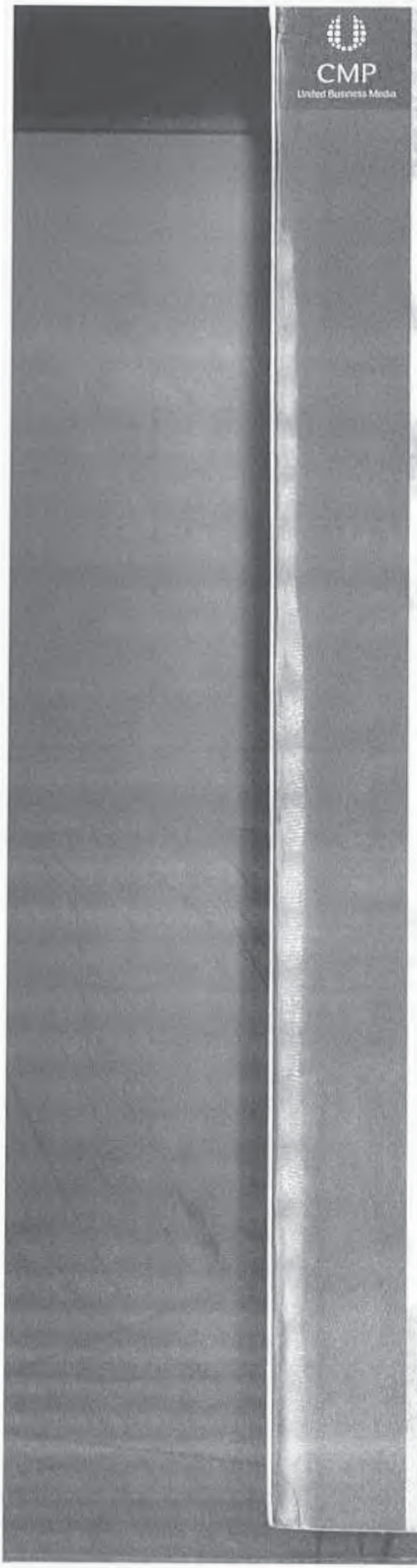

NINTH EDITION, 2005 – 2006

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Medical, Surgical, & Radiation Oncology

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CHAPTER 11

Stages III and IV breast cancer

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This chapter addresses the diagnosis and management of locally advanced, locally recurrent, and metastatic breast cancer, ie, stages III and IV disease.

Approximately 20%-25% of patients present with locally advanced breast cancer. Inflammatory breast cancer is a particularly aggressive form of breast cancer that falls under the heading of locally advanced disease and accounts for 1%-3% of all breast cancers.

Locoregional recurrence of breast cancer remains a major clinical oncologic problem. Rates of locoregional recurrence may vary from < 10% to > 50%, depending on initial disease stage and treatment.

Metastatic disease is found at presentation in 5%-10% of patients with breast cancer. The most common sites of distant metastasis are the lungs, liver, and bone.

The optimal therapy for stage III breast cancer continues to evolve. Recently, the use of neoadjuvant chemotherapy has been effective in downstaging locally advanced breast cancer prior to surgical intervention. The optimal neoadjuvant chemotherapeutic regimens continue to evolve, and studies are being performed to evaluate new agents and delivery methods.

Diagnosis

Locally advanced disease

Patients with locally advanced breast cancer do not have distant metastatic disease and are in this group based on tumor size and/or nodal status. Such patients often present with a large breast mass or axillary nodal disease, which is easily palpable on physical examination. In some instances, the breast is diffusely infiltrated with disease, and no dominant mass is evident.

Patients with inflammatory breast cancer often present with erythema and edema of the skin of the breast (peau d'orange) and may not have a discrete mass within the breast. These patients often are treated with antibiotics unsuccessfully for presumed mastitis.

Mammography is beneficial in determining the local extent of disease in the ipsilateral breast, as well as in studying the contralateral breast.

Fine-needle aspiration (FNA) or biopsy The diagnosis of breast cancer can be confirmed by either FNA cytology or core biopsy. Core biopsy is preferred to perform the wide variety of marker analyses.

Search for metastasis The presence of distant metastatic disease should be ruled out by physical examination, chest radiography, CT of the liver, bone scan, and CT of the chest. ^{18}Fluorodeoxyglucose-positron emission tomography (FDG-PET) has moderate accuracy for detecting axillary metastasis. It is highly predictive for nodal tumor involvement when multiple intense foci of tracer uptake are identified but fails to detect small nodal metastasis. The addition of FDG-PET to the standard workup of patients with locally advanced breast cancer may lead to the detection of unexpected distant metastases. Abnormal PET findings should be confirmed to prevent patients from being denied appropriate treatment.

Locoregional recurrence

Biopsy or FNA Locoregional recurrence of breast cancer can be diagnosed by surgical biopsy or FNA cytology. Whichever modality is appropriate, material should be sent for hormone-receptor studies, since there is only an 80% concordance in hormone-receptor status between the primary tumor and recurrent disease. When the suspected recurrent disease is not extensive, the biopsy procedure of choice is a negative margin excisional biopsy. For an extensive recurrence, an incisional biopsy can be used.

Search for distant metastasis Prior to beginning a treatment regimen for a patient with locoregional recurrence, an evaluation for distant metastasis should be instituted, since the findings may alter the treatment plan.

Distant metastasis from the breasts

Metastatic breast cancer may be manifested by bone pain, shortness of breath secondary to a pleural effusion, parenchymal or pulmonary nodules, or neurologic deficits secondary to spinal cord compression or brain metastases. In some instances, metastatic disease is identified after abnormalities are found on routine laboratory or radiologic studies.

Assessment of disease extent by radiography, CT, and radionuclide scanning is important. Organ functional impairment may be determined by blood tests (liver/renal/hematologic) or may require cardiac and pulmonary function testing. Biopsy may be required to confirm the diagnosis of metastasis; this is especially important when only a single distant lesion is identified.

Metastasis to the breasts

The most common source of metastatic disease to the breasts is a contralateral breast primary. Metastasis from a nonbreast primary is rare, representing < 1.5% of all breast malignancies. Some malignancies that could metastasize to the breast include non-Hodgkin's lymphoma, leukemias, melanoma, lung cancer (particularly small-cell lung cancer), gynecologic cancers, soft-tissue sarcomas, and GI adenocarcinomas. Metastasis to the breasts from a nonbreast pri-

mary is more common in younger women. The average age at diagnosis ranges from the late 30s to 40s. Treatment depends on the status and location of the primary site.

Mammographic findings Mammography in patients with metastatic disease to the breasts most commonly reveals a single lesion or multiple masses with distinct or semidiscrete borders. Less common mammographic findings include skin thickening or axillary adenopathy.

FNA or biopsy FNA cytology has been extremely useful in establishing the diagnosis when the metastatic disease has cytologic features that are not consistent with a breast primary. When cytology is not helpful, core biopsy or even open biopsy may be necessary to distinguish primary breast cancer from metastatic disease.

Treatment

TREATMENT OF LOCALLY ADVANCED DISEASE

The optimal treatment for patients with locally advanced breast cancer has yet to be defined, due to the heterogeneity of this group. There are approximately 40 different substage possibilities with the different combinations of tumor size and nodal status. Between 66% and 90% of patients with stage III breast cancer will have positive lymph nodes at the time of dissection, and approximately 50% of patients will have four or more positive nodes.

Patients with locally advanced breast cancer have disease-free survival rates ranging from 0% to 60%, depending on the tumor characteristics and nodal status. In general, the most frequent type of treatment failure is due to distant metastases, and the majority of them appear within 2 years of diagnosis.

With the increased utilization of multimodality therapy, including chemotherapy, radiation therapy, and surgery, survival for this patient population has improved significantly.

Neoadjuvant systemic therapy

Neoadjuvant therapy with cytotoxic drugs permits in vivo chemosensitivity testing, can downstage locally advanced disease and render it operable, and may allow breast-conservation surgery to be performed. Preoperative chemotherapy requires a coordinated multidisciplinary approach to plan for surgical and radiation therapy. A multimodality treatment approach can provide improved control of locoregional and systemic disease. When neoadjuvant therapy is used, accurate pathologic staging is not possible.

Active regimens Preoperative chemotherapy regimens reported to result in high response rates (partial and complete responses) include CAF (cyclophosphamide [Cytoxan, Neosar], doxorubicin [Adriamycin], and fluorouracil [5-FU]), FAC (5-FU, Adriamycin, and cyclophosphamide), CMF (cyclophosphamide, methotrexate, and 5-FU), and CMFVP (cyclophosphamide, methotrexate, 5-FU, vincristine, and prednisone). Combination chemotherapy with

TABLE 1: Doses and schedules of chemotherapy agents commonly used in patients with metastatic breast cancer

Drug/combination	Dose and schedule
FAC	
5-FU	500 mg/m^2 IV on days 1 and 8
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat cycle every 3-4 weeks.	
TAC	
Taxotere	75 mg/m^2 IV on day 1
Adriamycin	50 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat cycle every 21 days.	
FEC	
5-FU	500 mg/m^2 IV on day 1
Epirubicin	100 mg/m^2 IV on day 1
Cyclophosphamide	500 mg/m^2 IV on day 1
Repeat cycle every 21 days.	
Note: An absolute granulocyte count < 1,500/mm^3 and/or platelet count <100,000/mm^3 on day 21 will cause a treatment delay of at least 1 week. Treatment wil be terminated if hematology recovery takes more than 3 weeks.	
Paclitaxel	175 mg/m^2 by 3-h IV infusion every 3 weeks or 80-100 mg/m^2/week
Docetaxel	60-100 mg/m^2 by 1-h IV infusion every 3 weeks or 40 mg/m^2/week
Repeat if hematologic recovery has occurred (ie, absolute granulocyte count ≥ 1,500/μL and platelet count ≥ 100,000/μL).	
Capecitabine	2,000 to 2,500 mg/m^2 PO bid (divided dose, AM and PM) for 14 days, followed by 1-week rest
Repeat cycle every 21 days.	
Capecitabine + docetaxel	
Capecitabine	1,000 to 1,250 mg/m^2 orally twice daily on days 1 to 14, followed by 1-week rest
Docetaxel	75 to 100 mg/m^2 IV infusion over 1 hour
Repeat cycle every 3 weeks.	
Vinorelbine + trastuzumab	
Vinorelbine	25 mg/m^2 IV on day 1 every week
Trastuzumab	4 mg/kg IV loading dose, then 2 mg/kg IV every week

an anthracycline-based regimen—FAC or AC—is used most often. Recently published data suggest that the AT regimen of Adriamycin and docetaxel (Taxotere) given concomitantly may produce equivalently high response rates. Combination agents for metastastic breast cancer also include paclitaxel plus trastuzumab (Herceptin) with carboplatin (Paraplatin), gemcitabine (Gemzar)

Drug/combination	Dose and schedule
Docetaxel or paclitaxel + carboplatin + trastuzumab (every-3-week dosing)	
Docetaxel	75 mg/m^2 IV on day 1 every 21 days
	OR
Paclitaxel	175 mg/m^2 IV on day 1 every 21 days
	PLUS
Carboplatin	AUC of 5 to 6 on day 1 every 21 days
	PLUS
Trastuzumab	4 mg/kg IV loading dose on day 1, followed by 2 mg/kg weekly
Note: Patients must be premedicated with dexamethasone prior to docetaxel.	
Trastuzumab	4 mg/kg IV loading dose, then 2 mg/kg weekly
	8 mg/kg IV loading dose, then 6 mg/kg every 3 weeks
Paclitaxel or docetaxel + carboplatin + trastuzumab (weekly dosing)	
Paclitaxel	80 mg/m^2 IV on day 1 every week
	OR
Docetaxel	35 mg/m^2 IV on day 1 every week
	PLUS
Carboplatin	AUC 2 IV on day 1 every week
	PLUS
Trastuzumab	4 mg/kg IV loading dose, then 2 mg/kg every week
Gemcitabine + paclitaxel	
Gemcitabine	1,250 mg/m^2 IV on days 1 and 8 (as a 30-minute infusion) every 21 days
Paclitaxel	175 mg/m^2 IV on day 1 (over 3 hours) every 21 days
Note: Standard paclitaxel premedications should be given.	
Pegylated doxorubicin	
Doxil	30 to 50 mg/m^2 IV on day 1 every 21 to 28 days

and paclitaxel, and capecitabine (Xeloda) and docetaxel (Table 1). Although not yet definitive, recent data indicate that enhancing dose density may increase the pathologic complete response rate for women with locally advanced disease. The doses of these combination chemotherapy regimens are given in Table 1, chapter 10.

There seems to be no difference in survival in women with locally advanced disease who receive chemotherapy before or after surgery. Neoadjuvant chemotherapy results in complete response rates ranging from 20%-53% and partial response rates (≥ 50% reduction in bidimensionally measurable disease) ranging from 37%-50%, with total response rates ranging from 80%-90%. Patients with large lesions are more likely to have partial responses. Pathologic complete responses (pCRs) do occur and are more likely to be seen in patients with smaller tumors. A pCR in the primary tumor is often predictive of a com-

plete axillary lymph node response. Patients with locally advanced breast cancer who have a pCR in the breast and axillary nodes have a significantly improved disease-free survival rate compared with those who have less than a pCR. However, a pCR does not entirely eliminate the risk for recurrence.

Patients should be followed carefully while receiving neoadjuvant systemic therapy to determine treatment response. In addition to clinical examination, it may also be helpful to document photographically the response of ulcerated, erythematous, indurated skin lesions. Physical examination, mammography, and breast ultrasonography are best for assessing primary tumor response, whereas physical examination and ultrasonography are used to evaluate regional nodal involvement.

The role of MRI in evaluating response to preoperative chemotherapy is still evolving. Dynamic contrast-enhanced MRI performed at baseline, during chemotherapy, and before surgery has yielded more than 90% diagnostic accuracy in identifying tumors achieving a pCR and can potentially provide functional parameters that may help to optimize neoadjuvant chemotherapy strategies. However, despite its high sensitivity, a large number of patients still may have either false-negative or false-positive results on MRI scanning.

Multimodality approach

A multimodality treatment plan for locally advanced breast cancer (stage IIIA and IIIB, M1 supraclavicular nodes) is shown schematically in Figure 1. This approach has been shown to result in a 5-year survival rate of 84% in patients with stage IIIA disease and a 44% rate in those with stage IIIB disease. The most striking benefit has been seen in patients with inflammatory breast cancer, with 5-year survival rates of 35%-50% reported for a multimodality treatment approach including primary chemotherapy followed by surgery and radiation therapy and additional adjuvant systemic therapy. The same chemotherapy drugs, doses, and schedules used for single-modality therapy are employed in the multimodality approach.

Surgery Traditionally, the surgical procedure of choice for patients with locally advanced breast cancer has been mastectomy. In recently published studies, some patients with locally advanced breast cancer who responded to treatment with neoadjuvant chemotherapy became candidates for breast-conservation therapy and were treated with limited breast surgery and adjuvant breast irradiation. Patients who have been downstaged using neoadjuvant chemotherapy should be evaluated carefully before proceeding with conservative treatment. It may be helpful to mark the site of the primary tumor with the placement of a clip during the course of percutaneous biopsy prior to beginning adjuvant therapy. There can sometimes be a complete clinical and/or radiographic response after neoadjuvant chemotherapy or hormonal therapy, and this may facilitate a wide local incision.

