is consistent with updated guidelines from ESMO [6] and NCCN [5].

Paclitaxel plus carboplatin — Paclitaxel plus carboplatin is an effective chemotherapy regimen for anal SCC [166-168]. In the InterAACT trial, 91 patients with previously untreated advanced anal SCC were randomly assigned to carboplatin (area under the curve of concentration x time [AUC] 5 on day 1 every 28 days) plus weekly paclitaxel (80 mg/m^2 on days 1, 8, and 15 every 28 days) or to cisplatin (60 mg/m^2 on day 1 every 21 days) plus infusional FU (1000 mg/m^2 per 24 hours on days 1 through 4 every 21 days) [168]. The primary outcome was response rate. Carboplatin plus weekly paclitaxel had similar response rates to cisplatin plus FU (59 versus 57 percent), but it had better median overall survival (20 versus 12.3 months) and a more favorable toxicity profile (serious adverse events in 36 versus 62 percent).

Whether treatment-related toxicity is better using weekly paclitaxel in this regimen as compared with other regimens in which both carboplatin and paclitaxel are administered on day 1 every

three weeks (table 4) is not established. In our view, either regimen is acceptable. (See "Treatment protocols for anal cancer".)

Cisplatin/fluorouracil — The most widely published active regimen for the treatment of metastatic disease is cisplatin plus FU (table 5) [166,169-175]. However, while response rates of up to 60 to 65 percent are reported [169,175], they are seldom sustained. The best outcomes appear to be in patients who undergo multidisciplinary management for their metastatic disease; in one report, median survival for patients who underwent multidisciplinary management was 53 months compared with 17 months for those undergoing palliative systemic chemotherapy alone [166].

Docetaxel, cisplatin, and fluorouracil — Combinations of docetaxel, cisplatin, and FU (DCF) are also active but can be toxic [176,177]. In the largest phase II study, 66 patients received DCF in one of two combinations (standard and modified) depending on age and performance status [177]:

- For patients younger than 75 with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, six cycles of a standard DCF regimen (table 6)were recommended, although not mandatory.
- Older patients and those with an ECOG performance status of 1 were offered eight cycles of a modified DCF regimen (table 7).
- All patients received granulocyte colony-stimulating factor (G-CSF) support for primary prophylaxis of febrile neutropenia.

Of the 66 patients who received treatment, 36 received standard DCF, and 30 received modified DCF. The primary endpoint, progression-free survival at 12 months, was achieved by 47 percent of the entire cohort, and a similar percentage of patients with standard and modified DCF had disease progression at 12 months (61 versus 60 percent, respectively); the objective response rates (89 versus 83 percent), complete response rates (42 versus 47 percent), and median progression-free survival durations (11 months each) were also similar. Not surprisingly, toxicity was worse with standard DCF, including anemia, diarrhea, fatigue, nausea, and febrile neutropenia. Notably, only 2 of the 66 patients enrolled in this trial were HIV positive, and 62 percent had only locoregional and not metastatic disease.

In our view, modified DCF (table 7) is an option for patients with advanced disease, but more data are needed before it can be concluded that this is the appropriate first-step regimen for all individuals with metastatic disease.

Other combinations — The role of other combinations, such as mitomycin/doxorubicin/cisplatin or a taxane/carboplatin/FU, is uncertain, particularly for second-line therapy; few data are available, but objective responses are reported [174,176,178,179]. Single case reports and small series describe activity for single-agent carboplatin [180], doxorubicin [181], irinotecan [182], and paclitaxel [174,183], as well as for some combinations, including paclitaxel plus ifosfamide and cisplatin, paclitaxel plus carboplatin and FU, and cetuximab with or without irinotecan (in patients whose tumors do not carry *RAS* mutations) [167,184-188]. (See "Systemic therapy for metastatic colorectal cancer: General principles", section on 'RAS'.)

Eligible patients should be encouraged to enroll in clinical trials testing new strategies.

Immunotherapy — Immunotherapy monotherapy using agents that target the programmed cell death receptor 1 (PD-1) pathway is an option for patients who have progressed on first-line chemotherapy for metastatic SCC of the anus. The optimal selection of patients who are most likely to benefit from immunotherapy is not established. In our view, overexpression of programmed cell death ligand-1 (PD-L1) should not be used to select patients with advanced anal SCC for treatments targeting the PD-1 pathway. Combinations of immunotherapy plus cytotoxic chemotherapy are beginning to be studied for first-line therapy; however, until further information is available, this cannot yet be considered a standard approach outside of the context of a clinical trial.

Immunotherapy differs from traditional chemotherapy, which primarily targets rapidly dividing cells, and from targeted therapies, which interfere with key molecular events in tumor cells that drive tumor growth and invasion. Immunotherapeutic approaches to cancer treatment are based on the premise that the immune system plays a key role in the surveillance and eradication of malignancy, and that tumors evolve ways to elude the immune system. The general principles and rationale of immunotherapy are discussed separately. (See "Principles of cancer immunotherapy".)

Several immune checkpoints exist to dampen the immune response in order to protect against detrimental inflammation and autoimmunity. In the setting of malignancy, these immune checkpoints can be co-opted by tumors, resulting in immune tolerance and subsequent progression of malignancy. One well-characterized checkpoint being targeted in melanoma, non-small cell lung cancer (NSCLC), and renal cell cancer is PD-1, which is expressed on activated T-cells. PD-1 binds to its ligands PD1-L1 and PD1-L2, which are expressed on tumor cells, thereby preventing the immune system from rejecting the tumor. (See "Systemic treatment of metastatic melanoma lacking a BRAF mutation" and "Initial management of

advanced non-small cell lung cancer lacking a driver mutation" and "Systemic therapy of advanced clear cell renal carcinoma".)

Promising results with two immune checkpoint inhibitors that inhibit the PD-1 pathway, nivolumab and pembrolizumab, have been reported in advanced anal SCC:

- Nivolumab is a monoclonal antibody that targets PD-1. In a small, prospective, phase II trial conducted in patients with chemorefractory metastatic anal canal SCC, nivolumab was administered at a dose of 3 mg/kg intravenous (IV) every two weeks; programmed cell death ligand 1 (PD-L1) expression was not required [189]. Of the 39 enrolled patients, 37 were evaluable for toxicity and intent to treat (ITT) analysis. The median number of cycles delivered was six (interquartile range 3 to 10). There were nine objective responses (24 percent), two complete responses, and an additional 17 (46 percent) had stable disease as best response. Median progression-free survival was 4.1 months, and median overall survival was 11.5 months. Although the data were very limited (n = 13 patients), overexpression of PD-1 and PD-L1 seemed to correlate with responses. The side effect profile was as expected and consisted of one grade 2 pneumonitis, grade 3 anemia in 5 percent, and grade 3 fatigue, rash, and hypothyroidism in 3 percent each. (See "Toxicities associated with immune checkpoint inhibitors".)

  Dosing is variable. Some clinicians still use 3 mg/kg every two weeks, but others have transitioned to flat dosing of 240 mg once every two weeks or 480 mg every four weeks, which are both approved schedules.

- The KEYNOTE-028 trial of pembrolizumab, another anti-PD-1 monoclonal antibody, included 25 patients with PD-L1-positive anal cancer [190]. Pembrolizumab was administered IV at a dose of 10 mg/kg every two weeks for up to two years. Among the 24 with SCC histology, there were four confirmed partial responses (overall response rate 17 percent), and an additional 10 had stable disease as the best response (42 percent). The most common treatment-related adverse events were diarrhea, fatigue, and nausea.

  Additional information on the efficacy of pembrolizumab is available from the phase II KEYNOTE-158 trial, which administered pembrolizumab (200 mg IV every three weeks) to a cohort of 112 patients with metastatic or unresectable anal SCC that had progressed following frontline therapy [191]. Treatment continued for two years, or until disease progression, unacceptable toxicity, or withdrawal of consent. Study enrollment was not limited by the level of tumoral PD-L1 expression, although 67 percent of the patients had a PD-L1-positive tumor. At a median time from first dose to data cutoff of 34.7 months, there were 12 objective responses (11 percent) and 6 were complete. When analyzed according

to PD-L1 expression, responses were more frequent in those with a combined positive score of 1 or higher (15 versus 3 percent). Median duration of response was not reached at the time of data cutoff (range 6.0+ to 33.9+ months) but by Kaplan-Meier estimation, 90 percent of the responders had response duration ≥24 months. Although median progression-free survival was only 2.1 months, median overall survival in the entire cohort was 11.9 months. Toxicity was manageable; although approximately 61 percent had a treatment-related adverse event, and 22 percent of patients experienced at least one immune-mediated adverse effect, only five discontinued the drug for side effects.

If pembrolizumab is chosen, an alternative dosing schedule of 400 mg every six weeks, as is used in other settings, is acceptable.

Is there benefit in patients living with HIV? — Preclinical data suggest that the local tumor immune microenvironment is not different in people living with HIV (PLWH) as compared with HIV negative individuals with anal SCC, supporting clinical use of immunotherapy irrespective of HIV status [192].

We prefer that eligible patients be encouraged to enroll in available clinical trials. As examples:

- A trial of nivolumab in combination with ipilimumab, a monoclonal antibody that targets a different immune checkpoint, the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), is underway in PLWH who have solid tumors.
- In addition, a trial of pembrolizumab to treat HIV positive patients with a range of solid and hematologic malignancies (including anal cancer) is also accruing patients.

