ANAL CANCER

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The understanding and treatment of anal cancer has undergone a major changes. Twenty years ago, radical surgery in the form of abdominoperineal resection was the only possibility for cure. Combined modality treatment with irradiation and chemotherapy has resulted in increased survival and in sphincter preservation for most patients (1-7).

ANATOMY

The anal canal is about 3 cm to 4 cm long and extends from the anal verge to the level of the pelvic floor. The superior margin is determined clinically by the palpable upper border of the anal sphincter and puborectalis muscle as anorectal ring. The distal end of the canal at the anal verge can be defined as palpable groove between the lower edge of the internal sphincter and subcutaneous part of the external sphincter (8). The American Joint Committee on Clinical Staging and the Union Internationale Contre le Cancer (UICC) (9) recommend this definition of anal canal, rather than a convention used by some centers under which carcinomas that arise above or exactly at the dentate line are classified as anal canal tumors and those lying mainly or entirely below that line are called anal margin tumors (10-15). Perianal carcinomas are arbitrarily considered to be cancers arising from the skin within a 5 cm to 6 cm radius of the anal verge. This distinction is an important one, because squamous or basal cell cancers below the anal verge (perianal cancers) are skin cancers from a biologic and therapeutic perspective.

Four different types of epithelium are found within the anal region (8). The perianal skin is similar to hair-bearing skin elsewhere and contains many apocrine glands. At the anal verge, the skin become with a zone lined by modified squamous epithelium, which lacks hair or glandular structures. This squamous zone merges just below the dentate line (also called the pectinate line), which marks the line of the anal valves, with a transitional epithelium that incorporates features of rectal, urothelial, and squamous epithelia. The transitional zone extends proximally for about 20 mm until rectal mucosa becomes dominant.

PATHOLOGIC CLASSIFICATION

Epidermoid carcinomas now can be classified as squamous, basaloid or mucoepidermois tumors.

Squamous Cell Carcinomas may be keratinizing or nonkeratinizing. The well-differentiated type tend to arise from the skin of the anal margin, whereas the poorly differentiated tumours occur more frequently within the anal canal. According to Morson (16), more than 80% of tumors of the margin produce keratin whereas only 50% of tumors in the anal canal do so.

Basaloid Tumors arises from the cells of the anal transitional zone (17) and are also known as cloacogenic or transitional tumors18. They account for 30-50% of all anal canal cancers (19,20,21). These tumors may resemble carcinomas of anoepithelium or they may have patterns similar to basal cell carcinoma of the skin.

Mucoepidermois Tumors are rare. They occur in the anal canal and consist of squamous cells that produce both mucus and keratin (22). A careful search using mucin stains may find of mucinproducing cells in approximately 10-15% of patients with epidermoid cancers (23). These tumors behave in the same way as all other squamous cell carcinomas of the anus.

SPREAD

Direct spread of anal squamous cell carcinoma is preferentially in an upwards direction into the lower rectum. The reason is said to be because the line of least resistance is upwards in the submucous layer (24). Lymphatic spread commonly occurs to the inguinal nodes, but it is often not appreciated that spread to the superior haemorrhoidal lymph nodes and the nodes on the lateral wall of the pelvis is as common.

There is a relationship between the degree of histological differentiation and the incidence of lymph node metastases (12) since well-differentiated lesions rarely spread to the nodes. Although such a statement seems reasonable, in the absence of detailed microscopic examination of the inguinal nodes there are insufficient data to confirm this suggestion. Squamous cell carcinoma of the anal margin spreads in a way similar to skin carcinoma, with direct spread deep to the dermis. Lymphatic spread to the inguinal nodes is said to occur in 40% of cases (24).

Mesenteric lymph nodes are involved in one third to one half of patients with anal canal cancers treated by abdominoperineal resection (10,15,25-28). The risk of mesenteric lymph node spread from anal margin cancers is less defined. Patients treated by abdominoperineal resection, mesenteric lymph node spread was identical to that in patients with anal canal cancers (10,26), however, other two series, the risk was almost zero (25,29). Because the cure rate from local excision alone with anal margin cancers less than 5 cm in diameter is 90%, it appears that spread to mesenteric lymph nodes is infrequent, except in cases of massive disease (30). In a series of 45 patients with anal cancer (primarily of the anal canal) treated at Memorial Sloan-Kettering Cancer Center with a surgical procedure that included excision of the obturator and hypogastric nodes, pelvic node metastases were found in one third (27). However, case selection for such extensive surgery and pathology may result in overestimation of the risk of pelvic node spread.