The role of sentinel node biopsy in the treatment of breast cancer after neoadjuvant chemotherapy has yet to be defined. Studies have shown that pathologically positive axillary lymph nodes can be sterilized when neoadjuvant che-

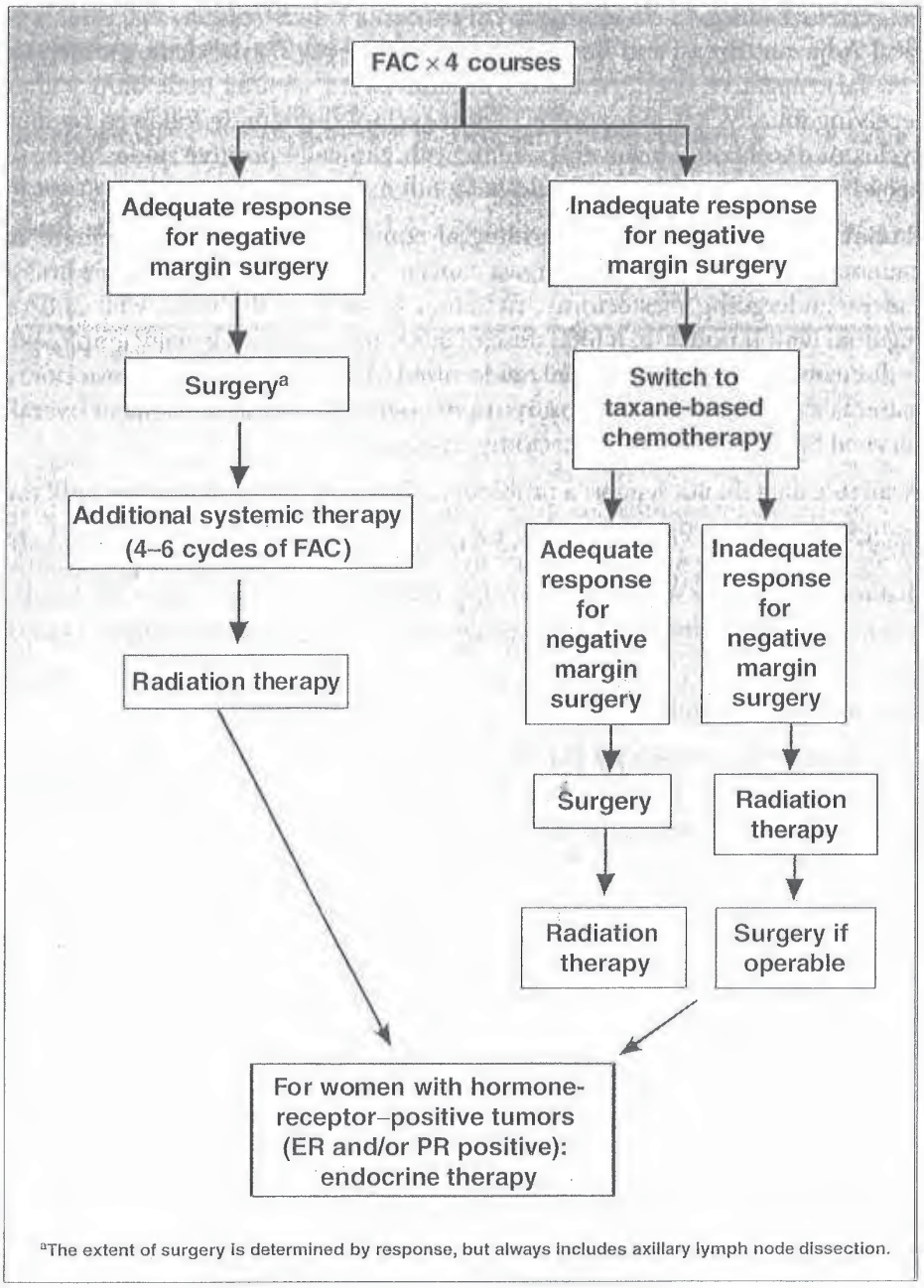

FIGURE 1: Multimodality approach to locally advanced breast cancer

motherapy is utilized. There are other biologic concerns with sentinel node biopsy after neoadjuvant chemotherapy. The lymphatics may undergo fibrosis or may become obstructed by cellular debris, making the mapping procedure unreliable, with false-negative rates of up to 25%. The rate of conversion from positive to negative nodes can be enhanced when four cycles of a doxorubicin-based regimen are followed by four cycles of docetaxel. Sentinel node biopsy will only be accurate then if all the metastatic deposits within the axilla respond

in a similar fashion to chemotherapy. Preliminary data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-27 trial demonstrated an 11% false-negative rate in women who underwent sentinel node biopsy after receiving four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel. However, patients with clinically positive nodes prior to neoadjuvant chemotherapy should have full node dissection.

Radiation therapy remains an integral component of the management of patients with locally advanced breast cancer. For patients with operable breast cancer undergoing mastectomy, radiation therapy to the chest wall and/or regional lymph nodes (to a total dose of 5,000-6,000 cGy) is usually employed, as discussed in chapter 10. Recent randomized trials suggest that postmastectomy patients with any number of positive nodes derive a disease-free and/or overall survival benefit from postmastectomy irradiation.

Available data do not suggest a problem in delaying radiation therapy until the completion of systemic chemotherapy. Even in patients undergoing high-dose chemotherapy with autologous bone marrow or stem-cell transplantation, irradiation is generally indicated following mastectomy for patients with locally advanced disease (primary tumors ≥ 5 cm and/or $\geq$ four positive axillary nodes).

For patients whose disease is considered to be inoperable, radiation therapy may be integrated into the management plan prior to surgery.

High-dose chemotherapy Patients with locally advanced breast cancer and those with multiple positive nodes may be candidates for protocol treatment with high-dose chemotherapy plus autologous stem-cell support. Preliminary results from three prospective, randomized trials of high-dose chemotherapy with autologous stem-cell support in women with high-risk primary breast cancer were recently presented. All three trials are summarized in Table 2, and two of the trials are discussed in more detail below.

In the largest trial yet reported, investigators from all of the bone marrow transplant centers in the Netherlands randomly assigned 885 women with stages II and III breast cancer with four or more tumor-positive nodes to a standard therapy arm of five courses of FEC (5-FU, epirubicin [Ellence], and cyclophosphamide) followed by radiation therapy and tamoxifen or an investigational treatment arm of four cycles of FEC followed by high-dose chemotherapy with cyclophosphamide, thiotepa, and carboplatin with peripheral blood stem-cell support followed by radiation therapy and tamoxifen. After a median follow-up of 57 months, there was a trend for improved 5-year relapse-free survival rates in the high-dose group, but it was not statistically significant (hazard ratio [HR] = 0.83; $P = .09$). In the subgroup of patients with 10 or more positive nodes, however, the relapse-free survival rate reached statistical significance (HR = 0.71; $P = .05$). There was also a suggestion that the benefit seen in the high-dose group may be confined to patients with HER-2/*neu*-negative tumors.

The second-largest trial evaluating high-dose chemotherapy was conducted by the Cancer and Leukemia Group B (CALGB) in patients with stage II or III breast cancer involving 10 or more axillary lymph nodes. This trial examined the value of consolidation high-dose therapy with cyclophosphamide, cisplatin,

TABLE 2: Randomized studies of high-dose chemotherapy in primary breast cancer

Investigators	Number of patients	Follow-up (median)	Survival benefit?	*P* value
Rodenhuis et al	885	36 mo	Yes	$P < .05$
Peters et al	783	36 mo	No	NS
Scandinavian Breast Cancer Study Group	525	20 mo	No	NS

NS = not significant

and carmustine (BiCNU) with autologous stem-cell support following adjuvant therapy with cyclophosphamide, doxorubicin, and 5-FU. Preliminary results of this study, with 783 participants, showed a reduction in relapse frequency of over 30% in patients receiving high-dose chemotherapy; a 3-year survival rate of 68% was observed in patients treated with high-dose chemotherapy, vs a 64% rate in those who received intermediate-dose consolidation therapy with the same drugs. However, follow-up is not yet long enough to define the ultimate benefit of this approach. Moreover, toxicity to date has been significantly higher and the relapse rate significantly lower in the high-dose group.

Nonrandomized studies of high-dose chemotherapy plus autologous stem-cell support have shown a disease-free survival of ~70%, as compared with historic data showing a 30% 5-year disease-free survival rate with conventional-dose chemotherapy.

To date, the results of available clinical trials have not all shown improved disease-free and overall survival in patients treated with dose-intensive regimens. However, trial design, power, and strategy have all been questioned. Outside the context of a clinical trial, high-dose chemotherapy cannot be recommended for patients with primary or metastatic breast cancer.

TREATMENT OF LOCOREGIONAL RECURRENCE AFTER EARLY INVASIVE CANCER OR DCIS

When a patient develops a local failure after breast-conservation treatment for early invasive cancer or ductal carcinoma in situ (DCIS), it is generally in the region of the initial primary tumor. The risk of ipsilateral breast tumor recurrence after conservative treatment in patients with early invasive cancer ranges from 0.5%-2.0% per year, with long-term local failure rates plateauing at about 15%-20%. Local failure rates after wide excision alone for DCIS vary from 10%-63%, as compared with rates between 7% and 21% after wide excision plus radiation therapy. Most patients whose disease recurs after conservative treatment for DCIS can be treated with salvage mastectomy. In one study, 14% of patients who developed local recurrence had synchronous distant metastatic disease.

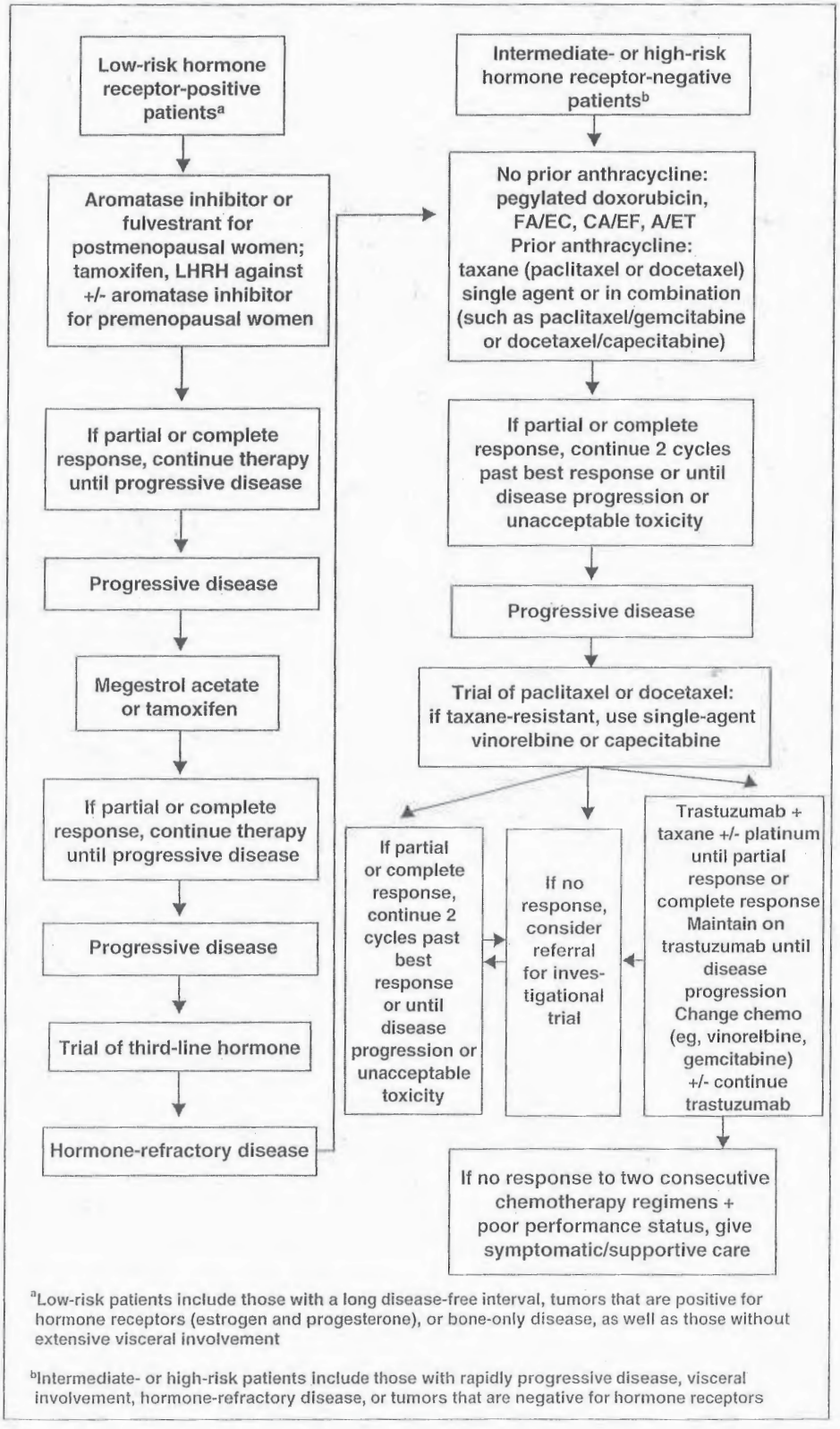

FIGURE 2: Treatment approach to metastatic breast cancer

The optimal treatment of a local or regional recurrence after mastectomy has yet to be defined. Locoregional recurrences are associated with initial nodal status and primary tumor size. Appropriate treatment may result in long-term control of locoregional disease. In many instances, these patients develop simultaneous distant metastasis, or distant disease develops some time after the locoregional recurrence manifests itself.

Recurrence of invasive cancer after breast conservation

Recurrence after wide excision and breast irradiation For patients with early invasive cancer who have undergone conservative surgery followed by irradiation and whose cancer recurs in the ipsilateral breast, salvage mastectomy is the most common treatment modality. The same is true for ipsilateral recurrence (of invasive or in situ disease) after conservative treatment for DCIS, when there is no evidence of distant metastatic disease.

Some studies with limited follow-up have reported acceptable results with repeated wide local excision for ipsilateral breast tumor relapses following conservative surgery and radiation therapy. Selection criteria for this approach are unclear, however, and use of this salvage procedure remains controversial. Although the use of limited-field reirradiation has been reported, selection criteria for this management option and long-term follow-up data are lacking.

Recurrence after wide excision alone In patients initially treated with wide local excision alone who sustain an ipsilateral breast tumor recurrence, small series with limited follow-up suggest that wide local excision followed by radiation therapy to the intact breast at the time of local recurrence may be a reasonable treatment alternative. In this situation, standard radiation doses would be employed.

Recurrent disease in the chest wall after mastectomy

In general, patients who develop minimal recurrent disease in the chest wall after a long disease-free interval may be treated by excision alone, although this approach is controversial and may not be ideal. Locoregional control obtained by radiation therapy alone is related to the volume of residual disease and may not be durable. When possible, disease recurring in the chest wall or axillary nodes should be resected and radiation therapy should be delivered to aid in local control.

Radiation treatment techniques are generally similar to those employed for patients treated with standard postmastectomy irradiation and consist of photon- and/or electron-beam arrangements directed at the chest wall and adjacent lymph node regions. Treatment planning should strive for homogeneous dose distributions to the target areas while minimizing the dose to the underlying cardiac and pulmonary structures.

Radiation dose and protocol Conventional fractionation of 180-200 cGy/d to the area of locoregional recurrence and immediately adjacent areas at risk, to a total dose of 4,500-5,000 cGy, is indicated. A boost to the area of recurrence or gross residual disease, to a dose of approximately 6,000 cGy, results in acceptable long-term locoregional control.

A double-blind, placebo-controlled study of exemestane (Aromasin) demonstrated that it had a modest effect on bone loss in women with early-stage postmenopausal breast cancer who had already undergone surgery and irradiation. The investigators evaluated its effects on bone loss in 147 women with bone mineral density (BMD) levels that fell within 2 SDs of the mean level for women aged 65. Patients were randomized to receive exemestane orally for 2 years or placebo. Exemestane was well tolerated, and no patient who had a normal BMD level at baseline developed osteoporosis. Of the 19 patients with osteopenia at baseline, 6 in the exemestane arm and 5 in the placebo arm developed osteoporosis in the spine, and 3 in the exemestane arm and 5 in the placebo arm developed osteoporosis in the femoral neck. A total of nine patients had bone fractures. The authors concluded that exemestane had no effect on the spine and little effect on the femoral neck (*Lonning PE, Geisler J, Krag LE,s et al: Proc Am Soc Clin Oncol [abstract] 23:6, 2004*).

Radical chest wall resection A select group of patients with local chest wall recurrence secondary to breast cancer may be candidates for a radical chest wall resection, which may include resection of skin, soft tissue, and bone. Flap coverage or prosthetic chest wall reconstruction is required. Appropriate candidates would include patients who do not have distant metastases and who have persistent or recurrent chest wall disease after chest wall irradiation and patients who present with a chest wall recurrence after a long disease-free interval.