Combined approaches — Combinations of immunotherapy plus cytotoxic chemotherapy are beginning to be studied for first-line therapy; however, until further information is available, this cannot yet be considered a standard approach outside of the context of a clinical trial.

Modified DCF (mDCF, (table 7)) is an effective and reasonably well tolerated regimen for advanced anal SCC, and at least some data suggest that it might stimulate antigen-specific T-cell responses [177], providing the rationale for studying the combination of mDCF with immune checkpoint inhibitor immunotherapy. (See 'Docetaxel, cisplatin, and fluorouracil' above.)

Unfortunately, benefit for combined therapy could not be shown in the randomized phase II SCARCE-PRODIGE 60 trial, in which 97 patients with previously untreated locally advanced or metastatic anal SCC were randomly assigned to mDCF alone or combined with the anti-PD-L1 monoclonal antibody atezolizumab [193]. In a preliminary report presented at the 2022 annual American Society of Clinical Oncology meeting, at a median follow-up of 22 months, the

addition of atezolizumab did not improve the objective response rate (75 versus 78 percent), 12-month progression-free survival rate (44 versus 43 percent), or 12 month overall survival (78 versus 81 percent), and it was more toxic.

Role of regional therapy for liver metastases — The role of regional therapy for patients with limited, isolated hepatic metastases is incompletely defined and must be addressed on a case-by-case basis.

Given that the liver is the most common site of metastatic disease, regional therapy is an option for patients with limited, isolated hepatic metastases. However, there is far less experience with resection or nonsurgical local ablative procedures for anal SCC than there is with isolated liver colorectal adenocarcinoma or neuroendocrine cancer liver metastases, and selection criteria are undefined. (See "Potentially resectable colorectal cancer liver metastases: Integration of surgery and chemotherapy" and "Metastatic well-differentiated gastroenteropancreatic neuroendocrine tumors: Presentation, prognosis, imaging, and biochemical monitoring".)

Scant published data [194-196] suggest that there may be a small subset of patients with isolated hepatic metastases who stand to benefit from resection or other regional treatments. In the largest experience, the role of regional therapy was addressed in a multicenter analysis of 52 patients who underwent hepatic resection (n = 47), radiofrequency ablation (n = 3), or both (n = 2) for metastatic SCC at eight major cancer centers; 27 for metastatic anal cancer [194]. The majority had received some form of systemic therapy prior to resection. At a median follow-up of 18 months, 33 patients had recurred, 21 in the liver. The actuarial disease-free survival rates at three and five years were each 19 percent. When the analysis was restricted to the 27 patients with metastatic anal cancer, the median disease-free and overall survival durations were 9.6 and 22.3 months. In multivariate analysis, hepatic metastasis size >5 cm and positive surgical resections margins were both associated with a twofold higher risk of recurrence.

DRUG SHORTAGES

There may be any number of cancer therapies in short supply at various times. Guidance in the setting of drug shortages has been provided by the American Society of Clinical Oncology (table 8).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Anal cancer".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Anal cancer (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Anatomy and tumor types** – Four categories of tumors arise in the anal region: anal canal squamous cell cancers (SCCs), anal canal adenocarcinomas, perianal skin cancers, and SCCs with an epicenter in the distal rectum. An algorithmic approach to selecting initial treatment for localized disease based on tumor location and histology is provided (algorithm 1). (See 'Anatomy and types of tumors' above.)

- **Anal canal SCC**

  - **Localized disease**

    - We suggest initial concurrent chemoradiotherapy (CRT) rather than surgery for most patients even T1-2N0M0 tumors (table 2) (**Grade 2B**). (See 'Initial chemoradiotherapy' above.)

      Local excision may be an option for carefully selected patients with <1 cm, superficially invasive tumors that are completely excised and have ≤3 mm of basement membrane invasion and a horizontal spread of ≤7 mm. (See 'Local excision for small T1 tumors' above.)

- During RT, for most patients, we suggest concurrent use of standard dose fluorouracil (FU) plus mitomycin (table 3) rather than FU alone or FU plus cisplatin (**Grade 2B**). The substitution of capecitabine for FU is acceptable (table 9). Treatment interruptions should be minimized during CRT, and overall treatment time and total dose maintained as much as possible. (See 'Role of mitomycin' above and 'Replacement of mitomycin by cisplatin' above and 'Capecitabine as an alternative to infusional fluorouracil' above.)

  For the extremely aged population with T1N0 (table 2) tumors, or those with significant comorbidities, reduction of mitomycin and FU doses during CRT may be considered, although this is not a standard approach. (See 'Elderly or extensive comorbidity' above.)

- We treat anal SCC in people living with HIV similarly to those without HIV. However, patients with active or a prior history of HIV/AIDS-related complications may not tolerate full-dose therapy or require chemotherapy dose adjustment. (See 'Patients living with HIV' above.)

- We assess treatment response clinically 8 to 12 weeks after completion of CRT. For patients with a clinical complete response, re-evaluation at three- to six-month intervals with digital rectal examination, anoscopy, and inguinal node palpation is recommended, with annual contrast-enhanced CT of the chest, abdomen, and pelvis or MRI for at least three years. Patients with clinical suspicion for persistent disease at 8 to 12 weeks can be watched for up to six months following completion of CRT. Biopsy is indicated for overt disease progression or a clinical suspicion for persisting disease ≥6 months after completion of CRT. (See 'Post-treatment surveillance and assessing the local response to primary chemoradiotherapy' above.)

- **Persistent or locally recurrent disease** – Persistent or locally recurrent anal SCC following CRT can be successfully salvaged with surgery (typically APR), with long-term control in approximately 25 to 40 percent. (See 'Management of recurrent or persistent disease' above.)

- **Metastatic disease**

  - Systemic therapy is the usual approach for metastatic anal SCC.

    For most patients, we recommend paclitaxel plus carboplatin (table 4) rather than cisplatin plus FU, because of better survival and tolerability (**Grade 1B**). (See

'Paclitaxel plus carboplatin' above and "Treatment protocols for anal cancer".)

Immunotherapy using agents that target the programmed cell death receptor 1 (PD-1) pathway is an option for patients who have progressed on first-line therapy. (See 'Immunotherapy' above.)

Combinations of immunotherapy plus cytotoxic chemotherapy are beginning to be studied for first-line therapy; however, until further information is available, this cannot yet be considered a standard approach outside of the context of a clinical trial. (See 'Combined approaches' above.)

- The role of regional therapy for patients with limited, isolated hepatic metastases is incompletely defined and must be addressed on a case-by-case basis. (See 'Role of regional therapy for liver metastases' above.)

- **Anal adenocarcinoma** – For patients with adenocarcinoma of the anal canal, we suggest treatment according to a rectal cancer paradigm rather than initial FU and mitomycin-containing CRT, as is used for anal SCCs (**Grade 2C**). For most patients this will include surgery (typically APR) plus fluoropyrimidine-based CRT. (See 'Anal adenocarcinoma' above.)

- **Perianal skin cancer** – For patients with T1N0 well-differentiated cancers of the perianal skin forming a discrete skin lesion that is clearly separate from the anal canal, we suggest wide local excision alone if negative margins can be achieved without compromising the sphincter muscles (**Grade 2C**). If the tumor is ≥T2 or node-positive (table 2), if sphincter function is at risk with surgery, or if it is not clear whether the tumor arose in the perianal skin or anal canal, we suggest CRT rather than initial surgery (**Grade 2C**). (See 'True perianal skin cancers' above.)

- **Rectal SCC** – Primary rectal SCCs, which are very rare, can be difficult to distinguish from anal cancers, and they should be treated according to the same approach as anal SCC. (See 'Rectal squamous cell cancers' above.)

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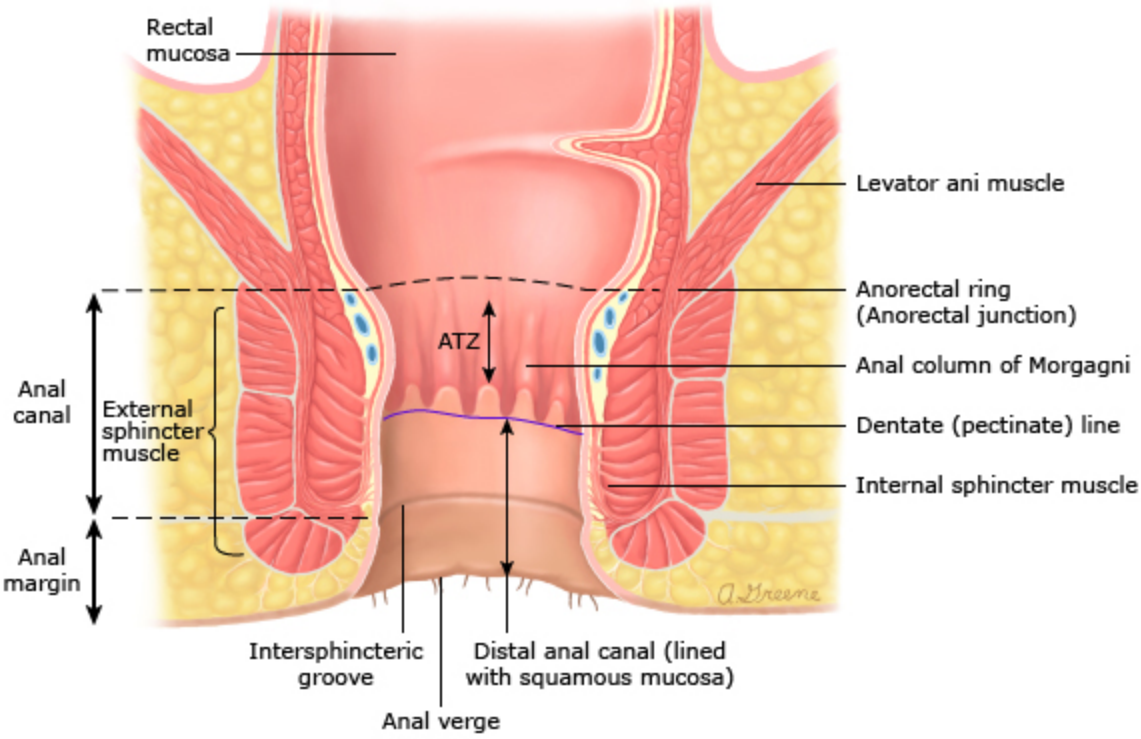
Topic 123063 Version 26.0

GRAPHICS

Anatomy of the anus and rectum



The anal canal is 2.5 to 4.0 cm long and begins superiorly where the rectal ampulla is narrowed by the anorectal ring. This palpable muscular ring is formed by fusion of the puborectalis muscle (part of the levator ani muscle complex) with the more inferior internal and external anal canal sphincters.