The inguinal and external iliac nodes are the regional lymphatics considered in the T N M staging system. Patients may present with synchronous or metachronous inguinal lymph node metastases. Inguinal node metastases are extremely rare for T1 tumors or if the surface area of the primary tumors less than 4 cm (2,10,31). The overall risk of inguinal node metastases approximately 30% (10,12,27). Hematogenous metastases occur in few patients. Because of the dual venous drainage of the area, metastases occur equally to the liver and lung (32).

DIAGNOSIS

Because the initial symptoms of anal cancer are similar to those of common benign anorectal conditions, the patient often delays seeking the diagnosis. Because anal cancer is rare and examination may be painful and difficult if spasm occurs, physician related delays also occurs. Almost one third of the patients even at the Cancer centers with squamous cell cancer of the anorectum were thought to have had benign disease until biopsies proved otherwise (27). More than half of the patients in the Mayo Clinic study had associated benign anal abnormalities, such as fistula in ano, fissure or hemorrhoids (33).

Bleeding, pain, and a sensation of a mass are the most common symptoms. Pruritus is less frequent, except in patients with perianal cancer (33). Physical examination should include digital anorectal examination, anoscopy and proctoscopy, and palpation of the inguinal lymph nodes. Associated Bowen's or Paget's disease of the perianal skin increase the likelihood of anal carcinoma. The differential diagnosis for bleeding, pain, or a mass sensation includes

thrombosed hemorrhoid, fissure, fistula, perianal or crypt abscess, benign anal papiloma, and adenocarcinoma of the rectum. Patients with severe pain and spasm may be treated empirically with analgesics, stool softeners, warm baths, and topical ointments for 1 to 2 weeks. Persistent symptoms may require examination under sedation or general anesthesia to avoid missing the diagnosis of cancer or an inadequately treated infection.

Biopsy is necessary to confirm the diagnosis. Excision should not be attempted, except for superficial lesions detected very early. Suspicious inguinal lymph nodes should be biopsied to differentiate inflammatory from metastatic lymphadenopathy. Formal groin dissection should be avoided. Needle aspiration of the groin nodes for cytology may be attempted first. It the results are negative, surgical biopsy should follow.

In addition to physical examination and surgical staging of a suspicious inguinal node site, staging includes chest radiography and ultrasonography tests. Computed tomography (CT) and intraanal sonography have been suggested as useful tools in evaluating primary anal tumors (34,35). Marker studies have not been clinically useful, but a squamous cell carcinoma antigen can be monitored in serum and can reflect tumor status in some patients (36).

STAGING

Staging of anal carcinoma is difficult. Duke's stages cannot be applied as the tumor spreads to inguinal and iliac nodes which are not routinely removed at operation. The T N M system has been applied, but it can be criticized since it is difficult to distinguish tumors limited to the internal sphincter (T1) from those that involve the external sphincter (T2), and because extension into the rectum or perianal skin (T3) does not necessarily indicate a poor outcome (37). Numerous modifications of the T N M system have been tried (19,20,37-39) but none has proved acceptable. There have been few attempts to stage margin tumors. Staging system is recommended by the International Union Against Cancer. Definition of anatomical regions is made where anal canal is divided into 3 parts and into 3 parts of circumference, describing primary tumor (T) of anal canal:

Tis pre-invasive carcinoma (carcinoma in situ).
TO No evidence of primary tumor.
T1 Tumor occupying not more than one third of the circumference or length of the anal canal and not infiltrating the external sphincter muscle.
T2 Tumor occupying more than one third of the circumference or length of the anal canal or tumor infiltrating the external sphincter muscle.
T3 Tumor with extension to rectum or skin but not to other neighboring structures.
T4 Tumor with extension to other neighboring structures.
TX The minimum requirements to assess the primary tumor cannot be met.