ADJUVANT SYSTEMIC THERAPY FOR LOCOREGIONAL RECURRENCE

Ipsilateral breast tumor recurrence

Limited data support the use of adjuvant systemic therapy at the time of ipsilateral breast tumor recurrence. Retrospective studies have suggested a 20%-50% risk of systemic metastases in patients who sustain an ipsilateral breast tumor recurrence. A study conducted at Yale University found that ipsilateral breast tumor recurrence was a significant predictor of distant metastases, particularly among women who relapsed within 4 years of the original diagnosis; these women had a rate of distant metastasis of approximately 50%. Similar findings were noted by the NSABP investigators.

These data suggest that women whose tumors recur in the ipsilateral breast within the first few years following the original diagnosis may be considered for adjuvant systemic therapy. Given the lack of prospective, randomized data, specific treatment recommendations for these women remain highly individualized.

Regional nodal recurrence and postmastectomy recurrence of disease in the chest wall

Although there are limited data addressing the use of adjuvant systemic therapy at the time of locoregional relapse following mastectomy, given the high rate of systemic metastasis in this population, these patients may be considered for adjuvant systemic therapy. A recently reported randomized trial demonstrated a disease-free survival benefit with the use of adjuvant tamoxifen fol-

lowing radiation therapy at the time of postmastectomy recurrence of disease in the chest wall in patients with estrogen-receptor–positive tumors. The 5-year disease-free survival rate was increased from 36% to 59%, and median disease-free survival was prolonged by > 4.5 years.

Patients with estrogen-receptor–negative tumors and aggressive locoregional recurrences may also be considered for systemic cytotoxic chemotherapy, given their relatively poor prognosis and the high rate of metastasis.

To determine whether weekly infusion of paclitaxel improves response rates vs the standard 3-hour infusion, 577 patients with metastatic breast cancer who had received one or two prior regimens were randomized to receive standard (175 mg/m²) or weekly (80 mg/m²) paclitaxel. Weekly paclitaxel was shown to be superior with respect to response rate (40% vs 28%, $P = .017$), time to disease progression (9 vs 5 mo, $P = .0008$), and overall survival (24 vs 16 mo). When trastuzumab became standard therapy for HER-2–positive tumors, all patients with HER-2–positive disease received trastuzumab, whereas patients with HER-2–negative disease were randomized to receive either addition of trastuzumab or not. The addition of trastuzumab did not improve any of these end points. Weekly paclitaxel caused more grade 3 sensory/motor neuropathy and less grade ≥ 3 granulocytopenia. The authors concluded that weekly is superior to standard paclitaxel in the management of metastatic breast cancer. (*Seidman A, Berry D, Cirrincione C, et al: Proc Am Soc Clin Oncol [late-breaking abstract 512] 23, 2004*).

MEDICAL TREATMENT OF METASTATIC BREAST CANCER

Patients with metastatic cancer can be divided into two groups: those with stage IV disease at presentation and those who develop metastases after primary treatment. The management of stage IV disease depends on the site and extent of metastases, comorbid conditions, and clinical tumor characteristics.

Patients with delayed metastatic disease can be divided into two groups, ie, so-called low risk and intermediate or high risk, based on the biologic aggressiveness of the disease. As shown schematically in Figure 2, the management approach to these two groups differs.

Low-risk patients

The low-risk group includes patients who develop metastatic disease after a long disease-free interval (ie, a long disease-free interval from primary breast cancer diagnosis to presentation with metastasis), those whose tumors are positive for hormone receptors (estrogen and progesterone), those with bone-only disease, and those without extensive visceral organ involvement.

Hormone therapy Low-risk patients, whose tumor is hormone receptor-positive (ie, estrogen receptor-positive and/or progesterone receptor-positive, may be treated with a trial of hormone therapy.

First-line hormonal therapy consists of an aromatase inhibitor, with careful serial assessment of clinical and disease responses.

Hormone therapy may be associated with a "flare" response, a temporary worsening of signs and symptoms of disease within the first few weeks of treatment. This response generally means clinical benefit will follow.

TABLE 3: Doses and schedules of hormonal agents commonly used in patients with metastatic breast cancer

Agent	Dose and schedule
Postmenopausal	
Tamoxifen	20 mg PO every day
or	
Toremifene	60 mg PO every day
Anastrozole	1 mg PO every day
or	
Letrozole	2.5 mg PO every day
or	
Exemestane	25 mg PO every day
Fulvestrant	250 mg IM every month
Megestrol	40 mg PO 4 times a day
Fluoxymesterone	10 mg PO 3 times a day
Aminoglutethimide	250 mg PO 4 times a day
Premenopausal	
Tamoxifen	20 mg PO every day
Luteinizing hormone-releasing hormone analogues	
Leuprolide	7.5 mg IM depot every 28 days 22.5 mg IM every 3 months 30 mg IM every 4 months
Goserelin	3.6 mg SC depot every 28 days 10.8 mg SC every 3 months
Megestrol	40 mg PO 4 times a day
Fluoxymesterone	10 mg PO 3 times a day

If the tumor initially responds to first-line hormone therapy and then progresses, a second hormonal manipulation is warranted. Various hormonal agents are available (Table 3). They may be used sequentially and may provide disease palliation for prolonged periods in some patients.

Second-line hormonal agents The choice of second-line endocrine therapy depends on the front-line endocrine agent used. Typically, if tamoxifen was used, the second-line agent includes an aromatase inhibitor or fulvestrant (Faslodex) for postmenopausal women. For premenopausal women, the choice may be megestrol acetate or induction of menopause with an LHRH agonist with or without an aromatase inhibitor. If aromatase inhibitors were used as front-line agents for postmenopausal women, second-line options can be to change to another class of aromatase inhibitor, fulvestrant, or tamoxifen.

The most commonly used second-line hormonal agents had been progestational drugs, such as megestrol. Recent randomized trials have indicated that the aromatase inhibitors, such as anastrozole (Arimidex), letrozole (Femara),

fulvestrant, and exemestane (Aromasin), are equally effective for palliation of metastatic disease, have less toxicity, and may provide a survival advantage compared with megestrol. Therefore, they are the drugs of choice for second-line therapy following tamoxifen administration. Tamoxifen may also be considered as second-line therapy for patients initially treated with an aromatase inhibitor.

Hormonal therapy continues until evidence of disease progression or drug-related toxicity precludes further therapy with the same agent. If a partial or complete response to the first hormonal treatment is documented at the time of disease progression, a second hormonal agent may provide further palliation of symptoms and avoid the initiation of systemic chemotherapy. However, subsequent hormonal responses tend to be of shorter duration, and, ultimately, the disease will become refractory to hormonal treatment.

Cytotoxic agents Hormone-refractory disease can be treated with systemic cytotoxic therapy. FAC, paclitaxel, TAC (Taxotere [docetaxel], Adriamycin [doxorubicin], cyclophosphamide), or docetaxel may be used in this situation. (For a more detailed discussion of these agents, see section on "Intermediate- or high-risk patients." For doses, see Table 1.)

Intermediate- or high-risk patients

Intermediate- or high-risk patients include those with rapidly progressive disease or visceral involvement, as well as those with disease shown to be refractory to hormonal manipulation by a prior therapeutic trial.

Anthracycline-containing combinations, such as FAC (see Table 1), are preferred for these patients. However, newer combinations of doxorubicin and a taxane are gaining favor for use in patients who have not received > 450 mg/m^2 of an anthracycline and whose relapse has occurred more than 12 months after the completion of adjuvant therapy.

Single agents Many single cytotoxic drugs have shown some activity in metastatic breast cancer (Table 1). They include vinblastine, mitomycin (Mutamycin), thiotepa, capecitabine, vinorelbine (Navelbine), and gemcitabine.

Paclitaxel One of the most active agents is paclitaxel. It has demonstrated antitumor activity in patients with anthracycline-resistant disease, as well as in those who have received three or more prior chemotherapy regimens for metastatic disease.

High-dose paclitaxel (250 mg/m^2 over 3 hours) has not been shown to be superior to 175 mg/m^2 over 3 hours. The higher dose regimen is associated with greater hematologic and neurologic toxicities.

Docetaxel, approved by the US Food and Drug Administration (FDA) for anthracycline-resistant locally advanced or metastatic breast cancer, has demonstrated overall response rates of 41% in patients with doxorubicin-resistant disease. It has been shown to be superior to mitomycin/vinblastine in patients whose disease progressed after an anthracycline-based chemotherapy regimen.

Abraxane, an albumin-bound form of paclitaxel is indicated for the second-line treatment of metastatic breast cancer. In a phase III multicenter trial comparing Abraxane with paclitaxel, 460 patients with metastatic breast cancer were randomized to receive either 260 mg/m^2 of Abraxane over 30 minutes or 175 mg/m^2 of paclitaxel over 3 hours. Patients treated with Abraxane had a significantly higher response rate of 21.5% than did patients treated with paclitaxel (11.1%). The toxicity profile of Abraxane was comparable to that of paclitaxel, although grade 3 sensory neuropathy occurred in 10% of patients treated with Abraxane (vs 2%). However, rapid improvement of neuropathy was documented in 58% of these patients after a median of 22 days. *(O'Shaughnessy JA, Tjulandin S, et al: Breast Ca Res Treat 82(supp 1) (abstract 44), 2003).*

The recommended starting dose of docetaxel—100 mg/m^2 as a 1-hour IV infusion—requires premedication with dexamethasone to avoid fluid retention and the capillary leak syndrome. The usual regimen of dexamethasone is 8 mg bid for a total of 3 days, beginning 24 hours prior to the administration of docetaxel.

Although 100 mg/m^2 is the dose of docetaxel approved by the FDA, many recent trials have demonstrated a high rate of grade 4 hematologic toxicity at this dose level; a dose of 60-70 mg/m^2 may achieve equivalent therapeutic benefit with improved safety. As with paclitaxel, the docetaxel dosage must be modified in patients who have hepatic impairment, manifested by elevated transaminase or alkaline phosphatase levels.

Capecitabine, an orally active fluorinated pyrimidine carbonate, has been shown to have substantial antitumor effect in patients whose disease has recurred or progressed after prior anthracycline chemotherapy or after taxane therapy. Prolonged survival, limited toxicity, and response in visceral as well as soft-tissue disease add to the benefit of capecitabine. Toxicities include diarrhea, stomatitis, and hand-foot syndrome.

New approaches Multiple new approaches to treating metastatic breast cancer are being explored. Weekly schedules of docetaxel and paclitaxel have been reported to produce high response rates and lower toxicity than 3-week schedules. Combinations of doxorubicin with paclitaxel or docetaxel have also shown substantial antitumor activity, as have combinations of capecitabine and docetaxel, carboplatin and paclitaxel, and gemcitabine and cisplatin. These newer combinations need to be compared with standard AC or FAC (CAF) regimens in phase III trials. Recent studies also suggest that sequential weekly chemotherapy may be as effective as more intensive combinations with respect to overall survival in patients with metastatic breast cancer.

Monoclonal antibody therapy

Trastuzumab, a humanized monoclonal antibody to the HER-2/*neu* protein, has been approved for use as a single agent in second- and third-line therapy for metastatic breast cancer and in combination with paclitaxel as first-line therapy in this setting. A randomized trial consisting of 469 women showed that the combination of trastuzumab with chemotherapy yielded a 45% overall response rate, as compared with a 29% rate with chemotherapy alone—a 55% increase. The addition of trastuzumab had the greatest impact on response when combined with paclitaxel. Among the study group as a whole, 79% of women

TABLE 4: Randomized studies of high-dose chemotherapy in metastatic breast cancer

Investigators	Number of patients	Median follow-up (yr)	Survival rate (%)		P value
			High-dose treatment	Standard treatment	
Stadtmauer et al	553	3	32.0	38.0	NS
Lotz et al	61	5	29.8	18.5	NS

NS = not significant

treated with trastuzumab chemotherapy were alive at 1 year, as compared with 68% of those given chemotherapy alone.

A recent update of those data has shown a superior median overall survival with chemotherapy plus trastuzumab compared with chemotherapy alone (25.4 vs 20.9 months). The survival advantage was seen with both AC plus trastuzumab and paclitaxel plus the monoclonal antibody.

In another single-arm trial involving 222 women who had not responded to prior chemotherapy, trastuzumab shrunk tumors by 50% in 14% of women, with a median duration of response of 9 months. Overall, trastuzumab was well tolerated in both trials. Due to an increased risk of cardiac dysfunction observed in women treated with trastuzumab plus an anthracycline, trastuzumab should not be used in combination with this drug class.

It is important to point out that trastuzumab also produces cardiac toxicity when administered by itself, particularly in patients who have had extensive prior exposure to an anthracycline. Finally, essentially all of the clinical benefit of trastuzumab (alone or in combination) is confined to patients whose breast cancer expresses high (3+) levels of the HER-2/*neu* oncoprotein.

High-dose chemotherapy

Patients who present with or subsequently develop distant metastasis may be candidates for high-dose intensive chemotherapy programs with autologous stem-cell support. Multiple feasibility and phase II studies of this approach have been undertaken. The majority of programs include the use of multiple alkylating agents. The role of high-dose chemotherapy in metastatic disease remains controversial, and analysis and observation of ongoing clinical trials continue to be important.

The results from multiple centers indicate an overall 5-year disease-free survival rate of 25% in patients with metastatic disease treated with high-dose chemotherapy. However, it must be remembered that these results were obtained in a select patient population—generally individuals < 60 years of age with good performance status; chemotherapy-sensitive disease; and normal cardiac, pulmonary, renal, and hepatic function. The use of intensive supportive out-

In a recent randomized trial, patients with one to three newly diagnosed brain metastases (breast as well as other sites) were randomly allocated to receive either whole brain radiation therapy (WBRT, 164 patients) or WBRT followed by a stereotactic radiosurgery boost (167 patients). Univariate analysis showed that there was a survival advantage in the WBRT and surgery group for patients with a single brain metastasis (median survival 6.5 vs 4.9 months, $P = .0393$). Patients in the stereotactic surgery group were more likely to have a stable or improved Karnofsky Performance Status score at 6 months' follow-up than were patients allocated to WBRT alone (43% vs 27%, respectively; $P = .03$; *Andrews DW, Scottt CB, Sperduto PW, et al: Lancet 363:1665-1672, 2004*).

patient care, such as colony-stimulating factors and antibiotics, has significantly reduced the morbidity and mortality associated with the high-dose chemotherapy approach.

In recently presented randomized trials of high-dose chemotherapy in patients with metastatic breast cancer (Table 4), it appears that most of the benefit occurs in women with low-bulk disease, especially those in complete clinical remission. A recent meta-analysis with longer follow-up also demonstrated a benefit for the addition of high-dose therapy to standard, anthracycline-containing chemotherapy for advanced disease in the setting of patients in complete clinical remission. This therapeutic modality remains investigational for patients with stage IV disease, however; women referred for high-dose therapy should be enrolled in a clinical trial.

Adjunctive bisphosphonate therapy

Multiple published reports have now confirmed the benefit of bisphosphonates as an adjunct to treatment of patients with bone metastasis. Use of these agents results in a significant reduction in skeleton-related events, including pathologic fracture, bone pain, and the need for radiation therapy to bone. Pamidronate (Aredia) and zoledronic acid (Zometa), both in IV formulations, are available in the United States. Oral bisphosphonates used for this indication, such ibandronate and clodronate, are not in the US market.

Patients with breast carcinoma who had all types of bone metastases (osteolytic, mixed, or osteoblastic) were randomized to receive treatment with either 4 mg or 8 mg of of zoledronic acid as a 15-minute infusion or 90 mg of pamidronate as a 2-hour infusion every 3-4 weeks for 12 months. The proportion of patients who had a skeleton-related event (defined as a pathologic fracture, spinal cord compression, radiotherapy, or surgery to bone) was comparable between treatment groups (approximately 45%). However, among patients who had breast carcinoma with at least one osteolytic lesion, treatment with 4 mg of zoledronic acid was more effective than 90 mg of pamidronate in reducing skeletal complications.

The most commonly reported adverse events for either zoledronic acid or pamidronate were bone pain, nausea, fatigue, emesis, and fever. The 4-mg dose of zoledronic acid results in elevated serum creatinine levels in about 7.7% of patients, vs 6.0% with pamidronate. A larger proportion of patients had elevated serum creatinine levels with 8-mg of zoledronic acid; therefore, this

dose is not recommended. Symptomatic hypocalcemia, although relatively rare, requires frequent monitoring of calcium and phosphate levels during treatment.