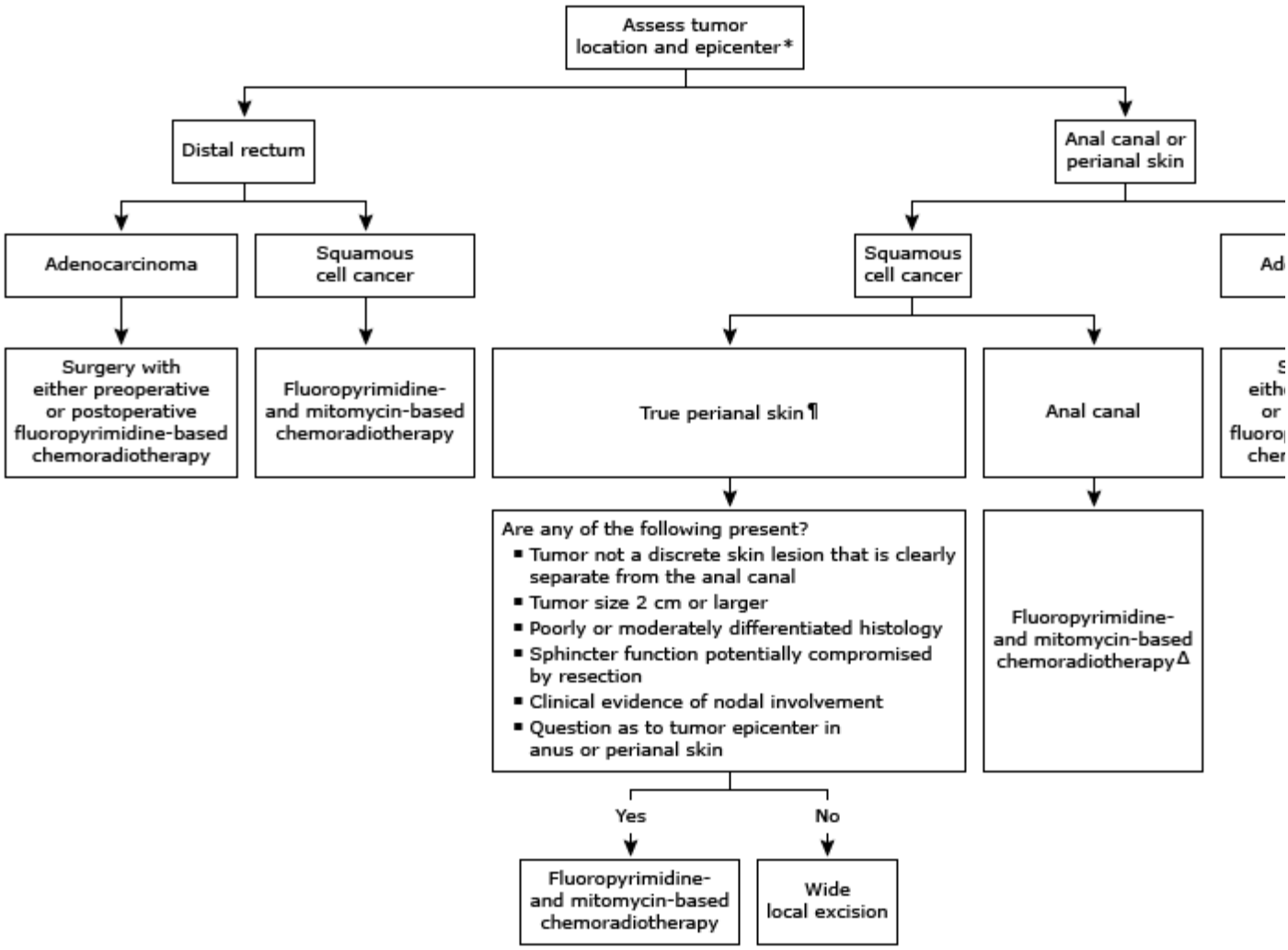
The external anal canal sphincter ends just distally to the internal anal canal sphincter; the intersphincteric groove is the palpable plane that can be palpated between the termination of the two sphincters. The presence of the intersphincteric groove coincides roughly with the anal verge, which marks the distal portion of the anal canal. The perianus or anal margin extends 5 cm laterally from the anal verge and is characterized by the presence of hair follicles and glands.

The interior of the anal canal can be divided into proximal and distal portions by an irregular line formed by the anal valves called the dentate (or pectinate) line (colored purple in the diagram). The portions of the anal canal proximal and distal to the dentate line have different origins of arterial supply, nerve innervation, and venous lymphatic drainage. The squamo-columnar junction (SCJ) lies within the proximal portion of the anal canal and marks the transition between rectal columnar epithelium to anal squamous epithelium. The exact position of the SCJ changes with time due to replacement of columnar epithelium with squamous epithelium in a process known as squamous metaplasia. The anal transformation zone (ATZ) is the zone where all aspects of squamous

metaplasia are currently found and/or have occurred. The ATZ is marked by the SCJ proximally and extends distally to approximately the level of the dentate line.

Graphic 62539 Version 16.0

Algorithmic approach to initial treatment for localized tumors of the anus, bas location and histology



* Determination of the anatomic site of origin of carcinomas that overlap the anorectal junction can be prob staging purposes, such tumors are classified as rectal cancers if their epicenter is located more than 2 cm pr dentate line or proximal to the anorectal ring on digital examination, and as anal canal cancers if their epice or less from the dentate line. The majority of rectal squamous cell cancers represent anal squamous cell can have extended into the distal rectum.

¶ Tumors that arise within the skin at or distal to the squamous mucocutaneous junction that can be seen ir entirety with gentle traction placed on the buttocks and are within 5 cm of the anus are classified as periana cancers.

Δ Local excision may be an option for carefully selected patients with very favorable, superficially invasive tu are completely excised and have ≤3 mm of basement membrane invasion and a maximal horizontal spread For the extremely aged population with T1N0 tumors or those with significant comorbidities, elimination of and administration of fluorouracil alone during radiation therapy could be considered.

Graphic 126187 Version 1.0

Anal canal cancer: Radiation therapy (RT) target volumes and doses used in the Radiation Therapy Oncology Group (RTOG) trial 0529[1]

Clinical tumor stage	Planning target volume dose to primary tumor	Planning target volume dose to uninvolved regional lymph nodes (elective)	Planning target volume dose to involved regional lymph nodes
T1-2, N0	50.4 Gy in 28 fractions (1.8 Gy/fraction)	42 Gy in 28 fractions (1.5 Gy/fraction)	
T3-4, N0	54 Gy in 30 fractions (1.8 Gy/fraction)	45 Gy in 30 fractions (1.5 Gy/fraction)	
Node-positive, ≤3cm	54 Gy in 30 fractions (1.8 Gy/fraction)		50.4 Gy in 30 fractions (1.68 Gy/fraction)
Node-positive, >3 cm	54 Gy in 30 fractions (1.8 Gy/fraction)		54 Gy in 30 fractions (1.8 Gy/fraction)

Reference:

1. *Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2013; 86:27.*

Graphic 138930 Version 1.0

Anal cancer TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor not assessed
T0	No evidence of primary tumor
Tis	High-grade squamous intraepithelial lesion (previously termed carcinoma *in situ*, Bowen disease, anal intraepithelial neoplasia II-III, high-grade anal intraepithelial neoplasia)
T1	Tumor ≤2 cm
T2	Tumor >2 cm but ≤5 cm
T3	Tumor >5 cm
T4	Tumor of any size invading adjacent organ(s), such as the vagina, urethra, or bladder
Regional lymph nodes (N)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups			
When T is…	**And N is…**	**And M is…**	**Then the stage group is…**
Tis	N0	M0	0
T1	N0	M0	I
T1	N1	M0	IIIA
T2	N0	M0	IIA

T2	N1	M0	IIIA
T3	N0	M0	IIB
T3	N1	M0	IIIC
T4	N0	M0	IIIB
T4	N1	M0	IIIC
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Graphic 110681 Version 7.0

Mitomycin and fluorouracil chemotherapy with concurrent radiotherapy* as non-surgical treatment for anal cancer[1,2]

Cycle length: Chemotherapy 28 days.
Duration of therapy: Chemotherapy for two cycles (cycle 2 starts on day 29) and radiotherapy for one cycle.