Primary tumor (T) of the anal margin are described as follows:
Tis pre-invasive carcinoma (carcinoma in situ).
TO No evidence of primary tumor.
T1 Tumor 2 cm or less in its greatest dimension strictly superficial or exophytic.
T2 Tumor more than 2 cm but not more than 5 cm in its greatest dimension or tumor with minimal infiltration of the dermis.
T3 Tumor more than 5 cm in its greatest dimension or with deep infiltration of the dermis.
T4 Tumor with extension to muscle and bone, etc.
TX The minimum requirements to assess the primary tumor cannot be met.

Regional lymph nodes of anal canal are the perirectal nodes and nodes distal to the origin of the inferior mesenteric artery, where
NO No evidence of regional lymph node involvement.
N1 Evidence of involvement of regional lymph nodes.
NX The minimum requirements to assess the regional lymph nodes cannot be met.

Regional lymph nodes of anal margin are inguinal lymph nodes and are classified as follows:
NO No evidence of lymph node involvement.
N1 Evidence of involvement of movable unilateral regional lymph nodes.
N2 Evidence of involvement of movable regional lymph nodes.
N3 Evidence of involvement of fixed regional lymph nodes.
NX The minimum requirements to assess the regional lymph nodes cannot be met.

TREATMENT

There are some differences in management of the anal margin and anal canal carcinoma in regard of local or extensive surgery, irradiation or chemotherapy modes.

ANAL MARGIN CARCINOMA

Local surgery

Superficial perianal skin carcinomas (i.e., squamous and basal cell) outside the anal verge may be treated with wide local excision with good results. Excision with 1 cm margins, using primary closure, is usually appropriate. A skin graft can be placed if the surgical defect is large. Rarely are formal skin flaps necessary or desirable. A split-thickness skin graft will shrink with time, leaving a relatively small defect that will not interfere with the defection of local recurrence.

Multiple biopsies from the margins are crucial (40,41). For early noninvasive lesions, oral retinoids have been successful (42). Primary abdominoperineal resection is almost never indicated as the initial treatment of anal margin lesions. The cure rate after local excision for superficial squamous cell tumors exceeds 80% (12,16,30,33,43).

Local failure rates are higher if the anal margin cancers includes tumors in the anal canal distal to (not involving) the dentate line. (30) In Memorial Sloan-Kettering Cancer Center experience, disease recurred locally in 9 of 31 pateints treated with local excision for anal margin cancers. (30) Eight of these tumors were amenable to second local excisions.

Deeply infiltrative anal canal margin carcinomas have been treated with abdominoperineal resection. (10,30) Although most patients were cured, the small number of reported cases of disease defined as anal margin cancers does not allows detailed analysis of end results. Patients with invasive Paget's disease or with an underlying associated anorectal carcinoma usually require abdominoperineal resection with wide excision of the perianal skin.

External Irradiation

Epidermoid carcinoma of the anal margin tends to be early or only moderately advanced at the time of diagnosis, with lymph nodes only rarely involved (0-15%), usually in larger tumors 9 (5 cm in diameter). (39,44-46) Although these early cancers of the anal margin are successfully treated by local excision, radiation therapy should be considered for some patients. Papillon suggested that radiation therapy should be used for patients with anal margin carcinoma that is considered unresectable or patients who have extensive or recurrent lesions, patients who are medically inoperable can have radiation therapy.

Although some early studies of anal margin irradiation used interstitial radium needle implants, the high incidence of radionecrosis and uncontrolled irradiation fields indicated that external-beam radiation therapy was a better modality. (44,84) Although photons are most frequently used for these treatments, electron-beam therapy may also be successfully used for early perianal epidermoid carcinomas. (47) Results of treating perianal lesions, stage for stage, are similar to results for anal canal lesions; more extensive lesions require more aggressive therapy. (45,48) Although some researches recommended abdominoperineal resections for extensive lesions, radiation therapy appears to be an excellent alternative that yields cures with sphincter preservation. (45)

Most patients with anal margin tumors can be treated with excision alone, or with irradiation alone for more advanced or recurrent tumors. Concurrent irradiation and chemotherapy is an interesting but still investigational approach to advanced margin tumors.