ROLE OF RADIATION THERAPY IN METASTATIC DISEASE

Irradiation remains an integral component of the management of metastatic breast carcinoma. Although bone metastases are the most commonly treated metastatic sites in patients with breast cancer, brain metastases, spinal cord compression, choroidal metastases, endobronchial lung metastases, and metastatic lesions in other visceral sites can be effectively palliated with irradiation.

Radiation dose and schedule Depending on the disease site and volume of the radiation field, fractionation schedules ranging from 20 Gy in 5 fractions to 30 Gy in 10 fractions are used most commonly. In some situations, more protracted courses using lower daily doses may be indicated.

Bone metastasis For patients with widespread bone metastasis, hemibody irradiation (6-7 Gy in one fraction to the upper body or 8 Gy to the lower body) has been shown to be effective. Strontium-89 chloride (Metastron) and other systemic radionuclides also provide effective palliation for widespread bone disease.

Consolidation after high-dose chemotherapy Since patients with metastatic disease treated with high-dose chemotherapy and autologous bone marrow or stem-cell transplantation often develop progressive disease in previously involved sites, studies have suggested the use of "consolidative radiation therapy" for patients undergoing high-dose chemotherapy. Although this approach appears to be well tolerated and preliminary data are encouraging, whether it will affect survival remains to be determined.

ROLE OF SURGERY IN METASTATIC DISEASE

There are selected indications for surgical intervention in patients with metastatic breast cancer, and the role of surgery at this point is generally palliative. Most commonly, palliative surgery is offered to patients with brain metastases, spinal cord compression, fractures, or symptomatic pleural or pericardial effusions not controlled by other means. It is also used for GI complications stemming from metastatic deposits. The curative benefit of surgery in the treatment of metastatic disease to the lungs or liver is not proven, but, in highly selected cases, surgery may be beneficial.

Spinal cord compression Patients with spinal cord compression who have progressive symptoms during irradiation, disease recurrence after irradiation, or spinal instability or who require diagnosis are candidates for surgery.

Solitary brain metastasis Patients with a long disease-free interval and solitary brain metastasis may be candidates for resection. Evidence suggests an improved disease-free survival, overall survival, and quality of life in this subset of patients when treated with surgery combined with postoperative cranial irradiation, as compared with radiation therapy alone.

Gamma- and cyber-knife radiosurgery is increasingly used to manage brain metastases. In some instances, these modalities have been used in patients who have multiple metastatic brain lesions or in patients who had previously received conventional treatment modalities for brain metastases, including whole-brain irradiation. No radiation-induced dementia and a remarkably low incidence of local failure were reported with these treatments. Although in the past, local control of brain metastasis was an issue, these treatment modalities are shifting the question of survival to that of systemic control.

Chest wall resection It is extremely rare for a patient with distant metastatic disease to be a candidate for chest wall resection; however, patients with symptomatic recurrence of disease in the chest wall who have limited distant disease and a life expectancy of > 12 months may be appropriate candidates.

Follow-up of long-term survivors

For recommendations on the type and timing of follow-up evaluations, see chapter 10.

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CHAPTER 14

Pancreatic, neuroendocrine GI, and adrenal cancers

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PANCREATIC CANCER

Pancreatic cancer is the fifth leading cause of cancer death in the United States. In the year 2005, an estimated 32,180 new cases will be diagnosed, and 31,800 deaths will be ascribed to this cancer.

Incidence and epidemiology

Gender The incidence of pancreatic cancer is slightly higher in males than in females. These gender differences are most prominent among younger individuals.

Age The peak incidence of pancreatic carcinoma occurs in the seventh decade of life. Two-thirds of new cases occur in people > 65 years old.

Race The incidence is higher in the black population, with an excess risk of 40%-50% over whites. Perhaps more importantly, black males probably have the highest risk of pancreatic cancer worldwide.

Survival Cancer of the pancreas is a highly lethal disease historically, with few reports of 5-year survivors. However, more recent series have shown a decrease in both operative mortality and overall morbidity. There has also been a significant increase in 5-year survival after curative resection (21%-25%). Factors that appear to be important in predicting long-term survival after resection include clear surgical margins, negative lymph nodes, and reduced perioperative mortality.

Adenocarcinoma of the pancreas, the most common histologic type, has a median survival of 9-12 months and an overall 5-year survival rate of 3% for all stages. At the time of diagnosis, over 50% of patients with pancreatic adenocarcinoma have clinically apparent metastatic disease. Among patients whose disease is considered to be resectable, 50% will die of recurrent tumor within 2 years.

Etiology and risk factors

The specific risk factors for pancreatic cancer are not as striking as those for other GI malignancies, such as esophageal and gastric carcinomas. There does, however, appear to be a significant relationship between pancreatic cancer and environmental carcinogens.

Cigarette smoking Cigarette smoke is one of the carcinogens directly linked to the causation of pancreatic malignancies. Heavy cigarette smokers have at least a twofold greater risk of developing pancreatic carcinoma than nonsmokers. In Japan, cigarette smoking carries an even greater risk, which can be as much as 10-fold in men smoking one to two packs of cigarettes daily.

N-nitroso compounds, found particularly in processed meat products, reliably induce pancreatic cancer in a variety of laboratory animals. No study has directly linked dietary carcinogens to pancreatic cancers in humans.

Caffeine The contribution of caffeine consumption to the development of pancreatic carcinoma is controversial. A case-controlled study showed a correlation between caffeine consumption and pancreatic cancer. However, other studies have been unable to confirm this relationship.

Alcohol A clear-cut relationship between alcohol use and pancreatic carcinoma has not been shown.

Diabetes does not seem to be a risk factor for pancreatic cancer. However, 10% of all patients with pancreatic carcinoma present with new-onset diabetes.

Genetic factors Cancer of the pancreas is a genetic disease. To date, more than 80% of resected pancreatic cancers have been found to harbor activating point mutations in K-*ras*. In addition, the tumor-suppressor genes *p16*, *p53*, and *DPC4* are all frequently inactivated in this cancer.

Familial pancreatic carcinoma has been associated with the following genetic syndromes: hereditary pancreatitis, ataxia-telangiectasia, hereditary nonpolyposis colorectal cancer (HNPCC), familial atypical mole melanoma (FAMM) syndrome, Peutz-Jeghers syndrome, and familial breast cancer. Families with *p16* germline mutations may be at higher risk of developing pancreatic cancer than those without these mutations.

Signs and symptoms

The initial clinical features of pancreatic carcinoma include anorexia, weight loss, abdominal discomfort or pain, and new-onset diabetes mellitus or thrombophlebitis. The vague nature of these complaints may delay diagnosis for several months.

Pain Specific symptoms usually relate to localized invasion of peripancreatic structures. The most common symptom is back pain, which stems from tumor invasion of the splanchnic plexus and retroperitoneum or pancreatitis. This pain is described as severe, gnawing, and radiating to the middle of the back. Pain can also be epigastric or in the right upper quadrant if bile duct obstruction is present.

Jaundice In a majority of cases, patients with pancreatic cancer present with epigastric or back pain and/or jaundice. Painless or sometimes painless jaundice occurs with early lesions near the intrapancreatic bile duct.

GI symptoms Tumor invasion of the duodenum or gastric outlet may give rise to nausea or vomiting as a presenting symptom. This symptom is rare early in the course of the disease. Changes in bowel habits related to pancreatic insufficiency may also be present, along with associated steatorrhea.

Glucose intolerance Recent onset of glucose intolerance in an elderly patient associated with GI symptoms should alert physicians to the possibility of pancreatic carcinoma.

A palpable gallbladder occurring in the absence of cholecystitis or cholangitis suggests malignant obstruction of the common bile duct until proven otherwise. This so-called Courvoisier's sign is present in about 25% of all pancreatic cancer patients.

Other physical findings include Trousseau's syndrome (migratory superficial phlebitis), ascites, Virchow's node (left supraclavicular lymph node), or a periumbilical mass (Sister Mary Joseph's node).

Screening and diagnosis

Early diagnosis of pancreatic carcinoma is difficult but essential if surgical resection and cure are to be improved. Defining early lesions at a resectable stage remains a diagnostic challenge. To date, leading medical organizations have not recommended routine screening of asymptomatic individuals for pancreatic cancer.

Serum markers The use of serologic tumor markers for pancreatic carcinoma, such as CA19-9, was originally thought to be appropriate as a screening tool. However, since the prevalence of pancreatic carcinoma in the general population is extremely low (0.01%), many false-positive screening results are generated. Also, the sensitivity of CA19-9 is not high (20%) in stage I cancers. Nevertheless, CA19-9 may be a useful marker for diagnosing patients at high risk with the appropriate symptoms, such as smokers, recent-onset diabetics, those with familial pancreatic cancer, or those with unexplained weight loss or diarrhea. This marker also is useful in following disease and in assessing the adequacy of resection or therapy.

No currently available serum marker is sufficiently accurate to be considered reliable for screening asymptomatic patients.

Laparoscopy is useful for staging patients with pancreatic carcinoma and for formulating treatment plans. Approximately 10%-15% of patients thought to have resectable disease are found to have distant metastases at laparoscopy. The false-negative rate of laparoscopy is < 10%. The strongest indications for laparoscopy are locally advanced disease and tumors of the body and tail of the pancreas.

Peritoneal cytology also is being explored for the diagnosis of pancreatic carcinoma. Cytology is positive in 5%-10% of patients who are thought to have localized disease. There are anecdotal cases of long-term survival after resection where positive cytology of peritoneal washings was noted. However, the clinical/prognostic value of this test is not yet known.

Imaging techniques

Imaging for pancreatic carcinoma is best performed with conventional ultrasonography and CT.

Ultrasonography The limit of sonographic resolution for early pancreatic carcinoma is a diameter on the order of 1.0-1.5 cm. A mass located in the pancreatic head will produce dilatation of the common bile duct and pancreatic duct. The actual sensitivity of ultrasonography in the diagnosis of pancreatic carcinoma is ~70%.

CT provides better definition of the tumor and surrounding structures than does ultrasonography and is operator-independent. CT correctly predicts unresectable tumors in 85% of patients and resectable tumors in 70% of patients. Findings of tumor unresectability on CT scanning include distant lymphadenopathy, encasement or occlusion of the superior mesenteric artery (SMA) or celiac artery, occlusion of the portal vein or superior mesenteric vein (SMV), and distant metastases.

Spiral CT More recently, spiral CT has emerged as a preferred technique for increasing the accuracy of detecting pancreatic carcinoma in general and vessel encasement in particular. This technique permits rapid data acquisition and computer-generated three-dimensional (3D) images of the mesenteric arterial and venous tributaries in any plane. Spiral CT is quicker and less expensive and uses less contrast medium than angiography.

PET The use of positron emission tomography with ^{18}fluorodeoxyglucose (FDG-PET) in the evaluation of patients with pancreatic cancer is expanding. A recent study of 126 patients with focal, malignant, or benign pancreatic lesions showed high sensitivity of FDG-PET for detection of small pancreatic neoplasms. Lack of focal glucose uptake excludes pancreatic neoplasms (sensitivity 85.4%, specificity 60.9%).

MRI At present, MRI is not as accurate as CT in diagnosing and staging pancreatic carcinoma. MRI may be as useful as CT in staging and can provide magnetic resonance angiography and magnetic resonance cholangiopancreatography (MRC) images if needed. As yet, MRC is not a standard test for the diagnosis of pancreatic carcinoma, but it may become helpful in the future.

Endoscopic ultrasonography (EUS) is a newer modality for the diagnosis of pancreatic carcinoma, with an overall diagnostic accuracy rate of approximately 85%-90%. For the assessment of regional lymph node metastases, the accuracy of EUS is 50%-70%. This technique is also important in the evaluation of portal vein/SMV involvement by tumor. In addition, EUS-guided fine-needle cytology of periampullary tumors may yield new information

with respect to the diagnosis of pancreatic cancer and may be less risky in spreading cells by needle tracking than percutaneous biopsies.

In a comparison of EUS and spiral CT, both techniques showed comparable efficacy in detecting tumor involvement of lymph nodes and the SMVs and portal veins. However, EUS is less helpful in the evaluation of the SMA.

Endoscopic retrograde cholangiopancreatography (ERCP) may someday be supplanted as a diagnostic tool by EUS, although, at present, ERCP is used in many clinics. Also, if a patient presents with jaundice and the CT scan reveals dilatation of the common bile duct without an obvious mass, ERCP may be complementary to spiral CT. ERCP findings of pancreatic cancer include an abrupt or tapered cutoff of either or both the main pancreatic and common bile ducts.

Pathology

Adenocarcinoma arising from the exocrine gland ductal system is the most common type of pancreatic cancer, accounting for 95% of all cases. Two-thirds of these cancers originate in the pancreatic head, and the remainder arise in the body or tail. Most ductal carcinomas are mucin-producing tumors and usually are associated with a dense desmoplastic reaction.

Although most pancreatic adenocarcinomas arise from the ductal epithelium, pancreatic acinar carcinomas and cancers arising from mucinous cystic neoplasms are also found.

Multicentricity, which is usually microscopic, is not unusual.

Metastatic spread Perineural invasion occurs in the majority of patients with pancreatic carcinoma. In addition, pancreatitis distal to and surrounding the tumor is usually present. Most patients present with lymph node metastases in the region of the pancreaticoduodenal drainage basins. Subpyloric and inferior pancreatic head, SMA, and para-aortic lymph node groups also may be involved.

Staging and prognosis

Pancreatic adenocarcinoma is staged according to local spread of disease, nodal status, and distant metastatic involvement using the American Joint Committee on Cancer (AJCC) TNM system (Table 1). The T staging of the primary tumor includes an analysis of direct extension of disease to the duodenum, bile duct, or peripancreatic tissues. A T4 advanced cancer may extend directly to the SMA or celiac axis, meaning that the cancer is unresectable.

Independent prognostic factors Lymph node metastases and tumor size and differentiation have independent prognostic value in patients with pancreatic carcinoma. Significantly improved survival is seen in patients with smaller lesions, lymph node-negative tumors, and tumors in which the surgical margins are not involved.

TABLE 1: TNM staging of pancreatic tumors

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
Tis	Carcinoma in situ
T1	Tumor limited to the pancreas, ≤ 2 cm in diameter
T2	Tumor limited to the pancreas, > 2 cm in diameter
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
Regional lymph nodes (N)	
N0	No involved regional lymph nodes
N1	Any involved regional lymph nodes
Distant metastases (M)	
Mx	Presence of distant metastases cannot be assessed
M0	No distant metastases
M1	Distant metastases

Stage grouping

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1-3	N1	M0
Stage III	T4	Any N	M0
Stage IV	Any T	Any N	M1

From Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

Lymph node and margin status Prior to the age of adjuvant therapy, lymph node status was the most dominant prognostic factor (Figure 1). It is now rivaled by surgical margin status in series where surgical margins have been meticulously examined.

Treatment

SURGICAL TREATMENT OF RESECTABLE DISEASE

The rate of resection for curative intent ranges from 10% to > 75%, with the higher percentage resulting from both a more aggressive approach and better preoperative staging for resectability. Also, there is growing evidence that patients with potentially resectable pancreatic cancer have a shorter hospital stay, reduced surgical mortality, and an overall better outcome if the surgery is performed at "high-volume" medical centers staffed by experienced surgeons (approximately 16 operable cases per year).

Extended resections may include portal or superior mesenteric vessels, colon, adrenal, or stomach. If resection of adjacent organs or tissues results in the conversion of a positive to a negative resection margin, it is of great potential benefit to the patient.

Determination of resectability

The initial approach to surgery for pancreatic carcinoma includes a determination of resectability. This determination should be first made preoperatively with high-quality CT or MRI and perhaps EUS. Operative determination of resectability includes careful examination of the liver, porta hepatis, and portal and superior mesenteric vessels. The head of the pancreas and uncinate process are mobilized by an extensive Kocher maneuver to evaluate the head of the pancreas. The SMA is palpated, and its relationship to the tumor is assessed. The hepatic artery and celiac trunk are examined to make certain there is no vascular encasement.

Criteria for unresectability include distant metastases and involvement of the SMA and celiac axis.