Drug	Dose and route	Administration	Given on days
Mitomycin	10 mg/m^2 IV (maximum 20 mg per dose)	Infuse as slow IV push or slow infusion in NS¶ (over 15 to 30 minutes).[3]	Days 1 and 29Δ
Fluorouracil (FU)	1000 mg/m^2 per day IV (maximum daily dose 2000 mg)	Dilute in 500 to 1000 mL D5W¶ and administer as continuous infusion over 24 hours per day for four days (96 hours).	Days 1 through 4, and days 29 through 32
Radiotherapy (45 to 50.4 Gy)	1.8 Gy daily, five days per week	Begin within 24 hours of the administration of chemotherapy.	Start on day 1 (total of five weeks)

Pretreatment considerations:

Emesis risk	▪ LOW on all days. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults and radiotherapy-induced nausea and vomiting.
Prophylaxis for infusion reactions	▪ Routine prophylaxis is not indicated. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Mitomycin is a potent vesicant and can cause ulceration, necrosis, cellulitis, and tissue sloughing; avoid extravasation.[3] FU is an irritant but can cause significant tissue damage with a large volume, concentrated extravasation; avoid extravasation.[4] ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF not indicated; use of G-CSF should be avoided in patients receiving concomitant chemoradiotherapy. ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.

Dose adjustment for baseline liver or renal dysfunction	▪ Lower initial doses of mitomycin may be needed in patients with renal insufficiency. Do not use mitomycin if serum creatinine >1.7 mg/dL.[3] A lower starting dose of FU may be needed for patients with liver impairment. ▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents; and chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents.

Monitoring parameters:

- CBC with differential weekly during treatment.
- Assess electrolytes and liver and renal function prior to each new chemotherapy cycle.
- Monitor for signs and symptoms of drug-induced TMA, which usually involves microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure. Other symptoms such as pulmonary edema, neurologic deficits, and hypertension may be present. Usually associated with cumulative doses ≥50 mg/m^2. Discontinue mitomycin immediately and permanently.
- Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
- Assess change in neurologic function prior to each new chemotherapy cycle
- Monitor for diarrhea, stomatitis, and cutaneous toxicity (palmar-plantar erythrodysesthesias)
- Monitor for signs and symptoms of mitomycin C-associated acute lung injury.
- Refer to UpToDate topics on mitomycin-C pulmonary toxicity.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ Thrombocytopenia with or without neutropenia may occur anytime within eight weeks, with an average time of four weeks. Management of the day 29 doses of chemotherapy is variable. In one study, if the nadir WBC count was <2400/microL but >1000/microL or nadir platelet count was >50,000/microL but <85,000/microL, the day 29 dose of mitomycin was reduced to 7.5 mg/m^2.[1] If the nadir WBC count was <1000/microL or the nadir platelet count <50,000/microL, the day 29 dose of mitomycin C was reduced to 5 mg/m^2. If on day 28, the WBC count was <2400/microL and/or the platelet count <85,000/microL, cycle 2 of both chemotherapy and RT was delayed one week. Others administer the day 29 dose of mitomycin to everyone regardless of interval hematologic toxicity, but reduce doses of day 29 cisplatin and FU by 50% for interval grade 4 neutropenia or febrile neutropenia.[2] Still, other clinicians delete the day 29 mitomycin dose depending on the degree of myelosuppression.

Local skin reaction	▪ The original protocol permitted a treatment interruption up to 10 days if severe local skin reaction developed.[1] However, treatment interruptions should be minimized, and overall treatment time and total dose maintained as much as possible.
Diarrhea, stomatitis	▪ Reduce week 5 dose of FU by 20% for grade 3 or 4 diarrhea or stomatitis. ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency.[4] ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Thrombotic microangiopathy	▪ TMA (also sometimes called thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]) has been associated with mitomycin.[3] Consider the possibility of TMA if the patient develops Coombs-negative hemolysis, thrombocytopenia, renal failure, and/or neurologic findings. Management consists of drug discontinuation and supportive care, without plasma exchange, as long as there is high confidence in a drug-induced etiology rather than TTP. ▪ Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
Pulmonary toxicity	▪ Mitomycin should be discontinued for any signs or symptoms of acute lung injury.[3]
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[4] ▪ Refer to UpToDate topics on fluoropyrimidine-associated cardiotoxicity.
Neurologic toxicity	▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[4]
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; G-CSF: granulocyte colony stimulating factors; CBC: complete blood count; TMA: thrombotic microangiopathy; WBC: white blood cell; RT: radiotherapy; DPD: dihydropyrimidine dehydrogenase.

* Modification of the original Wayne State (Nigro) regimen.[5]

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ Deletion of the day 29 dose of mitomycin, as was done in the control arm of the ACT II trial, may improve tolerability.[6]

References:

1. *Flam M, et al. J Clin Oncol 1996; 14:2527.*
2. *Ajani JA, et al. JAMA 2008; 299:1914.*
3. *Mitomycin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed June 12, 2012).*
4. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed June 12, 2012).*
5. *Nigro N et al. Dis Colon Rectum 1974; 17:354.*
6. *James RD, et al. Lancet Oncol 2013; 14:516.*

Graphic 87178 Version 23.0

Chemotherapy regimens for advanced anal squamous cell cancer: Every-three-week paclitaxel and carboplatin[1,2]

Cycle length: 21 days.
Duration of therapy: Until disease progression or unacceptable toxicity.

Drug	Dose and route	Administration	Given on days
Paclitaxel	175 mg/m^2 IV	Dilute in 250 to 500 mL NS or D5W* and administer over three hours.¶	Day 1
Carboplatin	AUC$^\Delta$ = 5$^\diamond$ mg/mL per min IV	Dilute in 250 mL NS or D5W* and administer over 30 minutes (administer after the completion of the paclitaxel infusion).	Day 1

Pretreatment considerations:

Emesis risk	▪ MODERATE (30 to 90% frequency of emesis).§ ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ Paclitaxel may cause severe hypersensitivity reactions. Premedication regimen should include dexamethasone (either 20 mg orally 12 and 6 hours before, or 20 mg IV 30 minutes before drug administration) plus both an H1 (diphenhydramine 50 mg IV) and an H2 receptor antagonist (famotidine 20 mg IV) 30 to 60 minutes prior to paclitaxel administration.[3] Severe infusion reactions (eg, skin rash, flushing, dyspnea, urticaria, back pain, hypotension, chest pain, tachycardia) occur primarily during the first and second infusions, typically within the first hour after the start of the infusion. Further information on infusion reactions, including management, is available. ▪ Carboplatin is also associated with infusion reactions. However, they usually occur after six cycles, and no specific premedication regimen is recommended. Further information on infusion reactions, including skin testing and desensitization, is available. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Paclitaxel can cause significant tissue damage; avoid extravasation. ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Dose adjustment for baseline liver or	▪ Each carboplatin dose should be calculated based upon renal function by use of the Calvert formula.$^\Delta$ A lower starting dose of paclitaxel may be needed in patients with liver impairment.

renal dysfunction	▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents; and Dosing of anticancer agents in adults.
Monitoring parameters:	
▪ CBC with differential weekly during treatment.	
▪ Serum electrolytes and liver and renal function tests prior to each treatment cycle.	
▪ Assess changes in neurologic function prior to each treatment cycle.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ Treatment with paclitaxel and carboplatin should be delayed until the ANC is >1500/microL and platelet count is >100,000/microL.[3,4] If a patient developed severe neutropenia (<500/microL) for a week or longer, or febrile neutropenia during the prior course, then the paclitaxel and carboplatin doses should be reduced by 20 to 25% for subsequent courses or initiation of hematopoietic growth factor support. Both the carboplatin and paclitaxel doses should be decreased by 25% in patients whose platelet count nadir is <25,000/microL for longer than five days.
Neurologic toxicity	▪ For patients who develop severe neuropathy (grade 3 or 4) for a week or longer, then the dose of paclitaxel should be reduced by 20% for subsequent courses.[3]
Dose adjustment for liver or renal dysfunction	▪ Alterations in renal function during therapy may require a recalculation of the carboplatin dose. Paclitaxel dose may need to be adjusted for hepatic impairment on day 1 of each cycle. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; AUC: area under the concentration × time curve; CBC: complete blood count; ANC: absolute neutrophil count; GFR: glomerular filtration rate; NCCN: National Comprehensive Cancer Network.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

¶ Paclitaxel can be administered in NS, D5W, or NS/D5W* at varying concentrations between 0.3 to 1.2 mg/mL. Use glass or polypropylene bottles or polypropylene or polyolefin plastic bags, and administer through polyethylene-lined administration sets with a microporous membrane 0.22 microns or less.

Δ AUC is converted to a patient-specific carboplatin dose (in mg) according to renal function by using the Calvert formula. The Calvert formula is total dose (mg) = (target AUC) × (GFR + 25). If an estimated GFR based upon measured serum creatinine is used in the Calvert equation, and renal function is normal, clinicians should consider capping the GFR at 125 mL/min, at least for the first dose. This recommendation does not apply if the GFR is directly measured. Refer to UpToDate topic on "Dosing of anticancer agents in adults", section on carboplatin.

◇ Some clinicians use a slightly higher carboplatin dose (AUC 6 mg/mL × min) for patients with a good performance status.[2]

§ Consensus-based guidelines from the NCCN classify higher carboplatin doses (AUC ≥4) as highly emetogenic; by contrast, the American Society of Clinical Oncology and the Multinational Association for Supportive Care in Cancer guidelines consider all carboplatin doses to be moderately emetogenic. Although many institutions classify carboplatin-containing regimens as moderately emetogenic, a benefit for adding a neurokinin 1 receptor antagonist on day 1 has been shown in many studies; additional prophylaxis beyond day 1 for delayed emesis is not needed for most patients. Refer to UpToDate topic on "Prevention and treatment of chemotherapy-induced nausea and vomiting in adults".