ANAL CANAL CARCINOMA

Local disease

None of 10 patients initially treated at the Cleveland Clinic by local excision experienced recurrence of the disease. (49) Included were cancers of the anal margin and anal canal that extended less than one half the circumference; cancers involving the dentate line were excluded. Internal or full thickness sphincter excision with skin-graft coverage resulted in acceptable continence. In a review from the Connecticut Cancer Registry reported by Kuehn and colleagues, 26 patients with anal cancer, including distal and canal cancers, were treated by local excision, and 20 (77%) were cured. (50)

Trie Mayo Clinic experience with anal cancers between the dentate line and the anal verge includes 19 patients treated by local excision. (51) Treatment failed locally in 1 of 12 superficial tumors, which was subsequently cured with abdominoperineal resection. Seven patients with underlying sphincter muscle invasion refused radical surgery and were treated by wide local excision, some with adjuvant irradiation. Disease recurred locally in 3. (51) In a group of 5 patients (4 with Tl disease) treated at the Lahey Clinic by local excision, none had disease recurrence. (52) Of 144 patients treated at Memorial Sloan-Kettering Cancer Center for anal canal cancers (dentate line involvement), only 11 were suitable candidates for local excision. The 5-years survival rate was only 45% and most had local recurrence. (53)

Locoregional Disease

Multimodality therapy. Because integrated multimodality therapy improves overall survival and allows radical surgery to be avoided for most patients, the scope of initial diagnostic surgery should be limited to maximize the final functional result.

For anal margin cancers distal to the anal verge, a punch or surgical incisional biopsy performed in the office can suffice. For patients with considerable spasm and pain, examination and incisional biopsy under general anesthesia is appropriate. If a decision is made to proceed with local excision only (i.e., small anal margin or Tl anal canal lesion), the bowel is prepared, and elective surgery is performed.

Grossly positive inguinal lymph nodes are studied initially by needle aspiration cytology; open biopsy is performed if the specimen is benign. Minimally suspicious nodes warrant an excisional biopsy of one or two lymph nodes, using great care to avoid a hematoma or lymphatic leak. A superficial groin dissection is not necessary or useful as part of the initial treatment strategy. It delays definitive chemotherapy and radiation treatment, and it may increase the risk of leg edema after combined treatment.

Chemotherapy and radiation. In the past 20 years, increasing evidence from single-arm studies indicates that initial chemotherapy plus radiation therapy yields a very high rate of tumor regression, including a high rate of complete remission, and that surgery may not be required for many patients, or it may be limited to an excisional biopsy of residual scar. Even patients with relatively large anal epidermoid tumors may be spared a colostomy and have an excellent survival expectation.

Table 1 summarizes the results of therapy from several large series. (6,54-63) There are also results from prospective controlled randomized trials comparing multimodality therapy with irradiation alone or surgery alone. One retrospective study suggested a higher cure rate with multimodality therapy in patients with higher-stage disease. (64) Because conducted trials have been so impressive, with only modest morbidity, chemotherapy plus irradiation has been accepted as conventional treatment for most patients with anal canal disease. Some investigators still favor irradiation alone, but few support abdominoperneal resection as first line therapy.

The series in Table 1 followed a chemotherapy protocol similar to that pioneered by Nigro and coworkers. 5-FU was given by continuous 24-hours infusion for 4 to 5 days with a single bolus dose of mitomycin-C. (65) Combined therapy has been given concurrently or sequentially. In the concurrent regimen, radiation therapy and chemotherapy are initiated on the same day. In the sequential regimen, chemotherapy is given before radiation therapy. In addition to differences in timing of administration, the dose of radiation therapy has also varied (see Table 1). In some centers chemotherapy plus radiation therapy has been given before a planned surgical procedure - initially abdominoperineal resection and later local excision. Others planed radiation therapy to higher total doses as definitive treatment, but surgery was not part of the treatment plan. Despite these differences between trials, there is little evidence from these studies that one schedule or dose level is markedly superior to another. Response and survival rates are similar, although fewer patients require an abdominoperineal resection after concurrent chemotherapy and radiation therapy to higher doses.