An analysis of 200 patients who underwent resection of pancreatic adenocarcinoma in the era prior to adjuvant therapy found that the most important factors influencing long-term survival were the diameter of the primary tumor, status of the resected lymph nodes, and status of the resected margins. Patients with tumors < 3 cm in diameter had significantly longer median survival and 5-year survival rates (21 months and 28%, respectively) than those with tumors ≥ 3 cm (11.5 months and 15%). Patients with no lymph node involvement had a 5-year survival rate of 36%, as compared with < 5% for those with positive nodes. Patients who underwent resections with negative margins had a 5-year survival rate of 26%, vs 8% for those with positive margins. The type of resection (pylorus-preserving vs standard Whipple procedure) did not influence survival.

Extent of resection

Whipple vs pylorus-preserving procedure If the tumor is deemed to be resectable, a standard pancreaticoduodenectomy (Whipple procedure) or pylorus-preserving Whipple procedure (PPW) is performed. The PPW theoretically eliminates the nutritional problems caused by a reduced gastric reservoir and gastric dumping, but this finding has not been shown to alter long-term nutritional status. If there is any doubt about cancer proximity or blood supply to the pylorus, an antrectomy should be performed. If the tumor approaches the pylorus or involves the subpyloric nodes, classic antrectomy is preferred.

Intraoperative biopsy Most patients with resectable periampullary tumors can successfully undergo pancreaticoduodenectomy without an intraoperative biopsy. A time-consuming frozen section interpretation may not be informative, and histologic confirmation may be impossible with small lesions associated with peritumoral pancreatitis. Most large series of pancreaticoduodenectomy for carcinoma include resections of benign pathology based on clinical judgment. A

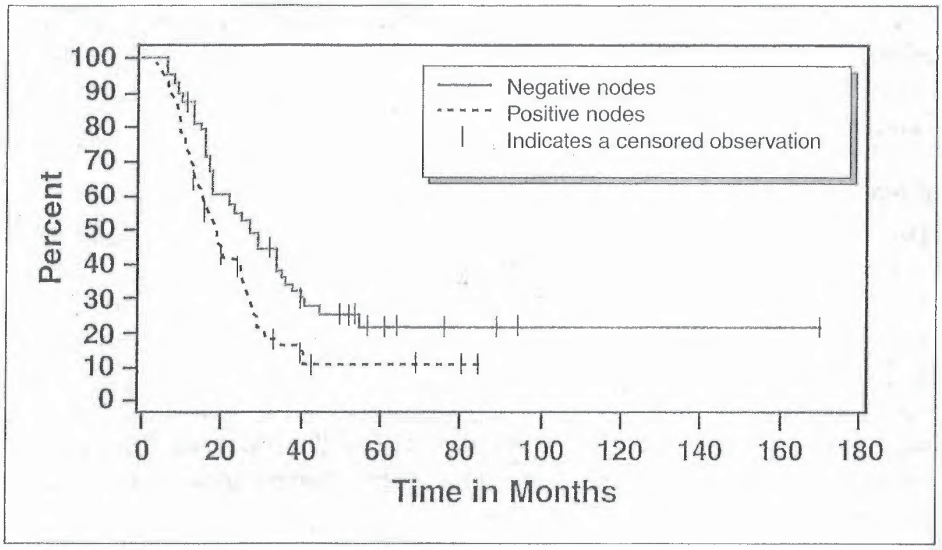

FIGURE 1: Actuarial survival as a function of regional lymph node status in patients with pancreatic cancer.

negative fine-needle cytology should not deter an experienced surgeon from proceeding with resection. However, medicolegal considerations may prompt a biopsy.

Reconstruction technique The most common reconstruction technique after a Whipple resection requires a single retrocolic jejunal loop to complete the pancreaticojejunostomy, which is followed by a cholangiojejunostomy and gastrojejunostomy. A duct-mucosal anastomosis is preferred to the pancreaticojejunostomy. Pancreaticogastrostomy is also an effective and safe means of creating the anastomosis.

Postsurgical complications Operative mortality of pancreaticoduodenectomy is currently < 6% in major surgical centers. The leading causes of postoperative mortality include postoperative sepsis, hemorrhage, and cardiovascular events. Most of the septic complications arise from pancreaticojejunostomy leaks.

In many series, early delayed gastric emptying is the leading cause of morbidity for pylorus-preserving procedures. The number-two cause of morbidity, seen in 5%-15% of all patients, is a leak or fistula from the pancreatic anastomosis. Today, most fistulas close spontaneously with the addition of somatostatin analog treatment and adequate drainage. Pancreatic fistulas heal with conservative measures in more than 95% of patients.

SURGICAL PALLIATION

Surgical palliation is also considered in patients undergoing exploration with curative intent. Jaundice, gastric obstruction, and pain may be alleviated by surgical palliation.

Biliary tract obstruction Either a choledochojejunostomy or cholecystojejunostomy can be used to bypass the biliary obstruction. Recurrent jaundice and cholangitis are less likely to develop when the common duct is used for decompression.

Duodenal obstruction Although duodenal obstruction is rare as a presenting symptom, duodenal involvement may occur eventually in 25% of patients. Some authors believe that prophylactic bypasses are safe and should be performed in all patients. One phase III trial supports prophylactic bypass, but another does not.

Pain relief Severe back pain may be an incapacitating symptom. Pain relief may be achieved by chemoablation of the celiac plexus or by alcohol injection, which may be performed intraoperatively or percutaneously. An intraoperative injection of 25 mL of ethanol (95%) on both sides of the celiac axis will ablate tumor pain. (For further discussion of these techniques, see chapter 37 on pain management.)

NEOADJUVANT AND ADJUVANT THERAPY

Radiation therapy

Even with apparently adequate surgical resection, pancreatic cancer has a high risk of locoregional recurrence. Moreover, most lesions are unresectable, even when there is no apparent distant metastatic disease. Thus, there is a theoretical rationale for the adjunctive use of radiation therapy, either before or after surgery, in almost all patients. Preoperative (neoadjuvant) radiation therapy may help render locally advanced lesions resectable with negative margins (RO resection). Postoperative (adjuvant) radiation therapy may help eliminate suspected residual microscopic disease in the tumor bed and/or regional lymphatics. Alternative radiation techniques, including intensity-modulated radiotherapy (IMRT) and 3D conformal radiation therapy, are being explored.

A Radiation Therapy Oncology Group (RTOG)/Southwest Oncology Group (SWOG)/ Eastern Cooperative Oncology Group (ECOG) intergroup trial, the largest of its kind, is comparing infusional 5-FU with gemcitabine, both agents given before and after chemoradiation therapy, in patients with resected pancreatic cancer. Radiation therapy is being administered without a treatment break and is being given with continuous-infusion 5-FU in both arms. End points include quality of life as well as survival. This study has recently completed its accrual goal, and analysis is pending.

With an effective chemotherapeutic agent, there is greater potential for adequate locoregional cytotoxicity—as well as control of subclinical distant disease—than could be obtained with limited doses of adjuvant radiation therapy alone.

Preoperative chemoradiation therapy Several single-institution studies have evaluated the role of preoperative irradiation in conjunction with fluorouracil (5-FU)- and gemcitabine (Gemzar)-based chemotherapy. In these studies, 60%-80% of the lesions were completely resected 1.0-1.5 months after the completion of chemoradiotherapy. Median survival has ranged from 16 to 36 months, but

no phase III trials have been conducted to evaluate preoperative therapy vs postoperative sequencing.

Preoperative radiation therapy, to 4,500-5,000 cGy, in conjunction with chemotherapy should be considered for patients with pancreatic adenocarcinoma who are medically fit but who have marginally resectable disease. There are research initiatives to further address the role of neoadjuvant chemotherapy. For example, a new Eastern Cooperative Oncology Group (ECOG) study will evaluate gemcitabine plus radiotherapy vs gemcitabine, 5-FU, and cisplatin followed by radiotherapy and 5-FU for patients with locally advanced disease. Other phase II studies involved high-dose gemcitabine and high-dose gemcitabine and cisplatin with short-term radiation therapy to locally advanced cancer.

Postoperative chemoradiation therapy A small Gastrointestinal Tumor Study Group (GITSG) trial demonstrated a significant prolongation of survival (median survival increase, from 11 to 20 months) among patients with pancreatic adenocarcinoma who received irradiation plus bolus 5-FU chemotherapy after curative resection, as compared with those given no adjuvant treatment. An improvement in the long-term cure rate was also observed among those given chemoradiation therapy.

The European Organization for Research and Treatment of Cancer (EORTC) completed a trial of 218 patients similar to that of the GITSG trial but without maintenance chemotherapy. Reported data suggest no significant difference between split-course radiation therapy with bolus 5-FU and observation only after curative resection (two-tailed P value = .099); however, there was a trend toward benefit in median survival favoring those who received treatment. The European trial is difficult to interpret because 20% of patients randomized to receive postoperative treatment were not treated, and the study was inadequately powered for survival.

The GITSG study utilized 4,000 cGy of radiation delivered in a split-course fashion—with a planned 2-week break midway through the treatment. However, single-institution studies indicate that 4,500-5,000 cGy can be safely delivered in 5.0-5.5 weeks without a treatment break.

Careful attention to field size is important. The GITSG trial allowed portals as large as 20 × 20 cm. However, ports that are approximately 12 × 12 cm are usually sufficient to cover the tumor bed with a 2- to 3-cm margin. The use of multiple beams and high-energy photons is also important.

A total of 541 patients were enrolled in a trial conducted by the European Study Group for Pancreatic Cancer (ESPAC). This study evaluated the benefits of adjuvant therapy. The design was complex, attempting to assess several options. It included no further therapy after surgery, chemoradiation therapy (bolus 5-FU with split-course radiotherapy), chemotherapy (5-FU with leucovorin), and chemoradiation therapy followed by chemotherapy.

Interpretation of the results is confounded by the fact that some institutions opted for a full 2 × 2 randomization (all four options), whereas others allowed

only two options (no further therapy vs chemotherapy or no further therapy vs chemoradiation therapy). Patients receiving these two options could also have therapy other than that prescribed in the randomization. Furthermore, no data were collected regarding time to recurrence or whether treatment was given after recurrence. Curiously, the median survival of those in the control group was more than 17 months, much longer than those of the control groups from the GITSG and EORTC trials.

Only the 5-FU with leucovorin arm would be considered a state-of-the-art approach, and it was demonstrated to improve survival significantly ($P = .0005$). This finding would suggest a strong benefit to postoperative chemotherapy. If radiation therapy is included, it would probably best be given after 1-2 months of full-dose chemotherapy. Most practitioners would recommend continuous-course radiation therapy rather than split-course treatment.

The ESPAC is now conducting a postoperative trial comparing various chemotherapy regimens with a control group. In the United States, the findings of several phase II trials of postoperative regimens as well as a phase III trial will be available soon. In addition, the GI Intergroup is considering a randomized phase II trial to explore new combinations incorporating the monoclonal antibodies bevacizumab (Avastin) and cetuximab (Erbitux), each given with gemcitabine; irradiation will be given with oral capecitabine (Xeloda).

Locally advanced but potentionally resectable lesions

These lesions comprise 10%-15% of the cases presenting to physicians. Data from preoperative chemoradiation series indicate that trimodality therapy is essential for long-term survival in these patients. There is now a randomized phase II ECOG trial (E1200) evaluating gemcitabine with radiation therapy (500 mg/m^2/50 min/wk during radiation therapy of 5,040 cGy with tightened fields) plus postresectional gemcitabine or preoperative chemotherapy, with a dose of two cycles of gemcitabine, 5-FU, and cisplatin, followed by 5-FU/radiation therapy, then surgery, and then postoperative gemcitabine. End points are margin-free resectability and survival.

TREATMENT OF UNRESECTABLE DISEASE

Irradiation can prolong and/or improve quality of life in some patients with unresectable adenocarcinoma of the pancreas. It is better combined with chemotherapy. Long-term survival is, unfortunately, highly unusual.

Chemoradiation therapy The addition of chemotherapy to radiation therapy has been shown to improve the survival of patients with unresectable pancreatic adenocarcinoma, with moderate doses of radiation only slightly less effective than higher doses. In a GITSG trial of unresectable disease, moderate-dose radiation (4,000 cGy) with 5-FU chemotherapy significantly improved survival, as compared with higher doses of radiation (6,000 cGy) and no chemotherapy (median survival, 9.6 vs 5.2 months). The GITSG has also compared chemotherapy plus irradiation with chemotherapy alone and demonstrated a significant improvement with combined-modality therapy (median survival, 42 vs 32 weeks).

TABLE 2: Chemotherapy regimens for pancreatic cancer

Drug/combination	Dose and schedule
Fluorouracil/radiation therapy (GITSG regimen)	
Fluorouracil	500 mg/m^2/d IV bolus for 3 consecutive days once every 4 weeks during radiation therapy
Radiation therapy	Two courses of 2,000 cGy each, separated by 2 weeks (total dose, 4,000 cGy)
Gastrointestinal Tumor Study Group: Cancer 59:2006–2010, 1987.	
Infusional 5-FU with radiation therapy	
Concurrent radiation therapy and chemotherapy phase:	
Fluorouracil	150-250 mg/m^2/d, 24 hours/day during radiation therapy
Radiation therapy	Median dose of 4,500 cGy/25 fractions (range 4,000 cGy/20 fractions to 5,040 cGy/28 fractions)
Fisher B, Perera F, Kocha W, et al: Int J Radiat Oncol Biol Phys 45:291–295, 1999.	
Single-agent regimen	
Gemcitabine	1,000 mg/m^2 IV infused over 30 minutes once a week for 7 weeks, followed by a 1-week rest period
Subsequent cycles once a week for 3 consecutive weeks out of every 4 weeks	
Burris HA, Moore MJ, Andersen J, et al: J Clin Oncol 15:2403–2413, 1997.	

Table prepared by Ishmael Jaiyesimi, DO

Based on these data, except in a protocol setting, the palliative management of a patient with unresectable pancreatic adenocarcinoma who has significant local symptoms should probably consist of moderate doses of radiation (4,000-5,000 cGy) in conjunction with 5-FU–based chemotherapy. As in adjuvant treatment, carefully shaped portals approximately 12 × 12 cm should be used.

Approaches under investigation At present, numerous trials are exploring a variety of chemoradiation therapy approaches, including single-agent or combination therapy with oral or infusional 5-FU, paclitaxel, cisplatin, gemcitabine, docetaxel (Taxotere), and oxaliplatin (Eloxatin). Trials with combined gemcitabine and irradiation are of particular interest due to the activity of this drug in pancreatic cancer and the fact that it is a potent radiosensitizer. The benefit of irradiation for patients with locally advanced disease, however, remains a research question because of toxicity concerns and the relatively brief survival rates. Therefore, a new ECOG trial will evaluate gemcitabine alone vs gemcitabine and irradiation for this group of patients.

If gemcitabine is given either before or after a course of radiation therapy, full doses of 1,000 mg/m^2 are possible. If irradiation and gemcitabine are given concurrently, doses of either modality must be sharply reduced. A current phase II trial is combining "full-dose" gemcitabine (1,000 mg/m^2) with radiation therapy

directed at the primary tumor alone (36 Gy). In addition, a Radiation Therapy Oncology Group (RTOG) randomized trial evaluated radiation therapy (50.4 Gy) and weekly gemcitabine and paclitaxel with or without the farnesyl transferase inhibitor R11577 for locally advanced pancreatic cancer. In that trial, the gemcitabine dose was 75 mg/m^2/wk and the paclitaxel dose was 40 mg/m^2/wk. Radiation was conventionally fractionated to a dose of 50.4 Gy. Both these trials are now completed and being analyzed.

The dose of gemcitabine that can be given concurrently with irradiation depends on the volume and dose of radiation. If full doses of gemcitabine (1,000 mg/m^2/wk) are given concurrently with irradiation, the dose of radiation must be makedly reduced to avoid unacceptable GI toxicity.

TREATMENT OF METASTATIC ADENOCARCINOMA

Pancreatic adenocarcinoma is still one of the most frustrating, resistant solid neoplasms to treat, and therapy for metastatic disease remains palliative. Few agents have demonstrated activity of > 10%. Moreover, most of the reported series have been small, and not all encouraging results have been duplicated.