References:

1. *Eng C, et al. Oncotarget 2014; 5:1133.*
2. *Kim R, et al. Oncology 2014; 87:125.*
3. *Paclitaxel injection. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on September 11, 2019).*
4. *Carboplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at www.dailymed.nlm.nih.gov, accessed on September 11, 2019).*

Graphic 122455 Version 6.0

Cisplatin and fluorouracil chemotherapy for advanced or metastatic anal squamous cell cancer[1]

Cycle length: 28 days.

Drug	Dose and route	Administration	Given on days
Cisplatin	75 mg/m^2 IV	Dilute in 250 mL NS* and administer over 60 minutes. Do not administer with aluminum needles or sets. Alternative: Dilute in 2000 mL D5W* in 1/2 or 1/3 NS* containing 37.5 g of mannitol and infuse over six to eight hours.[2] Do not administer with aluminum needles or sets.	Day 1
Fluorouracil (FU)	750 mg/m^2 per day IV	Dilute in 500 to 1000 mL D5W* and administer as a continuous infusion over 24 hours per day for five days (120 hours). Begin after completion of cisplatin on day 1. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS.*	Days 1 through 5

Pretreatment considerations:

Hydration	▪ IV fluid to establish a urine flow of at least 100 mL/hour for at least two hours prior to and two hours after cisplatin administration. ▪ Alternative: Pretreatment hydration with 1 to 2 L of fluid infused for 8 to 12 hours prior to each dose of cisplatin.[2] ▪ Supplemental electrolytes as per institutional guidelines. ▪ Refer to UpToDate topics on cisplatin nephrotoxicity.
Emesis risk	▪ HIGH (>90% frequency of emesis). ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ Routine prophylaxis is not indicated. ▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Cisplatin and FU are irritants but can cause significant tissue damage with a large volume, concentrated extravasation; avoid extravasation.

	[2,3] ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Routine primary prophylaxis with granulocyte colony stimulating factors not warranted. ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ The optimal approach to cisplatin therapy in patients with preexisting renal impairment is unknown.[2] A lower starting dose of FU may be needed for patients with liver impairment.[3] ▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents; chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents; and chemotherapy hepatotoxicity and dose modification in patients with liver disease, molecularly targeted agents.

Monitoring parameters:

- CBC with differential prior to each new treatment cycle.
- Assess electrolytes and liver and renal function prior to each new treatment cycle.
- Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.
- Assess change in neurologic function prior to each treatment.
- Monitor for diarrhea, stomatitis, and cutaneous toxicity (palmar-plantar erythrodysesthesias).

Suggested dose modifications for toxicity:

Myelotoxicity	▪ Hold new cycle of treatment until neutrophil count ≥1500/microL and platelet count >100,000/microL. Reduce dose of cisplatin and FU by 20% for nadir grade 4 thrombocytopenia persisting longer than five days or febrile neutropenia requiring hospitalization and antibiotics.
Diarrhea	▪ Hold both cisplatin and FU for grade 4 diarrhea until complete resolution and then resume with a 20% dose reduction for both drugs. ▪ **NOTE:** Severe diarrhea and mucositis after FU should prompt evaluation for dihydropyrimidine dehydrogenase deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents.
Nephrotoxicity	▪ Hold cisplatin until serum creatinine is <1.5 mg/dL and/or blood urea nitrogen is <25 mg/dL. For grade 2 or greater nephrotoxicity during treatment (creatinine >1.5 times normal value despite adequate

	hydration), creatinine clearance should be determined prior to next cycle, and cisplatin dose reduced if <60 mL/min.[2] ▪ Alternatively, consider substitution of carboplatin for cisplatin if renal impairment (creatinine clearance <50 mL/min).
Neurologic toxicity	▪ Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m^2, although there is marked interindividual variation. Patients with mild neuropathy can continue to receive full cisplatin doses. However, if the neuropathy interferes with function, the risk of potentially disabling neurotoxicity must be weighed against the benefit of continued treatment. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[3]
Palmar-plantar erythrodysesthesia	▪ For grade 4 palmar-plantar erythrodysesthesia, withhold treatment until complete resolution then resume with a 20% dose reduction of both cisplatin and FU. ▪ Refer to UpToDate topics on cutaneous complications of conventional chemotherapy agents.
Stomatitis	▪ For grade 4 mucositis, hold next cycle until complete resolution and resume with 20% dose modification. For grade 3 mucositis, reduce cisplatin and FU doses by 20%. ▪ Refer to UpToDate topics on oral toxicity associated with chemotherapy.
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[3]
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; G-CSF: granulocyte colony-stimulating factor; CBC: complete blood count.

* Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

References:

1. *Eng C, Chang GJ, You YN, et al. Oncotarget 2014; 5:11133.*
2. *Cisplatin injection, powder, lyophilized, for solution. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed June 12, 2012).*
3. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed June 12, 2012).*

Graphic 89157 Version 15.0

Chemotherapy regimens for advanced anal squamous cell cancer: Docetaxel, cisplatin, and fluorouracil (DCF)*[1]

Cycle length: 21 days.

Duration of therapy: Maximum: Six cycles.

Drug	Dose and route	Administration	Given on days
Docetaxel	75 mg/m^2 IV	Dilute in 250 mL NS or D5W¶ to a final concentration of 0.3 to 0.74 mg/mL and administer over 60 minutes.	Day 1
Cisplatin	75 mg/m^2 IV	Dilute in 500 mL NS¶ and administer over 60 minutes or at 1 mg per minute. Do not administer with aluminum needles or IV sets.	Day 1
Fluorouracil (FU)	750 mg/m^2 per day IV	Dilute in 500 to 1000 mL NS or D5W¶ and administer as a continuous infusion over 24 hours. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS or D5W¶.	Days 1 through 5
G-CSF	5 microg/kg per day SC		Days 6 through 12

Pretreatment considerations:

Hydration	▪ IV fluid to establish a urine flow of at least 100 mL/hour for 2 hours before and 2 hours after cisplatin administration. ▪ Refer to UpToDate topics on cisplatin nephrotoxicity.
Emesis risk	▪ HIGH (>90% frequency of emesis). ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ Premedicate with dexamethasone prior to docetaxel administration to reduce the incidence and severity of fluid retention and the severity of infusion reactions.[2]

	▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Docetaxel and cisplatin are irritants, but can cause significant tissue damage; avoid extravasation.[2,3] ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF is recommended (incidence of neutropenic fever 14%, even with prophylaxis[1]). In the original protocol, G-CSF was administered to all patients at a dose of 5 microg/kg per day, for 7 days. ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ The original protocol allowed treatment for AST and ALT ≤2.5 times the ULN (or ≤5 times the ULN in the case of known liver metastasis) and total bilirubin ≤2.5 times the ULN, regardless of the presence of liver metastases.[1] Recommendations in the United States Prescribing Information suggest that docetaxel not be initiated if serum bilirubin is above the ULN, or if the AST and/or ALT are >1.5 times the ULN concomitant with AP >2.5 times the ULN.[3] Dose modifications of FU may be needed for patients with hepatic impairment.[4] The optimal approach to cisplatin therapy in patients with pre-existing renal impairment is unknown; patients with a CrCl <60 mL/min were excluded from the original trial.[1] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Dose adjustment for known drug interactions	▪ Caution is required if administering docetaxel with strong CYP3A4 inhibitors.Δ According to the United States Prescribing Information, avoid the use of docetaxel with strong CYP3A4 inhibitors (if possible). If concomitant therapy cannot be avoided, monitor closely for toxicity and consider a docetaxel dose reduction.[2] Docetaxel dose reductions for concomitant therapies should be individualized based on patient factors (eg, performance status) and the intent of therapy (ie, curative or palliative). ▪ Refer to "Suggested dose modifications for toxicity" below.

Monitoring parameters:	
▪ Assess CBC with differential and platelet count weekly during treatment.	
▪ Assess basic metabolic panel including creatinine and electrolytes, and liver function tests at least prior to each treatment cycle; assess creatinine and electrolytes more frequently if clinically indicated (eg, diarrhea, vomiting).	
▪ Monitor for neurotoxicity, diarrhea, fluid retention, and cutaneous toxicity prior to each treatment cycle.	
▪ Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ The United States Prescribing Information for docetaxel states that patients should not be retreated with a new cycle of therapy until the ANC is >1500/microL, and platelet count is >100,000/microL.[3] However, the original trial allowed retreatment with a new cycle of therapy if neutrophils were ≥1000/microL and platelets ≥75,000/microL.[1] If the neutrophil nadir was <500/microL or there was febrile neutropenia and/or a nadir platelet count <50,000/microL, and it required more than 8 days to recover from myelosuppression, reduce docetaxel and cisplatin doses by 25% each, and FU dose by 33%; if recovery occurred within 8 days, reduce cisplatin and FU doses by 25% each.[1] ▪ For a second episode of neutrophils <500/microL or febrile neutropenia and/or platelet count <50,000/microL, reduce docetaxel and cisplatin by 33% of the original dose, and reduce FU by 50% of the original dose. For a nadir >500 but <1000 neutrophils/microL and/or platelets >50,000 but <75,000, and recovery takes longer than 8 days, reduce cisplatin and FU by an additional 25%. For recovery within 8 days, no further dose reduction is recommended.
Renal dysfunction	▪ CrCl should be determined prior to each cycle, and reduce cisplatin dose by 33% if CrCl >40 mL/min but <60 mL/min.[1] For CrCl <40 mL/min, stop cisplatin for up to 3 weeks. If recovery to ≥60 mL/min, and another cause found, reduce cisplatin dose by 33%.[1] If no other cause is found, discontinue cisplatin at the discretion of the clinician. ▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Neurotoxicity	▪ Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m^2, although there is marked interindividual