Long-term follow-up results are becoming available. These reports give a reasonable picture of the number of patients eventually requiring abdominoperineal resection and of the number of patients in whom anal continence remained for a long period after nonoperative treatment with radiation therapy and chemotherapy. For example, Tanum and colleagues reviewed the experience in 106 Norwegian patients who received radiation plus concurrent mitomycin and 5-FU. (61) The radiation dose was 50 Gy given in 2-Gy fractions to most patients by anteroposterior and posteroanterior (AP/PA) parallel opposed fields. The complete response rate to chemotherapy was 84%; 16% of patients (i.e., positive biopsy) underwent abdominoperineal resection. Of 89 patients who were followed for a minimum of 3 months after treatment, 14 (16%) had significant morbidity within 2 years of treatment, which eventually required surgery or seriously impaired normal social life. Similar data with 87% 5 years survival rate is reported by D.Beck. (7) When chemotherapy and irradiation are combined, AP/PA pelvic fields should probably not be treated to a dose higher than 40 Gy. Most investigators coned down to the primary site after 30 Gy. Miller and colleagues reported the results of 42 patients who received mitomycin and 5-FU followed by irradiation beginning 1 week after chemotherapy. (56) Twenty-three patients were initially treated with wide local excision. Two underwent abdominoperineal resection soon after local excision because of persistent cancer. Of 21 remaining patients, 3 patients later had abdominoperineal resections. Eighteen patients retained anal continence.

Some investigators found that any patient with a positive biopsy after initial treatment was certain to have recurrence of disease, (66) however, others has had long-term disease-free survival despite residual disease after induction therapy. (56,67,68) Of 44 patients in the original series, 18 (41%) had positive pathologic results after chemotherapy followed by irradiation. (67) At least half of these patients had no recurrent tumor detected at their most recent examinations.

Nigro made the point that combined therapy using chemotherapy plus irradiation can safely be given in a community setting 69 and it was supported by others studies. (59,60,70,71)

The best chemoradiation therapy regimen and the most appropriate radiation dose to use for patients with anal canal tumors limited to the primary site have not yet been defined. Distant failure is not the major problem. Local recurrence is more common, especially if the radiation dose is low (30Gy). 5-FU is probably a radiosensitizer, although there is some disagreement, but mitomycin is probably not synergistic. (72-74) Byfield and coworkers treated 11 patients with a 120 -hours infusion of 5-FU (25mg/kg/day) and concurrent irradiation, omitting mitomycin. (75) Radiation therapy was given in 4-day cycles (10Gy/cycle), separated by at least 9 days, to a total dose of 30 Gy to 47.5 Gy. All patients had complete clinical regressions; only 1 patient had active disease histologically. There was only a single local recurrence.

Table 1. Results of Multímodality Therapy for Anal Canal Carcinoma

Investigations	Chemotherapy Regimen	Radiation Therapy Regimen	Patients Evaluable	Abdominoperineal Resection Performed	Treatment Related Deaths	5-Years Survival (%)
Wayne State (55)	5-Fu: 1000 mg/m^2/4 days 2 cycles* Mito: 15 mg/m^2 d 1	30 Gy/15 fx	104	31	0	80
Memorial Sloan-Kettering (56)	5-Fu: 750 mg/m^2/5 days* Mito: 15 mg/m^2 d 1	30 Gy/15 fx	42	23	0	82
RTOG (57)	5-FU: 1000 mg/m^2/4 days 2 cycles* Mito: 10 mg/m^2 d 2	40.8 Gy/24fx	79	8	0	73 (3y)
Highland Hospital (58)	5-FU: 1000 mg/m^2/4 days 2 cycles* Mito: 10 mg/m^2 d 2	50-57.5 Gy/ 25-32 fx	33	4	0	
Fresno Community Hospital (59,60)	5-FU: 1000 mg/m^2/4 days 2 cycles* Mito: 10-15 mg/m^2 x2	41-50 Gy/ 23-28 fx	30	1	0	90
Norwegain Radium Hospital (61)	5-FU: 1000 mg/m^2/4 days* Mito: 10-15 mg/m^2	50 Gy/25 fx	94	17	3 (3%)	72
Istituto Nazionale Tumori, Milano (62)	5-FU: 750 mg/m^2/5 days 2–3 cycles* Mito: 15 mg/m^2	54 Gy/30fx (split)	38	6	0	
Princess Margaret (63,64)	5-FU: 1000 mg/m^2/4 days* Mito: 10 mg/m^2 d 1	48–50 Gy/ 24-20 fx (split or continuous)	69	10	0	65
	5-FU: 1000 mg/m^2/4 days*	48-50 Gy/ 24-20 fx (split)	66	18	1 (2%)	64
M. D. Anderson (65)	5-FU: 300 mg/m^2/days for 32 days (median)*	45 Gy/25 fx	25	8	1 (4%)	
Ochsner Clinic (7)	5-FU: 1000 mg/m^2/5 days and days 31-35 Mito: 10 mg/m^2 d1	40 Gy/20 fx	35	9	0	87

5-FU, 5-fluorouracil; Mito, mitomycin C; fx, fractions.
*Continuous 24-hour infusion.