Chemotherapy

As metastatic pancreatic carcinoma is incurable, the anticipated risks of chemotherapy, which are often substantial, must be balanced against the gains that may be achieved; unfortunately, they are few. Patients who are debilitated due to their underlying or comorbid disease should not be offered chemotherapy, as their likelihood of deriving any benefit is exceedingly slim. However, patients who desire therapy and who, while symptomatic, still have a good performance status may be offered "standard" chemotherapy (Table 2) or, if possible, should be encouraged to participate in a clinical trial.

5-FU Historically, single-agent 5-FU has been associated with a response rate of 25% in pancreatic cancer. FAM (5-FU, Adriamycin [doxorubicin], and mitomycin [Mutamycin]) and 5-FU plus doxorubicin offer no advantage over 5-FU alone. 5-FU plus leucovorin appears to be ineffective.

Gemcitabine is indicated for the treatment of locally advanced or metastatic pancreatic adenocarcinoma. Gemcitabine was compared with 5-FU in a group of 126 previously untreated patients and showed a small, but statistically significant, improvement in response rate. Median survival in the gemcitabine group was 5.7 months, with 18% of patients alive at 12 months, as compared with a median survival of 4.4 months in the group receiving 5-FU, with 2% of patients alive at 12 months. Perhaps more important, clinical benefit response (a composite measurement of pain, performance status, and weight) occurred in 23.8% of the gemcitabine-treated group, as compared with 4.8% of the 5-FU–treated group. Due to its palliative potential, gemcitabine has become the standard of care for patients with unresectable pancreatic adenocarcinoma.

A recent randomized, phase II trial of dose-intense gemcitabine administered by standard infusion vs a fixed-dose rate (10 mg/m^2/min) suggested an improved 1-year survival with the fixed-dose rate.

Three Intergroup metastatic pancreatic trials are currently accruing patients. The ECOG is about to complete a trial of gemcitabine (Gemzar) vs fixed-rate infusion gemcitabine vs fixed-rate gemcitabine plus oxaliplatin (Eloxatin, nearly 800 patients). The CALGB is comparing bevacizumab (Avastin) plus gemcitabine with gemcitabine alone, and the SWOG is accruing patients for a trial of gemcitabine with and without cetuximab (Erbitux).

Combination therapy There have been a number of recent attempts to improve the therapeutic outcome for patients with metastatic pancreatic cancer by comparing promising combinations of agents in randomized clinical trials. Unfortunately, the results have been disappointing. The ECOG compared gemcitabine with or without 5-FU, demonstrating a median survival of 5.4 months for gemcitabine vs 6.7 months for the combination; however, this difference was not statistically significant. Another trial explored the addition of irinotecan to gemcitabine. There was no survival benefit when this regimen was compared with gemcitabine alone, although the combination did increase tumor response rate (16.1% vs 4.4%, $P < .001$),

Combination trials were presented during ASCO 2004. A European study of the topoisomerase inhibitor exatecan (DX-89511) vs gemcitabine included 339 patients, showing no significant difference in survival. Furthermore, pain, quality of life, and time to tumor progression were worse in the exatecan arm. Another trial evaluated exatecan and gemcitabine vs gemcitabine alone in 349 patients. Efficacy parameters were similar for both arms of the trial.

A phase III study of 565 patients compared gemcitabine with the combination of gemcitabine plus the multitargeted antifolate pemetrexed (Alimta) and demonstrated a significant response benefit with the combination (14.8% vs 7.1%, $P = .004$). However, survival and disease progression-free survival were comparable. There was increased hematologic toxicity with the combination.

A fourth trial evaluated standard-dose gemcitabine vs a fixed-rate infusion of gemcitabine plus oxaliplatin. The trial accrued 326 patients and showed a superior response rate for the combination (26.8% vs 11.3%) and superior disease progression-free survival (5.8 vs 3.7 months). Although these results were not statistically significant, a trend toward increased survival was shown with the gemcitabine/oxaliplatin combination. Furthermore, during ASCO 2003, a trial exploring the combination of cisplatin plus gemcitabine showed no survival advantage for the combination.

Agents with marginal activity include mitomycin, doxorubicin, ifosfamide (Ifex), streptozocin (Zanosar), and docetaxel. To date, monoclonal antibody therapy and hormonal manipulation have been ineffective. A phase II study of anti–epidermal growth factor receptor (EGFR)–antibody IMC-C225 (cetuximab) combined with gemcitabine has shown a 12% partial response rate and 39% stable disease in advanced pancreatic cancer. Side effects included rash/folliculitis and fatigue. A phase III trial of the combination is accruing patients (see boxed item).

The ECOG is also exploring EGFR-directed therapy in pancreatic cancer with a new randomized phase II trial comparing docetaxel and irinotecan (CPT-11,

Camptosar) with or without cetuximab. The trial will correlate EGFR expression with outcome after therapy. Other "targeted" therapies are under investigation.

Novel approaches A progressively better understanding of the molecular biology of pancreatic cancer has revealed numerous new therapeutic targets. Areas of active current research include attempts to replace tumor-suppressor genes (ie, *p53*) and to inhibit K-*ras* protein function.

Many patients seek "complementary" or "alternative" treatment strategies. The NCI (National Cancer Institute) has activated a phase III study of gemcitabine vs intensive pancreatic proteolytic enzyme therapy with ancillary nutritional support for pancreatic cancer patients based on phase II data.

PANCREATIC ENDOCRINE TUMORS

Pancreatic endocrine tumors (PETs) cover a spectrum of neoplasms. Many, although not all, originate from the pancreatic islets of Langerhans.

PETs are not rare. Autopsy studies have documented an incidence as high as 1.5%. Most of these lesions are clinically silent.

The normal islet contains α, β, γ cells and enterochromaffin cells, which primarily secrete glucagon, insulin, somatostatin, and serotonin, respectively. All of these hormones may be secreted in excess by PETs. Other hormones that may be secreted by these tumors include vasoactive intestinal peptide (VIP), gastrin, pancreatic polypeptide (PP), and calcitonin. The aggressiveness of a PET in terms of its metastatic potential appears to be due to the cell of origin.

Approximately 20% of patients with ZES develop the syndrome in the setting of the MEN-1 syndrome. MEN-1 is inherited as an autosomal-dominant trait and is characterized by tumors of multiple endocrine organs, including the pituitary, pancreas, and parathyroid. The gene for MEN-1, which has been localized to the long arm of chromosome 11, was recently identified and named *MENIN*.

Types of tumors

Insulinomas are β-cell tumors of the pancreatic islets that produce insulin. Four-fifths of insulinomas occur as a solitary lesion, and < 10% of these tumors demonstrate malignant potential (in terms of invasiveness or the development of metastases). In patients with the multiple endocrine neoplasia type 1 (MEN-1) syndrome, insulinomas are multicentric (10% of patients). In addition, a small group of insulinomas are associated with diffuse islet-cell hyperplasia or nesidioblastosis.

Gastrinomas are gastrin-secreting tumors associated with the Zollinger-Ellison syndrome (ZES). These tumors can be either sporadic or familial. Sporadic gastrinomas do not have associated endocrinopathies, whereas hereditary gastrinomas occur in patients with MEN-1 syndrome. Patients with the sporadic form of ZES may have single or multiple gastrinomas. This finding contrasts with patients with hereditary MEN-1 PETs, who generally have a more diffuse tumor process within the pancreas.

It is known that 80%-90% of gastrinomas are located within the "gastrinoma triangle," defined as the junction of (1) the cystic and common duct, (2) the second and third portions of the duodenum, and (3) the neck and body of the pancreas. Although tumors most characteristically are located within the pancreas, a significant percentage of patients with ZES demonstrate primary tumors of the duodenal wall. Extrapancreatic and extraintestinal locations occur in approximately 10% of patients.

More than 90% of gastrinomas are malignant. The spectrum of clinical disease progression includes localized tumors, regional lymph node metastases, and widespread metastatic disease.

Other types Approximately three-quarters of VIPomas and approximately half of all glucagonomas and somatostatinomas are malignant.

'Nonfunctional' tumors Although many PETs cause considerable morbidity due to the inappropriately elevated levels of the hormones that they secrete, even "nonfunctional" PETs, ie, those without an associated demonstrable hormone-related syndrome (such as PPomas, neurotensinomas, and nonsecretory PETs), may be aggressive. Nonfunctional tumors account for up to 30% of all PETs. Two-thirds of these nonfunctional tumors will demonstrate metastatic lesions at some point during the patient's lifetime.

Signs and symptoms

The symptom complex that is observed depends on which hormone or hormones are secreted in excess.

Insulinomas are associated with symptoms of recurrent hypoglycemia. Diagnosis of these tumors is made by the demonstration of inappropriately elevated levels of insulin, proinsulin, and C peptide at the time of hypoglycemia and an elevated insulin-glucose ratio (> 0.3).

Gastrinomas Symptoms of gastrinoma-ZES are due to the effect of elevated levels of circulating gastrin. Ulceration of the upper GI tract is seen in > 90% of patients. Diarrhea is the second most common symptom. Approximately 25% of gastrinomas occur in the context of MEN-1 and are associated with parathyroid hyperplasia and hypercalcemia.

The diagnosis of ZES is established by the demonstration of hypergastrinemia (fasting serum gastrin concentration > 1,000 pg/mL) and gastric acid hypersecretion in a patient with ulcerative disease.

VIPomas VIP excess causes a profuse, watery diarrhea, hypokalemia, hypophosphatemia, and hypochlorhydria (WDHA syndrome).

Glucagonomas are associated with a rash (described as a necrotizing migratory erythema), glossitis, cheilosis, constipation and ileus, venous thrombosis, and hyperglycemia. Not all of these manifestations are secondary to elevated glucagon levels alone. The etiology of these signs and symptoms remains unknown, but some patients respond to supplemental zinc and amino acid infusions.

Somatostatinomas, which are rare, are associated with elevated blood glucose levels, achlorhydria, cholelithiasis, and diarrhea.

Tumor localization

Insulinomas Ultrasonography, CT, MRI, and selective arteriography with portal vein sampling have been utilized for the preoperative localization of insulinomas. The sensitivity of these preoperative imaging tests ranges from approximately 30% to 60%. This is because 40% of insulinomas are ≤ 1 cm and two-thirds of these tumors are < 1.5 cm.

Because the success of preoperative localization tests is disappointing and 90% of these tumors will be found and successfully resected by an experienced endocrine surgeon, there is a general trend toward performing fewer tests. Some centers utilize preoperative ultrasonography if the patient has not undergone prior pancreatic surgery. Other centers still routinely employ portal vein catheterization and angiography.

More recently, intraoperative sonography has been shown to aid the surgeon. In one series, 84% of tumors not localized preoperatively were correctly located by surgical exploration and intraoperative sonography. Many lesions not discovered by surgical palpation may be found by this technique. At present, there is much less reliance on blind distal resection than was previously advocated. Obviously, the technique of intraoperative ultrasonography may not be as helpful in the MEN-1 syndrome, in which multiple small insulinomas may be found.

Gastrinomas CT, ultrasonography, selective abdominal angiography, selective venous sampling of gastrin, intraoperative ultrasonography, EUS, and intraoperative endoscopy have all been reported to be useful in localizing gastrinomas. More recently, somatostatin receptor scintigraphy (SRS) has become a valuable tool for PET localization; several studies have suggested greater sensitivity and specificity when compared with other diagnostic tests.

Treatment

Surgery for insulinomas

For larger insulinomas in the body or tail of the pancreas, a distal pancreatectomy may be preferable to enucleation. For tumors in the head of the pancreas, enucleation of the tumor is usually possible. Patients with MEN-1 or islet-cell hyperplasia may benefit from an 80% distal pancreatectomy. If the insulinoma is not found at surgery, a blind pancreatectomy is not warranted. Further imaging and venous sampling studies may reveal the exact location of the tumor.

A surgical cure results in normal values on subsequent provocative testing, during which blood insulin and glucose concentrations are measured simultaneously. Some insulinoma recurrences actually represent persistent disease after incomplete tumor excisions or overlooked secondary multiple tumors.

Surgery for gastrinoma-ZES

The ideal treatment for gastrinoma-ZES is surgical excision of the gastrinoma. However, this approach is possible in only 20% of patients, most of whom have a sporadic tumor. With the development of effective antisecretory agents and preoperative localization with octreotide scanning, the majority of patients demonstrating widespread metastatic disease can be identified and spared surgical exploration. In addition, some series report that patients with nonmetastatic sporadic gastrinoma may have a higher incidence of extrapancreatic sites than was previously thought. One series has reported that two-thirds of gastrinomas are extrapancreatic.

Patients with sporadic gastrinoma All patients with sporadic gastrinoma should undergo localization studies and be considered for exploratory laparotomy, with the goal of potential cure of ZES. Recent evidence suggests that resection of primary gastrinoma decreases the incidence of liver metastases and ZES. Overall, surgery produces complete remission in approximately 60% of patients with sporadic ZES, and subsequent survival is excellent.

Patients with ZES and MEN-1 Some experts believe that surgery should not be used in the management of patients with MEN-1 and ZES. Instead, they recommend treatment with antisecretory medications. This approach is somewhat controversial, as some authors believe that all patients without demonstrated liver metastases should undergo surgery to remove duodenal and pancreatic gastrinomas.

Moreover, since many patients with ZES and MEN-1 die of metastatic gastrinoma at a young age, a surgical approach may be warranted. Surgery should be performed only if imaging studies localize the tumor. Although radical surgery may not provide a cure, removal of large tumors may decrease metastatic potential and increase survival.

Surgical procedure During surgery, the entire pancreas should be mobilized and scanned ultrasonographically to permit a thorough examination of the pancreatic head, duodenum, stomach, mesentery, liver, and splenic hilum. Intraoperative endoscopy with transillumination of the bowel wall may also be useful in identifying duodenal lesions. In general, enucleation is the treatment of choice, except for lesions within the duodenal wall, which may require pancreaticoduodenectomy. If no tumor is found, blind distal pancreatectomy should be avoided, since 90% of gastrinomas are located within the gastrinoma triangle.

Surgical resection of liver metastases is controversial. However, several authors have demonstrated meaningful survival in patients with small, isolated lesions. The use of ablative procedures, with open, laparoscopic, or percutaneous techniques, can reduce the neurohormonal tumor burden.

Radiation therapy for PETs

Adjuvant therapy The role of adjuvant radiation therapy for PETs of the pancreas is unclear. Because of the rarity of these lesions and their often indolent behavior, the role of this therapy will probably never be demonstrated. However, postoperative irradiation can be considered for patients with positive nodes

or microscopically close margins. Concurrent chemotherapy with such agents as 5-FU and/or streptozocin also can be considered. Radiation doses are the same as are used in adjuvant treatment of pancreatic cancer.

Palliative therapy Anecdotal reports indicate that pancreatic PETs may respond to palliative doses of irradiation. Long-term control of unresectable disease has been reported.

Chemotherapy for PETs

PETs are more sensitive to chemotherapy than are carcinoid tumors.

Single agents Agents that have demonstrated antitumor activity include recombinant human interferon alfa-2a and alfa-2b (Roferon-A, Intron A, respectively), 5-FU, doxorubicin, dacarbazine (DTIC-Dome), and streptozocin.

Combination regimens Combination chemotherapy is often more effective than monotherapy. For example, in an ECOG study, the combination of 5-FU and streptozocin demonstrated a higher response rate than streptozocin alone (63% vs 36%) in PETs, as well as a better complete response rate (33% vs 12%) and median survival duration (26.0 vs 16.5 months). Therapy with doxorubicin plus streptozocin was superior to therapy with both 5-FU plus streptozocin and single-agent chlorozotocin in terms of response and survival and is the combination most widely used in the United States. Etoposide combined with cisplatin is active in poorly differentiated neuroendocrine malignancies but is marginally effective in well-differentiated lesions.

TREATMENT OF SYMPTOMS

Octreotide

Octreotide (Sandostatin) is often successful in palliating symptoms in patients with PETs, although this success depends somewhat on the cell type. For example, insulinomas are marginally responsive to octreotide, whereas gastrinomas and VIPomas often respond. However, compared with carcinoid tumors, the median duration of response of PETs to octreotide is significantly shorter (~10 weeks).

As discussed more fully in the section on carcinoid tumors below, a promising experimental approach for patients whose tumors express somatostatin receptors is the use of octreotide conjugated to a therapeutic radioisotope.