	variation. Reduce cisplatin dose 25% for grade 1 neurotoxicity for >14 days.[1] Reduce docetaxel by 25%, and cisplatin by 33% for grade 2 peripheral neuropathy and discontinue both drugs for grade 3 neuropathy.[1] If recovery to <grade 2 neurotoxicity, may restart docetaxel with a 25% dose reduction. Permanently discontinue both docetaxel and cisplatin for grade 4 neurotoxicity. ▪ Stop cisplatin for grade 3 or worse hearing impairment during therapy. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[4] ▪ Refer to UpToDate topics on overview of neurologic complications of conventional non-platinum cancer chemotherapy.
Gastrointestinal toxicity	▪ For the second episode of grade 2 diarrhea, reduce subsequent FU dose by 25%. Hold FU, docetaxel, and cisplatin treatment for any grade 3 or worse diarrhea and restart with a 25% lower dose of FU after recovery to grade 0 or 1.[1] For the second episode of grade 3 diarrhea, reduce subsequent FU doses by an additional 25% after recovery to ≤grade 1. Discontinue all treatment for grade 4 diarrhea. ▪ For the first episode of grade 2 mucositis, reduce subsequent FU doses by 25%. For the first episode of grade 3 stomatitis, stop chemotherapy. If recovery to grade 0 or 1 within 3 weeks, reduce docetaxel and cisplatin by 25%, and FU by 50% for subsequent doses. For second episode of grade 3 or first episode of grade 4 mucositis, stop chemotherapy. ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents and oral toxicity associated with chemotherapy.
Cutaneous erythema/desquamation/HFS	▪ For ≥grade 2 toxicity despite optimal local therapy, hold FU and resume only when it recovers to grade ≤1.[1] For the second appearance of grade 2, or first appearance of grade 3 symptoms, reduce subsequent doses of FU by 25%. Stop docetaxel for up to 3 weeks for grade 3 symptoms; if it recovers to ≤grade 2, reduce subsequent docetaxel dose by 25%. Discontinue docetaxel for grade 4 HFS.

	▪ Refer to UpToDate topics on cutaneous side effects of conventional chemotherapy agents.
Hepatotoxicity	▪ Guidelines on dose reductions for intracycle hepatotoxicity from the original protocol are less stringent than those provided in the United States Prescribing Information for docetaxel given in conjunction with cisplatin and FU. For intracycle increases of AST/ALT >2.5 but ≤5 times the ULN, and AP <2.5 times the ULN **or** AST/ALT >1.5 to ≤5 times the ULN **and** AP >2.5 to ≤5 times the ULN, hold treatment until recovery to grade 0 or 1, and reduce subsequent docetaxel by 25%. Discontinue docetaxel if AST/ALT is >5 times the ULN **and/or** AP is >5 times the ULN.[3] The original trial suggested holding docetaxel for any AST/ALT >3 times the ULN or bilirubin ≥1.5 times the ULN; resume only after recovery to ≤grade 1 within three weeks, with a 25% dose reduction. Discontinue if recovery is more prolonged. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents.
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[4] ▪ Refer to UpToDate topics on fluoropyrimidine-associated cardiotoxicity.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; SC: subcutaneous; G-CSF: granulocyte colony-stimulating factors; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; AP: alkaline phosphatase; CrCl: creatinine clearance; CYP3A4: cytochrome P450 3A4; CBC: complete blood count; ANC: absolute neutrophil count; DPD: dihydropyrimidine dehydrogenase; HFS: hand-food syndrome; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group.

* In the original trial, use of this standard DCF regimen was suggested for individuals aged 75 years or younger and with an ECOG performance status of 0, and modified DCF regimen was suggested for older individuals or those with an ECOG performance status of 1.[1]

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ A list of strong and moderate CYP3A4 inhibitors is available as a separate table in UpToDate. Specific interactions may be determined by use of the Lexicomp drug interactions program included within UpToDate.

References:

1. *Kim S, et al. Lancet Oncol 2018; 19:1094.*
2. *Docetaxel injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on March 15, 2022).*
3. *Cisplatin injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on March 19, 2020).*
4. *Fluorouracil injection. United States Prescribing Information. US National Library of Medicine. (Available online at dailymed.nlm.nih.gov, accessed on March 19, 2020).*

Graphic 130020 Version 6.0

Chemotherapy regimens for advanced anal squamous cell cancer: Modified docetaxel, cisplatin, and fluorouracil (modified DCF)*[1]

Cycle length: 14 days.

Duration of therapy: Eight cycles.

Drug	Dose and route	Administration	Given on days
Docetaxel	40 mg/m^2 IV	Dilute with 250 mL NS or D5W¶ to a final concentration of 0.3 to 0.74 mg/mL and administer over 60 minutes.	Day 1
Cisplatin	40 mg/m^2 IV	Dilute with 250 mL NS¶ and administer over 60 minutes or at 1 mg per minute. Do not administer with aluminum needles or IV sets.	Day 1
Fluorouracil (FU)	1200 mg/m^2 per day IV	Dilute with 500 to 1000 mL NS or D5W¶ and administer by continuous infusion over 24 hours. To accommodate an ambulatory pump for outpatient treatment, can be administered undiluted (50 mg/mL) or the total dose can be diluted in 100 to 150 mL NS or D5W¶.	Days 1 and 2
G-CSF	5 microg/kg per day SC		Days 3 through 7

Pretreatment considerations:

Hydration	▪ IV fluid to establish a urine flow of at least 100 mL/hour for at least 2 hours prior to and 2 hours after cisplatin administration. ▪ Refer to UpToDate topics on cisplatin nephrotoxicity.
Emesis risk	▪ HIGH (>90% frequency of emesis). ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults.
Prophylaxis for infusion reactions	▪ Premedicate with dexamethasone prior to docetaxel administration to reduce the incidence and severity of fluid retention and the severity of infusion reactions.[2]

	▪ Refer to UpToDate topics on infusion reactions to systemic chemotherapy.
Vesicant/irritant properties	▪ Docetaxel and cisplatin are irritants but can cause significant tissue damage; avoid extravasation.[2,3] ▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF is recommended to maintain dose intensity.[1] In the original protocol, G-CSF was administered to all patients at a dose of 5 microg/kg per day, for 5 days. ▪ Refer to UpToDate topics on use of granulocyte colony stimulating factors in adult patients with chemotherapy-induced neutropenia and conditions other than acute leukemia, myelodysplastic syndrome, and hematopoietic cell transplantation.
Dose adjustment for baseline liver or renal dysfunction	▪ The original protocol allowed AST and ALT to be <2.5 times the ULN (or <5 times the ULN in the case of known liver metastasis) and total bilirubin <2.5 times the ULN, regardless of the presence of liver metastases. Recommendations in the United States Prescribing Information suggest that docetaxel not be given if serum bilirubin is above the ULN, or if the AST and/or ALT are >1.5 times the ULN concomitant with AP >2.5 times the ULN.[2] Dose modifications of FU may be needed for patients with hepatic impairment.[4] The optimal approach to cisplatin therapy in patients with pre-existing renal impairment is unknown; patients with a CrCl <60 mL/min were excluded from the original trial.[1] ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents and chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Dose adjustment for known drug interactions	▪ Caution is required if administering docetaxel with strong CYP3A4 inhibitors.Δ According to the United States Prescribing Information, avoid the use of docetaxel with strong CYP3A4 inhibitors (if possible). If concomitant therapy cannot be avoided, monitor closely for toxicity and consider a docetaxel dose reduction.[2] Docetaxel dose reductions for concomitant therapies should be individualized based on patient factors (eg, performance status) and the intent of therapy (ie, curative or palliative). ▪ Refer to "Suggested dose modifications for toxicity" below.