Poorer local control was reported by the M. D. Anderson Cancer Center group when low-dose 5-FU (300mg/m^2/day) was used throughout the irradiation course (45-66 Gy). (54) Local control without an abdominoperineal resection was 67% in 24 patients, but 9 of 10 patients who received at least 55 Gy were controlled. Toxicity was considerable, with 6 of 25 patients experiencing grade 4 diarhhea, resulting in the death of 1 patient.
Radiation Therapy Oncology Group study is currently underway comparing irradiation (45Gy) and concurrent 5-FU to irradiation plus concurrent mitomycin and 5-FU. This trial, which is nearing its projected accrual, addresses the role of mitomycin. Patients with positive biopsies after initial treatment are eligible for cisplatin-based chemotherapy treatment, which addresses the issue of additional chemotherapy in poor-risk patients. Because the definitive results of this trial are not yet available, it is too early to conclude that mitomycin is not a necessary part of therapy, especially because the complications related to the use of this agent are quite small.
The chemotherapy regimen of mitomycin and 5-FU is quite active against anal canal tumors, but some patients do not respond or have less than a complete remission with this combination. The effectiveness of cisplatin-based treatment for patients with advanced disease has made use of this agent as part of multimodality therapy attractive. A few trials investigated the use of cisplatin with 5-FU anf irradiation for initial therapy with promising results, especially for high-risk patients. (75-79)

Radical surgery. Before the widespread use of multímodality therapy, more than 90% of patients with potentially curable anal canal cancers required abdominoperineal resection. A wide perineal dissection in association with a posterior vaginectomy in women was recommended. (28,80) Despite initial enthusiasm of the oncology group at Memorial Sloan-Kettering Cancer Center for vaginectomy, á more recent analysis discounted its routine application. (14) Lateral pelvic lymphadenopathy was initially advocated by the same group on the basis of a 24% incidence of pathologically positive nodes. (27) Subsequent analysis could not define any therapeutic benefit for this extended abdominoperieal resection. (14) The overall cure rate with abdominoperineal resection is approximately 50%. (81) Some reports show that wide resections of the canal carcinomas with continence preserving could be feasible and curative. (82)
The Mayo Clinic experience initially reported in 1976 by Beahrs and Wilson (33) was updated by Boman and associates. (51) Disease recurred in 40% of the 114 patients, with subsequent treatment resulting in a 71 % 5-years survival rate. The M. D. Anderson Hospital group reported a 62% 5-year survival rate for 109 patients treated with only abdominoperineal resection. (39) One sixth of the cases were anal margin cancers. A Memorial Sloan-Kettering Cancer Center update included 103 patients treated by radical surgery, with a 55% 5-year survival rate. (53) A11 of these tumors involved the dentate line. The 5-year survival rate for patients with tumors larger than 5 cm was only 40%. At St. Mark's Hospital, the 5-year survival rate among 83 patients with anal cancers involving the dentate line treated by radical surgery was 48%. (12)
Treatment failure despite radical surgery is locoregional and distant. In the Mayo Clinic experience, 84% of initial sites of failure included local and regional disease. (51) Most cancer-related deaths are secondary to uncontrolled locoregional tumor. One third to one half of patients with locally advanced anal cancers treated by abdominoperineal resection at the major centers known for their expertise in this disease still had local recurrence in the pelvis or perineum. (12,28,39,51,53)
With the success of combined modality therapy, abdominoperineal resection should be reserved for salvage of the few patients in whom multímodality treatment fails or for morbidity related to therapy, such as severe proctitis.