Other agents

Omeprazole (Prilosec), an inhibitor of the function of the parietal cell hydrogen pump, is more effective than H_2-receptor antagonists in blocking gastric acid production and is useful in the symptomatic management of gastrinomas.

Other agents available for symptomatic treatment of insulinomas include diazoxide (Hyperstat), an insulin-release inhibitor, and, more recently, glucagon, by continuous infusion through a portable pump. Both of these agents are used in conjunction with frequent high-carbohydrate meals.

Patients with the glucagonoma syndrome are treated symptomatically with insulin, high-protein meals, supplemental zinc, amino acid infusions, and anticoagulants.

Hepatic arterial embolization

Hepatic arterial embolization, with or without chemotherapy (chemoembolization), is an alternative palliative therapy for patients with either carcinoid tumors or a PET who have predominant liver metastases or who are symptomatic. Embolization is best reserved for patients with < 75% tumor involvement of the liver, bilirubin level < 2 mg/dL, and an ECOG performance status of ≤ 2.

CARCINOID TUMORS OF THE GI TRACT

Carcinoid tumors typically arise from components derived from the primitive gut, lungs, and, rarely, the gonads. Approximately 85% of all carcinoids originate from the gut, predominantly the appendix, followed by the small bowel and rectum.

These tumors have the propensity to cause considerable morbidity by virtue of creating a syndrome of hormonal excess. For example, although the majority of carcinoids are hormonally inert, these neoplasms may produce excessive amounts of serotonin (from dietary tryptophan), prostaglandins, kinins (secondary to kallikrein release), and a variety of other hormones, which may account for the "carcinoid syndrome."

Signs and symptoms

Flushing The most common sign of the carcinoid syndrome is flushing, which is often triggered by alcohol, catecholamines, or emotional stress. It ranges in severity from a minor annoyance to profound vasodilatation with near syncope and hypotension.

Diarrhea is also common and is due to GI hypermotility. It usually occurs after meals and is rarely voluminous, bulky, or foul-smelling.

Abdominal cramps Diarrhea may be associated with crampy pain, although other etiologies for the pain must be considered, including bowel obstruction due to tumor or mesenteric fibrosis.

Bronchospasm Patients may also develop bronchospasm, which may be mediated by histamine. This problem is often associated with (although less common than) flushing.

Valvular heart disease A late finding is right-sided valvular heart disease, although left-sided lesions may be noted occasionally. The fibrous deposits may lead to tricuspid insufficiency and/or pulmonary stenosis. Valve replacement is rarely necessary, however.

Symptom triad If there is sufficient shunting of dietary tryptophan from niacin to serotonin synthesis, patients may develop diarrhea, dermatitis, and dementia, although this symptom triad is rare if patients maintain adequate intake of a balanced diet.

Diagnosis

Diagnostic studies include CT/MRI of the abdomen and a 24-hour urine test for 5-hydroxyindoleacetic acid (5-HIAA). Some radiologists prefer to obtain a triple-phase CT scan of the liver to detect these highly vascular liver metastases.

Octreotide scanning Indium-111 octreotide scintigraphy (OctreoScan) has been shown to have a higher sensitivity for detecting pancreatic tumors and is superior to CT or MRI for detecting metastatic disease, particularly extrahepatic disease. One study suggests that indium-111 octreotide scintigraphy can reduce costs by avoiding unnecessary surgeries. Also, a positive scan may predict which patients may benefit from treatment with somatostatin analogs (eg, octreotide). Initial studies with a new peptide tracer, indium-111 DOTA-lanreotide, suggest high tumor uptake and a more favorable dosimetry than is seen with indium-111 DTPA-D-Phel-octreotide.

Prognosis

Site and size of tumor The site of tumor origin is potentially prognostic, as most appendiceal carcinoids (75%) are < 1 cm when found and are usually cured by resection. Similarly, rectal carcinoids are usually small and completely resectable for cure.

In contrast, small bowel carcinoids tend to present at a more advanced stage, and approximately one-third have multicentric primary lesions. However, if the disease is completely resectable, patients have a 20-year survival rate of 80%; patients with unresectable intra-abdominal or hepatic metastases have median survival durations of 5 and 3 years, respectively.

Treatment

The management of carcinoid tumors focuses not only on treating bulky disease, in common with other solid malignancies, but also on treating the complications of hormonal excess.

TREATMENT OF BULKY DISEASE

Surgery

Appendiceal carcinoids For tumors that are found incidentally in the appendix and that are probably between 1 and 2 cm, appendectomy is the treatment of choice. For tumors > 2 cm, a right hemicolectomy and lymph node dissection are appropriate.

Small intestine and rectal carcinoids should be resected with a wedge lymphadenectomy to evaluate nodal disease. Duodenal lesions should be locally excised if small (< 2 cm), with radical resection reserved for larger tumors.

Tumor debulking Liver resection or ablation of liver metastases with cryotherapy or radiofrequency techniques is useful in patients with limited extrahepatic disease and/or asymptomatic carcinoid syndrome. Tumor debulking can protect liver functional reserve and improve quality of life.

Liver transplantation may be of benefit in selected patients without extrahepatic disease whose cancer progresses after other therapeutic interventions.

Radiation therapy

Carcinoid tumors are responsive to radiation therapy and frequently are well palliated with this modality. Overall, treatment with higher radiation doses (29-52 Gy) has been associated with higher response rates (40%-50%) than treatment with lower doses (10%).

Chemotherapy

Since carcinoid tumors tend to be resistant to most chemotherapeutic agents, there are no standard regimens for the treatment of unresectable tumors.

Single agents Agents that have reported activity include 5-FU, doxorubicin, and recombinant human interferon alfa-2a and alfa-2b. However, the response rate with these agents is in the range of 10%-20%, the response duration is < 6 months, and complete remission is rare.

Combination regimens Combination chemotherapy regimens represent little improvement over single-agent therapy, with response rates ranging from 25% to 35%, response durations < 9 months, and rare complete remissions.

TREATMENT OF SYMPTOMS

Somatostatin analogs

Octreotide The most active agent is the somatostatin analog octreotide. Even though native somatostatin is effective in controlling many symptoms, due to its short half-life (< 2 minutes), this agent would have to be administered via continuous infusion to be clinically useful. However, octreotide may be administered subcutaneously every 8-12 hours, facilitating outpatient therapy. The initial dose of octreotide is 100-600 μg/d in 2-4 divided doses, although the effective dose varies between patients and must be titrated to the individual patient's symptoms.

Octreotide not only is useful in managing the chronic problems of the carcinoid syndrome but also is effective in treating carcinoid crisis (volume-resistant hypotension), which may be precipitated by surgery or effective antitumor treatment.

Octreotide is well tolerated, although chronic treatment may be associated with cholelithiasis, increased fecal fat excretion, fluid retention, nausea, and glucose

intolerance. Occasional objective antitumor responses have been observed in patients who have received octreotide; the median duration of symptomatic improvement is 1 year. One report evaluating the cost-effectiveness of octreotide suggested that it may double survival time. Other somatostatin analogs, including lanreotide and vapreotide, are under investigation.

SMS 201-995 pa LAR is a long-acting somatostatin analog that allows for monthly dosing, avoiding the need for three daily injections. This new agent improves quality of life while apparently maintaining the same activity seen with daily octreotide. The usual monthly dose is 20 or 30 mg.

Patients who demonstrate disease resistance with somatostatin analog treatment alone may benefit from combination therapy with interferon-α and this somatostatin analog.

Radiolabeled somatostatin analogs A promising experimental treatment approach involves the use of octreotide or other somatostatin analogs conjugated to radioisotopes (eg, indium-111 or yttrium-90) in patients whose tumors express somatostatin receptors (eg, those with a positive OctreoScan result). This approach allows targeted in situ radiotherapy by taking advantage of internalization of the radioligand into the cell to produce DNA damage and cell death, with little effect on normal tissue. Initial reports have shown favorable results with this technique.

Other agents

Other agents that have been used for symptomatic management include H_1- and H_2-receptor antagonists, methoxamine (Vasoxyl), cyproheptadine, and diphenoxylate with atropine. The symptom complex of diarrhea, dermatitis, and dementia may be prevented or treated with supplemental niacin.

Hepatic arterial embolization

Hepatic arterial embolization with such agents as Ivalon or Gelfoam, with or without chemotherapy (chemoembolization), is an option for patients with either a carcinoid tumor or an islet-cell carcinoma who have predominant liver metastases or who are symptomatic. These lesions often are hypervascular, and, thus, peripheral hepatic embolization may provide symptomatic relief in some patients. It is unclear whether this therapy has any effect on patient survival.

ADRENOCORTICAL CARCINOMA

Adrenocortical carcinoma is a rare, highly malignant neoplasm that accounts for about 0.2% of cancer deaths. Long-term survival is dismal overall; the survival rate is 23% at 5 years and 10% at 10 years.

Etiology

The etiology of adrenocortical cancer is unknown, but some cases have occurred in families with a hereditary cancer syndrome.

Signs and symptoms

Approximately half of adrenocortical neoplasms produce hormonal and metabolic syndromes of hormone hypersecretion (such as Cushing's syndrome, virilizing or feminizing syndromes, and hyperaldosteronism). In children, Cushing's syndrome is rare but is often due to adrenal carcinoma. Mixed syndromes, such as Cushing's syndrome and virilization, strongly suggest adrenal carcinoma. The combination of hirsutism, acne, amenorrhea, and rapidly progressing Cushing's syndrome in a young female is a typical presentation. In men, estrogen-secreting tumors are associated with gynecomastia, breast tenderness, testicular atrophy, impotence, and decreased libido.

Often the diagnosis of adrenocortical carcinoma is not evident until the discovery of metastases or until the primary tumor becomes large enough to produce abdominal symptoms. Smaller tumors may be discovered incidentally, when unrelated abdominal complaints are investigated radiographically.

Treatment

Surgery

Complete surgical resection is the treatment of choice in patients with localized disease, as it offers the best chance of extending the disease-free interval and survival.

Medical therapy

Mitotane (Lysodren) is one of only a few effective agents; it exerts a specific cytolytic effect on adrenocortical cells and has been used to treat unresectable or metastatic adrenocortical carcinoma. Only 15%-30% of patients experience objective tumor regression, with a median duration of about 7 months. Mitotane is given at a dose of 4-8 g/d as tolerated, although the dose is variable.

Chemotherapy Doxorubicin has been of benefit in a limited number of patients, and combination chemotherapy is under investigation.

Suramin (Metaret), a sulfonated drug that is cytotoxic to human adrenocortical carcinoma cell lines, has been evaluated but has not proven useful in inoperable adrenocortical cancer. Innovative chemotherapy programs are clearly needed for this disease.

Controlling hormone hypersecretion Hormone hypersecretion can be controlled medically in most cases. Agents that are effective in reducing steroid production and in palliating associated clinical syndromes include the antifungal drug ketoconazole (Nizoral), 800 mg/d; aminoglutethimide (Cytadren), 1-2 g/d; and metyrapone (Metopirone), 1-4 g/d or higher as needed to control cortisol levels. These agents may be used alone or with mitotane.

PHEOCHROMOCYTOMA

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells in the adrenal medulla or extra-adrenal sympathetic ganglia. These tumors constitute a surgically correctable cause of hypertension in 0.1%-1.0% of hypertensive persons.

Only about 10% of pheochromocytomas are considered to be malignant. The vast majority (90%) of pheochromocytomas are found in the adrenal medulla, and 97% are located below the diaphragm. Approximately 10% each of pheochromocytomas are bilateral, malignant, multifocal, extra-adrenal, found in children, or associated with a familial syndrome.

Pheochromocytomas in patients with familial syndromes, such as MEN-2 and von Hippel-Lindau syndrome (VHL), are less likely to be malignant than other adrenal lesions. In contrast, pheochromocytomas in patients with a family history of malignant pheochromocytoma are more apt to be malignant.

Epidemiology and etiology

Pheochromocytomas occur in all age groups, but the incidence peaks in the third to fifth decades of life. Most pheochromocytomas (90%) are sporadic. Approximately 10% of cases are inherited as an autosomal-dominant trait, either independently or as a part of the MEN-2 syndrome; bilateral tumors are more common in this setting.

Both MEN-2A and MEN-2B include medullary thyroid carcinoma and pheochromocytoma. MEN-2A includes hyperparathyroidism, whereas MEN-2B includes ganglioneuromas and marfanoid habitus. In MEN-2 families, pheochromocytoma occurs in 5.5%-100% (mean, 40%), depending on the kindred studied. Bilateral medullary hyperplasia is almost always present. Pheochromocytomas are bilateral in 70% of cases and usually multicentric, but they are rarely extra-adrenal or malignant.

Signs and symptoms

Patients can present with various symptoms, ranging from mild labile hypertension to hypertensive crisis, myocardial infarction, or cerebral vascular accident, all of which can result in sudden death. The classic pattern of paroxysmal hypertension occurs in 30%-50% of cases; sustained hypertension may also occur and resembles essential hypertension. A characteristic presentation includes "spells" of paroxysmal headaches, pallor or flushing, tremors, apprehension, palpitations, hypertension, and diaphoresis.

Diagnosis

The diagnosis of pheochromocytoma relies on an appropriate history and documentation of excessive catecholamine production.

Catecholamine measurements Measurement of 24-hour urinary catecholamines and their metabolites, vanillylmandelic acid and metanephrine, is commonly used; the metanephrine level is considered to be the most specific single test. Serum catecholamine measurements are more susceptible to false elevations due to stress-related physiologic fluctuations. The evaluation of serum catecholamines after clonidine suppression, however, provides a useful diagnostic tool that is more convenient than urine collection. Dynamic provocative tests are rarely indicated.

Radiologic studies Almost all pheochromocytomas are localized in the abdomen, mostly in the adrenal medulla; other locations include the posterior mediastinum or any distribution of the sympathetic ganglia. After the diagnosis is established biochemically, radiologic methods may be needed for preoperative localization of the lesion; CT and MRI are most widely used. Iodine methyliodobenzyl guanidine (MIBG) and SRS provide a "functional" image; they are most helpful in the detection of occult contralateral or extra-adrenal lesions.

Differentiating benign from malignant tumors The histologic differentiation between benign and malignant lesions is extremely difficult and often impossible to make; this distinction may require the development of lymph node, hepatic, bone, or other distant metastases. Recurrent symptoms of pheochromocytoma, often emerging many years after the original diagnosis, are suggestive of malignancy. Biochemical confirmation of recurrent catecholamine hypersecretion and localization of metastatic lesion(s) with iodine-131–MIBG scan constitute diagnostic proof.

Treatment

PREOPERATIVE MEDICAL MANAGEMENT

Phenoxybenzamine (Dibenzyline), an oral, long-acting, noncompetitive α-adrenoceptor blocker, is a widely used, very helpful first drug; it is given at a dose of 10-40 mg/d. Propranolol, a β-blocker (20-80 mg/d), is usually added after a few days to prevent tachycardia or arrhythmia. The use of β-blockers alone is hazardous because they may precipitate a paradoxical rise in blood pressure. The tyrosine hydroxylase inhibitor metyrosine (Demser) may be added in patients whose blood pressure is not well controlled with the combination of an α- and a β-blocker.

SURGERY

The principles of pheochromocytoma resection are complete tumor resection, avoidance of tumor seeding, and minimal tumor manipulation. Adrenalectomy can be performed by means of an open anterior transabdominal, open posterior retroperitoneal, laparoscopic lateral transabdominal, or laparoscopic posterior retroperitoneal approach. In the past, an open anterior approach was the standard because it allowed for complete exploration and inspection for potential tumor foci. However, with the improved accuracy of preoperative imaging and increased experience with laparoscopic procedures, there is little need for exploration in areas in which a tumor has not been identified.

Except for in tumors < 6 cm, the laparoscopic approach to pheochromocytoma is probably the technique of choice. In the absence of obvious local tumor invasion or metastatic disease, a laparoscopic procedure is acceptable to many experienced endocrine surgeons.

The most critical intraoperative aspect of surgery is control of blood pressure immediately after removal of the tumor, when all agonistic effects are abolished and the effects of α- and β-blockers are still present. Close cooperation with the anesthesiologist to expand fluid volume and prepare the appropriate infusions of agonists to support vascular stability is critical.

TREATMENT OF METASTATIC MALIGNANT PHEOCHROMOCYTOMA

The treatment of choice for metastatic malignant pheochromocytoma remains problematic.