Monitoring parameters:	
▪ Assess CBC with differential and platelet count on day 1 prior to each new course of treatment, weekly if clinically indicated.	
▪ Assess basic metabolic panel including creatinine and electrolytes, and liver function tests at least prior to each new treatment course; assess creatinine and electrolytes more frequently if clinically indicated (eg, diarrhea, vomiting).	
▪ Monitor for neurotoxicity, diarrhea, fluid retention, and cutaneous toxicity prior to each treatment cycle.	
▪ Monitor for hearing loss prior to each dose of cisplatin; audiometry as clinically indicated.	
Suggested dose modifications for toxicity:	
Myelotoxicity	▪ The United States Prescribing Information for docetaxel states that patients should not be retreated with a new cycle of therapy until the ANC is >1500/microL, and platelet count is >100,000/microL.[2] However, the original trial allowed retreatment with a new cycle of therapy if neutrophils were ≥1000/microL and platelets ≥75,000/microL.[1]. If the nadir was <500 neutrophils or febrile neutropenia and/or <50,000 platelet count, and it takes more than 8 days to recover from myelosuppression, reduce docetaxel and cisplatin doses dose by 25%, and FU dose by 33%; if recovery occurs within 8 days, reduce cisplatin and FU doses by 25%.[1] For a second episode of <500 neutrophil count or febrile neutropenia and/or <50,000 platelets, reduce docetaxel and cisplatin by 33% of the original dose, and reduce FU by 50% of the original dose. For a nadir >500 but <1000 neutrophils/microL and/or platelets were >50,000 but <75,000, and recovery takes longer than 8 days, reduce cisplatin and FU by 25%. For recovery within 8 days, no dose reduction is recommended.
Nephrotoxicity	▪ CrCl should be determined prior to each cycle, and reduce cisplatin dose by 33% if CrCl >40 mL/min but <60 mL/min.[1] For CrCl <40 mL/min, stop cisplatin for up to 3 weeks. If recovery to ≥60 mL/min, and another cause is found, reduce cisplatin dose by 33%.[1] If no other cause is found, discontinue cisplatin at the discretion of the clinician. ▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with kidney impairment, conventional cytotoxic agents.
Neurotoxicity	▪ Neuropathy usually is seen with cumulative doses of cisplatin >400 mg/m^2, although there is marked interindividual variation. Reduce cisplatin dose 25% for grade 1 neurotoxicity

	for >14 days.[1] Reduce docetaxel by 25%, and cisplatin by 33% for grade 2 peripheral neuropathy and discontinue both drugs for grade 3 neuropathy.[1] If recovery to <grade 2 neurotoxicity, may restart docetaxel with a 25% dose reduction. Permanently discontinue both docetaxel and cisplatin for grade 4 neurotoxicity. ▪ Stop cisplatin for a grade 3 or worse hearing impairment during therapy. ▪ Refer to UpToDate topics on overview of neurologic complications of platinum-based chemotherapy. ▪ There is no recommended dose for resumption of FU administration following development of hyperammonemic encephalopathy, acute cerebellar syndrome, confusion, disorientation, ataxia, or visual disturbances; the drug should be permanently discontinued.[4] ▪ Refer to UpToDate topics on overview of neurologic complications of conventional non-platinum cancer chemotherapy.
Gastrointestinal toxicity	▪ For the second episode of grade 2 diarrhea, reduce subsequent FU dose by 25%. Hold FU, docetaxel, and cisplatin treatment for any grade 3 or worse diarrhea and restart with a 25% lower dose of FU after recovery to grade 0 or 1.[1] For the second episode of grade 3 diarrhea, reduce subsequent FU doses by additional 25% after recovery to ≤grade 1. Discontinue all treatment for grade 4 diarrhea. ▪ For the first episode of grade 2 mucositis, reduce subsequent FU doses by 25%. For the first episode of grade 3 stomatitis, stop chemotherapy. If recovery to grade 0 or 1 within 3 weeks, reduce docetaxel and cisplatin by 25%, and FU by 50% for subsequent doses. For a second episode of grade 3 or first episode of grade 4 mucositis, stop chemotherapy. ▪ **NOTE:** Severe diarrhea, mucositis, and myelosuppression after FU should prompt evaluation for DPD deficiency. ▪ Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents and oral toxicity associated with chemotherapy.
Cutaneous erythema/desquamation/HFS	▪ Hold FU for grade 2 or greater HFS, and resume only when it recovers to grade 0 or 1.[1] For the second appearance of grade 2 HFS, or first appearance of grade 3 symptoms, reduce subsequent doses of FU by 25%. Stop docetaxel for up to 3 weeks for grade 3 HFS; if it recovers to grade 0 or 1, reduce docetaxel dose by 25%. Discontinue docetaxel for grade 4 HFS.

	▪ Refer to UpToDate topics on cutaneous side effects of conventional chemotherapy agents.
Hepatotoxicity	▪ Guidelines on dose reductions for intracycle hepatotoxicity from the original protocol are less stringent than those provided in the United States Prescribing Information for docetaxel given in conjunction with cisplatin and FU. For intracycle increases of AST/ALT >2.5 but ≤5 times the ULN, and AP <2.5 times the ULN **or** AST/ALT >1.5 to ≤5 times the ULN **and** AP >2.5 to ≤5 times the ULN, hold treatment until recovery to grade 0 or 1, and reduce subsequent docetaxel by 25%[2]. Discontinue docetaxel if AST/ALT is >5 times the ULN **and/or** AP is >5 times the ULN.[2] The original trial suggested holding docetaxel for any AST/ALT >3 times the ULN or bilirubin ≥1.5 times the ULN; resume only after recovery to ≤grade 1 within 3 weeks, with a 25% dose reduction[1]. Discontinue if recovery is more prolonged. ▪ Refer to UpToDate topics on chemotherapy hepatotoxicity and dose modification in patients with liver disease, conventional cytotoxic agents.
Cardiotoxicity	▪ Cardiotoxicity observed with FU includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, ECG changes, and cardiomyopathy. There is no recommended dose for resumption of FU administration following development of cardiac toxicity, and the drug should be discontinued.[4] ▪ Refer to UpToDate topics on fluoropyrimidine-associated cardiotoxicity.
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; NS: normal saline; D5W: 5% dextrose in water; G-CSF: granulocyte colony stimulating factors; SC: subcutaneous; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal; AP: alkaline phosphatase; CrCl: creatinine clearance; CYP3A4: cytochrome P450 3A4; CBC: complete blood count; ANC: absolute neutrophil count; DPD: dihydropyrimidine dehydrogenase; HFS: hand-foot syndrome; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group.

* In the original trial, use of this modified DCF regimen was suggested for individuals older than age 75 and/or with an ECOG performance status of 1 and standard DCF regimen was suggested for individuals with age 75 years or younger with an ECOG performance status of 0.[1]

¶ Diluent solutions should not be modified without consulting a detailed reference due to potential incompatibility(ies).

Δ A list of strong and moderate CYP3A4 inhibitors is available as a separate table in UpToDate. Specific interactions may be determined by use of the Lexicomp drug interactions program included within UpToDate.

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Graphic 130021 Version 7.0

Summary of ASCO Clinical Guidance for Drug Shortages

The following statements provide general guidance on managing anticancer drugs in limited supply.

Provider-specific guidance

- Decisions to use a drug in short supply should incorporate the treatment goals for each patient. Settings with a demonstrated survival benefit should be prioritized for use (both in the early and advanced disease settings).*
- Reprioritize use of drugs that are in limited supply. If an alternative treatment strategy with similar efficacy and safety can be used,¶ opt for that strategy.
- If clinically appropriate, extend the time between treatment cycles and/or decrease the amount of drug used to the lowest effective dose.Δ
- Limit the use of the agent in shortage for cancers that have recurred despite multiple therapies.◇
- Decrease waste by optimizing the size of vials, rounding down on doses (if appropriate), and using multi-use vials.
- Discuss with colleagues in hematology and oncology to identify alternative treatment options, including clinical trials.

Support services for shortage-related distress

- Drug shortages cay cause distress both for clinicians and for patients. Clinicians may feel emotional distress if unable to provide optimal care; patients may experience distress if their care is impacted, and the therapeutic relationship with their provider may suffer.
- Institutions should communicate to clinicians about available resources to manage distress related to drug shortages. Possible support resources include ASCO Safe Haven,[1] group forums, and peer to peer discussions.
- Clinicians should refer patients with distress for counseling. Other appropriate support options include patient support groups.

ASCO: America Society of Clinical Oncology; SCLC: small cell lung cancer; CRT: chemoradiation; FU: fluorouracil; FOLFOX: oxaliplatin, leucovorin, and fluorouracil; RT: radiation therapy; CAPOX: capecitabine and oxaliplatin; FLOT: docetaxel, oxaliplatin, leucovorin, and fluorouracil; TCHP: docetaxel, carboplatin, trastuzumab, and pertuzumab; HER2: human epidermal growth factor 2; AUC: area under the curve; AC: doxorubicin and cyclophosphamide.

* As an example of when to prioritize use of an agent in limited supply, patients with limited-stage SCLC treated should be referred to a center where a platinum agent is available.[2]

¶ Most locally advanced, resectable esophageal and/or gastroesophageal junction carcinomas are managed with neoadjuvant CRT, followed by surgical resection. Radiosensitizing regimens for CRT include carboplatin plus paclitaxel, FU plus cisplatin, or FOLFOX. As examples of using an alternative treatment strategy:

- If cisplatin and carboplatin are in limited supply, neoadjuvant CRT with FOLFOX plus RT is an appropriate option.[3] If FU is also limited, CAPOX may be used concurrently with RT.

- For gastroesophageal junction cancers, appropriate alternatives to neoadjuvant CRT may include perioperative chemotherapy. If FU is available, perioperative regimens include FOLFOX or FLOT.
- For further details and supporting evidence, refer to UpToDate topics on treatment of resectable esophageal, gastroesophageal, and gastric cancers.

Δ For the TCHP regimen used in early HER2-positive breast cancer,[4] consider decreasing carboplatin to an AUC of 5 instead of 6 or omitting carboplatin.[5] Similarly, for the KEYNOTE-522 regimen used as neoadjuvant treatment in triple-negative breast cancer,[6] the standard dose of weekly carboplatin is an AUC of 1.5, but modifying to an AUC of 1 is acceptable given shortages of carboplatin. One could also start with AC plus pembrolizumab to be followed by paclitaxel and pembrolizumab, with or without carboplatin. ASCO recommends that providers consider prioritizing carboplatin for those whose tumors did not have a good response to AC plus pembrolizumab, but also notes that the incremental benefit of carboplatin in the KEYNOTE-522 regimen is unknown. For further details on the indications and efficacy of these regimens, refer to UpToDate topics on selecting neoadjuvant chemotherapy for HER2-negative and HER2-positive breast cancer.