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Locally Advanced, Residual, or Recurrent Cancer

Anal Margin Cancer

Recurrent anal margin cancer, after local excision, may require further local excision for salvage. In a study from Memorial Sloan-Kettering Cancer Center, 16 patients in whom disease recurred underwent additional surgical procedures; of these, 12 were alive at 5 years, and only 2 had died of disease. (83) One patient was unavailable for follow-up. Eleven of the 12 patients with local failure underwent local excision only for salvage. More advanced primary or recurrent anal margin lesions may be salvaged by external radiation therapy. (84)

Residual Anal Canal Cancer

Whether anal canal patients are treated by radiation therapy alone or chemoradiation therapy, histologic confirmation of complete remission should be obtained several weeks after irradiation is completed.56 Patients with clinically complete remissions but microscopically residual superficial tumors should undergo sphincter-sparing wide local excisions. The deep margin may be increased by including a portion of the internal sphincter, with minimal impact on subsequent continence. If the margins are positive, an additional radiation boost may be used, if feasible, with external beam or an interstitial implant. If a radiation boost is not possible because maximal radiation has already been delivered, an abdominoperineal resection is probably required for cure, what yields up to 72% 3 year survival rate. (85)

Recurrent Anal Canal Cancer

Patients with recurrent anal canal cancer after surgery should be considered for multimodality therapy. Locoregional failures after initial multimodality therapy have been successfully treated with abdominoperineal resection (2,85) or with additional irradiation and chemotherapy. (59) The success rate of surgical salvage averaged about 60% for seven series (54,57,63,86-89) ,but only 29% in some others (85). Mitomycin plus 5-FXJ can also induce major remissions in previously treated patients who have locally recurrent disease. (90)

Locally Advanced Anal Canal Cancer

Multimodality therapy for locally advanced primary anal canal tumors may yield good palliation and, in some cases, cure. In a study reported from the University of Virginia, major regressions of disease were observed in 6 of 7 patients, 3 of whom were treated with chemotherapy alone and 3 with chemotherapy plus irradiation. (91) Abdominoperineal resections were performed on all patients, and all had delayed wound healing. Three of the 7 patients remained disease free for 24 to 26 months and 4 died, 2 of cancer and 2 of other causes. Another form of multimodality therapy mitomycin and 5-FU with external and interstitial irradiation. (92) Ir implant, was tried in 29 patients with advanced local disease. (93) After a follow-up of 5 to 54 months, 25 of 29 patients were alive and free of disease; only 2 patients required radical salvage surgery with loss of sphincter function. Papillon achieved a 90% local control rate in T3 tumors larger than 4 cm in diameter with a combination of mitomycin, 5-FU, external irradiation, and an 54 Ir implant. (94)

Brachytherapy combined with external irradiation has been used for advanced disease. (94-96) There was a 70% local control rate in Papillon's analysis of T3 tumors larger than 4 cm in diameter, which were treated with (97) Co external irradiation and an (92) Ir implant without combined chemotherapy.

Inguinal Node Involvement

The initial experience suggested that patients with grossly positive inguinal lymph nodes synchronous with the primary tumor were incurable. (98) A subsequent report indicated that 2 of 13 patients survived 5 years after abdominoperineal resection, followed 6 weeks later by inguinal lymphadenectomy. (99) Other studies confirmed a small cure rate for surgical treatment of patients with synchronous unilateral inguinal nodes. (10,33) External irradiation (84) postoperatively may improve these results slightly, but radical external irradiation alone (84,86,88,100) can achieve a nodal control rate of about 65%, and external irradiation combined with chemotherapy (58,101,102) can achieve nodal control in approximately 90% of patients. Current recommendations are for limited surgical sampling, combined chemotherapy and radiation therapy with boost doses to the involved groin (45-50Gy); surgical salvage may be done for isolated inguinal recurrence.

The development of unilateral metachronous inguinal lymph nodes usually does not carry such an ominous prognosis. After therapeutic groin dissection, the 5 to 7 years survival rate reported from Memorial Sloan-Kettering Cancer Center and St. Mark's Hospital exceeded 50%, (29,83) but it was zero in a small series reported from the other hospitals. (33) Current strategies in patients with metachronous isolated inguinal node metastases after multimodality therapy include a formal groin dissection followed by chemotherapy. The use of radiation under these circumstances depends on prior dose and fields.

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