◇ As an example, consider decreasing the dose or omitting use of either cisplatin or carboplatin in recurrent platinum-resistant ovarian cancer.[7]

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Graphic 141828 Version 1.0

Mitomycin and capecitabine with concurrent radiation therapy for locally advanced anal carcinoma[1]

Cycle length: 6.5 weeks (chemoradiotherapy).

Drug	Dose and route	Administration	Given on days
Mitomycin	10 mg/m^2 (maximum 15 mg*) IV	Infuse as slow IV push (over 5 to 10 minutes).	Day 1¶
Capecitabine$^{\Delta}$	825 mg/m^2 per dose by mouth	Twice daily (total dose 1650 mg/m^2 per day) on radiation days; swallow whole with water within 30 minutes after a meal, with each dose as close to 12 hours apart as possible. Do not cut or crush tablets.◇	Days 1 through completion of radiotherapy (do not give with boost fractions)
Radiotherapy§	59.4 Gy primary tumor; elective 45 to 49.5 Gy to pelvic and inguinal lymph nodes	Three dimensional CF-RT: 25 fractions (45 Gy) followed by three weeks rest then 8 to 11 additional fractions (1.8 Gy per boost) based on clinical/radiographic assessment (week 5). IMRT: 33 fractions (59.4 Gy) followed by a boost of three fractions (1.8 Gy each), if needed, based on clinical/radiographic assessment (week 5).	Five days per week beginning week 1 and continuing through at least week 6

Pretreatment considerations:

Emesis risk	▪ Mitomycin: LOW. ▪ Capecitabine: LOW. ▪ Refer to UpToDate topics on prevention of chemotherapy-induced nausea and vomiting in adults and radiotherapy-induced nausea and vomiting: Prophylaxis and treatment.
Infection prophylaxis	▪ Primary prophylaxis with G-CSF is not indicated. G-CSF should be used with caution, if at all, with chemoradiotherapy. ▪ Refer to UpToDate topics on prophylaxis of infection during chemotherapy-induced neutropenia in high-risk adults.
Vesicant/irritant properties	▪ Mitomycin is a potent vesicant and can cause ulceration, necrosis, cellulitis, and tissue sloughing; avoid extravasation.[2]

	▪ Refer to UpToDate topics on extravasation injury from chemotherapy and other non-antineoplastic vesicants.
Dose adjustment for baseline renal dysfunction	▪ Lower initial doses of mitomycin may be needed in patients with renal insufficiency. A lower starting dose of capecitabine may be needed for patients with moderate renal impairment.[3] ▪ Refer to UpToDate topics on chemotherapy nephrotoxicity and dose modification in patients with renal insufficiency, conventional cytotoxic agents.

Monitoring parameters:

- Assess CBC with differential and platelet count prior to treatment and weekly for at least eight weeks after starting treatment. Thrombocytopenia with or without neutropenia may occur anytime within eight weeks, with an average time of four weeks.[2] Recovery occurs within 10 weeks; however, myelosuppression is cumulative and counts may not recover in about 25% of cases.
- Assess basic metabolic panel (including serum creatinine) and liver function tests prior to starting treatment then weekly during chemoradiotherapy.
- Monitor for signs and symptoms of localized dermatological toxicity and for changes in urinary and bowel habits during and after radiation therapy.
- More frequent anticoagulant response (INR or prothrombin time) monitoring is necessary for patients receiving concomitant capecitabine and oral coumarin-derivative anticoagulant therapy.
- Monitor for diarrhea, stomatitis, and cutaneous toxicity (palmar-plantar erythrodysesthesias) during treatment.
- **NOTE:** Severe diarrhea, mucositis, and myelosuppression after capecitabine should prompt evaluation for dihydropyrimidine dehydrogenase deficiency.
- Refer to UpToDate topics on enterotoxicity of chemotherapeutic agents and cutaneous side effects of conventional chemotherapy agents.
- Monitor for signs and symptoms of mitomycin-associated acute lung injury.
- Refer to UpToDate topics on mitomycin-C pulmonary toxicity.
- Monitor for signs and symptoms of drug-induced TMA, which usually involves microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure. Other symptoms such as pulmonary edema, neurologic deficits, and hypertension may be present. TMA is usually associated with cumulative doses ≥50 mg/m^2. Discontinue mitomycin immediately and permanently.
- Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
- Cardiotoxicity observed with capecitabine includes myocardial infarction/ischemia, angina, dysrhythmias, cardiac arrest, cardiac failure, sudden death, electrocardiographic changes, and cardiomyopathy. These adverse reactions may be more common in patients with a prior history of coronary artery disease.

- Refer to UpToDate topics on cardiotoxicity of cancer chemotherapy agents other than anthracyclines, HER2-targeted agents, and fluoropyrimidines.

Suggested dose modifications for toxicity:

Myelotoxicity	▪ This regimen should not be initiated unless white blood cells are ≥4000/microL, neutrophils are ≥1500/microL, and platelets are ≥100,000/microL.[2,3] At some institutions, the mitomycin dose is repeated on day 29, as was used in RTOG 98-11.[4] The day 29 mitomycin dose should be reduced to 7.5 mg/m^2 if the nadir WBC is <2400/microL but >1000/microL, or if the nadir platelet count is >50,000/microL but <85,000/microL. If the nadir WBC is <1000/microL or the nadir platelet count is <50,000/microL, the day 29 dose of mitomycin is reduced to 5 mg/m^2. If the day 28 WBC is <2400/microL or platelet count <85,000/microL, we delay the start of the second cycle of therapy by one week. Reduce subsequent mitomycin doses if leukocyte nadir is <3000/microL or platelet nadir is <75,000/microL. The authors of this study do not state specific chemotherapy dose adjustment parameters for toxicity observed; however, other studies of capecitabine chemoradiotherapy[5,6], and the United States Prescribing Information[3], suggest withholding capecitabine for grade 3 or 4 hematologic toxicity, and that capecitabine be restarted after at least seven days or when recovered to ≤grade 1.
Nonhematologic toxicity (including hepatotoxicity)	▪ The authors of this study do not specify chemotherapy dose adjustments for nonhematologic toxicity; however, other studies of capecitabine-based chemoradiotherapy[5,6] recommend interrupting capecitabine for ≥grade 2 nonhematologic toxicity (except alopecia) that is likely related to capecitabine until it decreases to ≤grade 1 for the first incidence.[5,6] Decrease subsequent capecitabine dose by 25% for ≥grade 3 nonhematologic toxicity or recurrent grade 2 toxicity (except alopecia).[5,6] ▪ **The United States Prescribing Information for capecitabine provides the following guidelines for capecitabine dose modification:**[3] • Grade 2: For the first, second, and third occurrence, hold capecitabine therapy. After resolution to grade 1 or less, resume treatment (first occurrence, no dosage adjustment; second occurrence, 75% of the starting dose; third occurrence, 50% of the starting dose).[3] For the fourth occurrence of a grade 2 toxicity, discontinue capecitabine therapy. • Grade 3: For the first and second occurrence, hold capecitabine therapy. After resolution to grade 1 or less, resume treatment at a reduced dose (first occurrence, 75% of the starting dose; second occurrence, 50% of the starting dose). For the third occurrence of a grade 3 toxicity, discontinue capecitabine therapy. • Grade 4: Discontinue capecitabine therapy. Alternatively, hold capecitabine therapy, and begin next treatment at 50% of the starting

	dose when toxicity resolves to grade 1 or less; discontinue treatment for first recurrence of grade 4 toxicity.
Pulmonary toxicity	▪ Mitomycin should be discontinued for any signs or symptoms of acute lung injury.[2]
Thrombotic microangiopathy	▪ TMA, also sometimes called thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) has been associated with mitomycin. Consider the possibility of TMA if the patient develops Coombs-negative hemolysis, thrombocytopenia, renal failure, and/or neurologic findings. Management consists of drug discontinuation and supportive care, without plasma exchange, as long as there is high confidence in a drug-induced etiology rather than TTP. ▪ Refer to UpToDate topics on drug-induced thrombotic microangiopathy.
Omitted capecitabine doses for toxicity are not replaced or restored.	
If there is a change in body weight of at least 10%, doses should be recalculated.	

This table is provided as an example of how to administer this regimen; there may be other acceptable methods. This regimen must be administered by a clinician trained in the use of chemotherapy, who should use independent medical judgment in the context of individual circumstances to make adjustments, as necessary.

IV: intravenous; Gy: gray; CF-RT: conformal radiotherapy; IMRT: intensity-modulated radiotherapy; G-CSF: granulocyte colony stimulating factor; CBC: complete blood count; INR: international normalized ratio; TMA: thrombotic microangiopathy; RTOG: Radiation Therapy Oncology Group; WBC: white blood cell count; DPD: dihydropyrimidine dehydrogenase; RT: radiation therapy.

* At other institutions, the mitomycin dose is capped at 20 mg total dose.

¶ At some institutions, the mitomycin dose is repeated on day 29, as was used in RTOG 98-11.[4]

Δ No capecitabine dose has been shown to be safe in patients with complete DPD deficiency, and data are insufficient to recommend a dose in patients with partial DPD activity.

◇ Extemporaneous compounding of liquid dosage forms has been recommended, but IV therapies may be more appropriate for patients with significant swallowing difficulty.

§ The original trial administered three-dimensional chemoradiotherapy with conventional fractionation RT prior to March 2006 and then received integrated boost IMRT thereafter.

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