Medical and radiation therapy

Medical therapy with α- or β-blockers, as well as metyrosine, is almost always required to maintain hemodynamic stability. Chemotherapy utilizing streptozocin-based regimens or the combination of cyclophosphamide (Cytoxan, Neosar), vincristine, and dacarbazine has yielded promising responses. Treatment with iodine-131–MIBG or (in Europe) with radiolabeled somatostatin has met with only limited success. In most cases, uncontrolled catecholamine hypersecretion eventually escapes biochemical blockade, and fatal hypertensive crisis ensues.

Surgery

In those cases in which limited and resectable lesions can be identified, surgery can effect complete and lasting remission of the disease.

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CHAPTER 16

Colon, rectal, and anal cancers

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COLORECTAL CANCER

Despite the existence of excellent screening and preventive strategies, colorectal carcinoma remains a major public health problem in Western countries. An estimated 104,950 new cases of colon cancer and 40,340 cases of rectal cancer are expected to occur in the United States in 2005, with an estimated 56,290 deaths, accounting for approximately 10% of cancer deaths.

Colorectal carcinoma is the third leading cause of death from cancer in both males and females, comprising 11% of all cancers diagnosed in men and women. It also is the third most common malignancy in both men (after prostate and lung cancers) and women (after breast and lung cancers).

Colon cancer is more than 2.4 times as common as rectal cancer. Rectal cancer is defined as cancer arising below the peritoneal reflection, up to approximately 12-15 cm from the anal verge.

Epidemiology

Gender The overall incidence of colorectal cancer is nearly identical in men and women; tumors of the colon are slightly more frequent in women than in men (1.2:1), whereas rectal carcinomas are more common in men than in women (1.7:1).

Age The risk of developing colorectal tumors begins to increase at age 40 years and rises with age. In the United States, the median age at presentation is 72 years.

Race The incidence of colon carcinomas has increased by 30% in blacks since 1973 and is now higher than in whites.

Geography The incidence of colorectal carcinoma is higher in industrialized regions (the United States, Canada, the Scandinavian countries, northern and western Europe, New Zealand, Australia) and lower in Asia, Africa (among blacks), and South America (except Argentina and Uruguay).

Disease site Colon carcinomas constitute approximately 70% of all cancers in

TABLE 1: Five-year survival in colorectal cancer[a]

Time of detection	5-year survival rate (%)
In early, localized stage	90
After spread to adjacent organs or lymph nodes	67
After spread to distant sites	9

[a] Source: Cancer Facts & Figures—2005. Atlanta, American Cancer Society, 2005.

the large bowel, with occurrence in the proximal colon becoming more common.

Survival Five-year survival rates (Table 1) for patients with stages I, II, and III colorectal carcinomas have improved in recent years. This fact may be due to wider surgical resections, modern anesthetic techniques, and improved supportive care. In addition, better pathologic examination of resected specimens, preoperative staging, and abdominal exploration reveal clinically occult disease and allow treatment to be delivered more accurately. Survival also has improved through the use of adjuvant chemotherapy for colon cancer and adjuvant chemoradiation therapy for rectal cancer.

Etiology and risk factors

The specific causes of colorectal carcinoma are unknown, but environmental, nutritional, genetic, and familial factors, as well as preexisting diseases, have been found to be associated with this cancer.

Environment Asians, Africans, and South Americans who emigrate from low-risk areas assume the colon cancer risk for their adopted country, suggesting the importance of environmental factors in colorectal cancer. Smoking and alcohol intake (more than one drink per day) increase the risk of colorectal cancer.

Diet Diets rich in fat and cholesterol have been linked to an increased risk of colorectal tumors. Dietary fat causes endogenous production of secondary bile acids and neutral steroids and increases bacterial degradation and excretion of these acids and steroids, thereby promoting colonic carcinogenesis. Historically, diets rich in cereal fiber or bran and yellow and green vegetables are said to have protective effects, although recent studies have failed to prove a risk reduction with increasing dietary fiber intake. A protective role also has been ascribed to calcium salts and calcium-rich foods, because they decrease colon-cell turnover and reduce the cancer-promoting effects of bile acid and fatty acids.

Inflammatory bowel disease Patients with inflammatory bowel disease (ulcerative colitis, Crohn's disease) have a higher incidence of colorectal carcinoma. The risk of colorectal carcinoma in patients with ulcerative colitis is associated with the duration of active disease, extent of colitis, development of mucosal dysplasia, and duration of symptoms.

TABLE 2: Hereditary polyposis syndromes

Adenomatous polyposis

Familial adenomatous polyposis (FAP)

Characterized by hundreds or thousands of sessile or pedunculated polyps throughout the large intestine; histologic examination reveals microscopic adenomas; average age at onset of polyps, 25 years; at onset of symptoms, 33 years; at diagnosis, 36 years; at diagnosis of colon cancer, 42 years; extracolonic features include mandibular osteomas, upper GI polyps, and congenital hypertrophy of the retinal pigment epithelium.
An attenuated form of FAP that is clinically characterized by the presence of tens or hundreds of polyps exists

Gardner's syndrome

Same colonic manifestations as FAP; extracolonic features more evident and varied, including osteomas of the skull, mandible, and long bones; desmoid tumors; dental abnormalities; neoplasms of the thyroid, adrenal glands, biliary tree, and liver; upper GI polyps; and congenital hypertrophy of the retinal pigment epithelium; fibromatosis of the mesentery is a potentially fatal complication (occurring in 8%-13% of patients)

Turcot's syndrome

This rare syndrome is characterized by malignant colon and brain tumors. Two different types of Turcot's have been identified: one characterized by an adenomatous polyposis coli (APC) mutation resulting in colon cancer and malignant glioblastoma; the second characterized by a mismatch repair gene mutation resulting in colon cancer and astrocytoma

Hamartomatous polyposis

Peutz-Jeghers syndrome

In infancy and childhood, melanin deposits manifest as greenish-black to brown mucocutaneous pigmentation (which may fade at puberty) around the nose, lips, buccal mucosa, hands, and feet; polyps (most frequent in small intestine; also found in stomach and colon) are unique hamartomas with branching bands of smooth muscle surrounded by glandular epithelium; may produce acute and chronic GI bleeding, intestinal obstruction, or intussusception; 50% of patients develop cancer (median age at diagnosis, 50 years); ovarian cysts and unique ovarian sex-cord tumors reported (5%-12% of female patients)

Juvenile polyposis

Three forms: familial juvenile polyposis coli (polyps limited to the colon), familial juvenile polyposis of the stomach, and generalized juvenile polyposis (polyps distributed throughout the GI tract); polyps are hamartomas covered by normal glandular epithelium, found mostly in the rectum in children and sometimes in adults; may produce GI bleeding, obstruction, or intussusception; mixed juvenile/adenomatous polyps or synchronous adenomatous polyps may lead to cancer, but gastric cancer has not been reported in patients with familial juvenile polyposis of the stomach

Cowden's disease (multiple hamartoma syndrome)

Multiple hamartomatous tumors of ectodermal, mesodermal, and endodermal origin; mucocutaneous lesions are prominent and distinctive; also reported: breast lesions ranging from fibrocystic disease to cancer (50% of patients), thyroid abnormalities (10%-15%), cutaneous lipomas, ovarian cysts, uterine leiomyomas, skeletal and developmental anomalies, and GI polyps; no associated risk of cancer in GI polyps; probably does not warrant clinical surveillance

A study designed to determine the usefulness of immunohistochemical analysis for the diagnosis of mismatch repair (MMR) gene defective colorectal tumors in 172 cases of colorectal cancer detected microsatellite instability (MSI) in 13 (1.6%) tumors. All showed loss of protein expression of hMLH1 (11 of 13) or hMSH2 (2 of 13; $P < .000$). Patients with MMR-defective tumors more frequently had poorly differentiated tumors (5 of 13 [38%] vs 18 of 159 [11%]; $P = .02$) located in the ascending colon (8 of 13 [62%] vs 30 of 159 [19%]; $P = .0001$) and a personal history of other neoplasms (4 of 13 [31%] vs 18 of 159 [11%]; $P = .05$). There were no differences in age, family history of cancer, or TNM stage (*Jover R, Paya A, Alenda C, et al: Am J Clin Pathol 122:389-394,2004*).

The risk of colorectal cancer increases exponentially with the duration of colitis, from approximately 3% in the first decade to 20% in the second decade to > 30% in the third decade. Colorectal cancer risk also is increased in patients with Crohn's disease, although to a lesser extent.

Adenomatous polyps Colorectal tumors develop more often in patients with adenomatous polyps than in those without polyps. There is approximately a 5% probability that carcinoma will be present in an adenoma; the risk correlates with the histology and size of the polyp. The potential for malignant transformation is higher for villous and tubulovillous adenomas than for tubular adenomas. Adenomatous polyps < 1 cm have a slightly greater than 1% chance of being malignant, in comparison with adenomas > 2 cm, which have up to a 40% likelihood of malignant transformation.

Cancer history Patients with a history of colorectal carcinoma are at increased risk of a second primary colon cancer or other malignancy. Women with a history of breast, endometrial, or ovarian carcinoma also have an increased chance of developing colorectal cancer.

Prior surgery Following ureterosigmoidostomy, an increased incidence of colon cancer at or near the suture line has been reported. Cholecystectomy also has been associated with colon cancer in some studies but not in others.

Genetic factors The risk of developing colorectal cancer is significantly increased in several forms of inherited susceptibility (Table 2). The risks of developing colorectal cancer in the subgroups of familial or hereditary colorectal cancer vary from 15% in relatives of patients with colorectal cancer diagnosed before 45 years of age, through 20% for family members with two first-degree relatives with colorectal cancer, to approximately 70%-95% in patients with familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (HNPCC).

Familial adenomatous polyposis (FAP) is inherited as an autosomal-dominant trait with variable penetrance. Patients characteristically develop pancolonic and rectal adenomatous polyps. Approximately 50% of FAP patients will develop adenomas by 15 years of age and 95% by age 35. Left untreated, 100% of patients with FAP will develop colorectal cancer, with an average age at diagnosis ranging from 34 to 43 years. Total colectomy, usually performed on patients in their mid-to-late teens, is the preventive treatment of choice in this group of patients. The familial adenomatous polyposis coli *(APC)* gene has been localized to chromosome 5q21. Currently, it is possible to detect mutations in the

APC gene in up to 82% of families with FAP. Mutations in the *APC* gene combined with mutational activation of proto-oncogenes, especially K-*ras*, occur sequentially in the neoplastic transformation of bowel epithelium in patients with FAP. Use of cyclo-oxygenase-2 (COX-2) inhibitors such as celecoxib has been shown to reduce the number of polyps in patients with FAP.

HNPCC is transmitted as an autosomal-dominant trait. It is associated with germline mutations in one of five DNA mismatch repair genes (*MSH2*, *MLH1*, *PMS1*, *PMS2*, and *MSH6)*. The incidence a mutated mismatch repair gene is approximately 1 in 1,000 people. The Amsterdam criteria were proposed in 1991 as a way to help identify patients at risk of HNPCC. In 1999, they were revised (Amsterdam II) to recognize extracolonic manifestations as part of the family history. The criteria include the following factors:

- three or more relatives with a histologically verified HNPCC-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis), one of whom is a first-degree relative of the other two (FAP should be excluded)
- colorectal cancer involving at least two generations
- one or more colorectal cancers diagnosed before the age of 50.

The Bethesda criteria were developed based upon an analysis of high-risk patients who did not meet the Amsterdam criteria but still demonstrated germline mutations in either *MSH2* or *MLH1* gene. These criteria are much less restrictive than the Amsterdam criteria and serve to help identify those individual patients at risk of HNPCC who might benefit from further evaluation, such as the following:

- individuals with cancer in families who meet the Amsterdam criteria
- individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated extracolonic cancers; endometrial, ovarian, gastric, hepatobiliary, small bowel, or transitional cell carcinoma of the renal pelvis or ureter
- individuals with colorectal cancer and a first-degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at age younger than 45 years; and the adenoma diagnosed at age younger than 40 years
- individuals with colorectal cancer or endometrial cancer diagnosed at age < 45 years
- individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribriform) on histology diagnosed at age < 45 years
- individuals with signet ring-cell–type colorectal cancer diagnosed at age < 45 years
- individuals with colorectal adenomas diagnosed at age < 40 years.

Poynter and colleagues investigated the association between 3-hydroxy-2-methylglutaryl coenzyme A (HMG CoA)-reductase inhibitors and colorectal cancer in a population-based case-control study of incident colorectal cancer. Of 3,342 participants, 267 reported using HMG CoA-reductase inhibitors for at least 5 years. Investigators found that use of these agents was associated with a 51% reduction in the risk of colorectal cancer, and the protective effect seems to be specific to the class of lipid-lowering agents (*Poynter JN, Rennert G, Bonner JD, et al: Proc Am Soc Clin Oncol [abstract] 23:1, 2004*).

Mutations in the DNA mismatch repair genes *MLH1* or *MSH2* can be found in approximately 40% of individuals who meet these criteria. Genetic evaluation for HNPCC should be considered in families that meet the Amsterdam criteria, in affected individuals who meet the Bethesda criteria, and in first-degree relatives of those individuals with known mutations. For situations in which HNPCC is suspected but the first three Bethesda criteria are not met, microsatellite instability (MSI) testing may be considered. Over 90% of HNPCC colorectal cancers will demonstrate MSI, compared with 15%-20% of sporadic colorectal cancers, and thus a normal result in the absence of compelling clinical criteria usually excludes the diagnosis of HNPCC. Alternatively, *MSH6* may be involved in a substantial proportion of patients in whom HNPCC is suspected and should be considered in those with tumors that are low in MSI.

Chemoprevention

Chemoprevention aims to block the action of carcinogens on cells before the development of cancer.

Antioxidants and calcium Controlled trials of vitamins C and E and calcium have produced mixed results. Clinical trials have shown that calcium supplementation modestly decreases the risk of colorectal adenomas.

Nonsteroidal anti-inflammatory drugs inhibit colorectal carcinogenesis, possibly by reducing endogenous prostaglandin production through COX inhibition. Sulindac has induced regression of large bowel polyps in patients with FAP. Controlled studies have shown a reduction in the incidence of colorectal polyps with regular, long-term use of aspirin.

COX-2 inhibitors Expression of COX-2 mRNA is enhanced in tissue obtained from human colorectal adenomas and adenocarcinomas. In December 1998, the US Food and Drug Administration (FDA) approved celecoxib (Celebrex), a COX-2 inhibitor, for the chemoprevention of polyps in FAP. In December 2004, NCI stopped drug administration in an ongoing clinical trial investigating a new use of Celebrex to prevent colon polyps because of an increased risk of cardiovascular (CV) events in patients taking Celebrex versus those taking a placebo (see sidebar).

Signs and symptoms

Early stage During the early stages of colorectal cancer, patients may be asymptomatic or complain of vague abdominal pain and flatulence, which may be attributed to gallbladder or peptic ulcer disease. Minor changes in bowel movements, with or without rectal bleeding, are also seen; they are frequently ignored and/or attributed to hemorrhoids or other benign disorders.

Left colon Cancers occurring in the left side of the colon generally cause constipation alternating with diarrhea; abdominal pain; and obstructive symptoms, such as nausea and vomiting.

Right colon Right-sided colon lesions produce vague, abdominal aching, unlike the colicky pain seen with obstructive left-sided lesions. Anemia resulting from chronic blood loss, weakness, weight loss, and/or an abdominal mass may also accompany carcinoma of the right side of the colon.

TABLE 3: American Cancer Society guidelines on screening and surveillance for the early detection of colorectal adenomas and cancer—Average risk

Test	Interval (beginning at age 50)	Comment
FOBT and flexible sigmoidoscopy	FOBT annually and flexible sigmoidoscopy every 5 years	Flexible sigmoidoscopy together with FOBT is preferred over FOBT or flexible sigmoidoscopy alone. All positive tests should be followed up with colonoscopy[a]
Flexible sigmoidoscopy	Every 5 years	All positive tests should be followed up with colonoscopy[a]
FOBT	Annually	The recommended take-home multiple sample method should be used. All positive tests should be followed up with colonoscopy[a,b]
Colonoscopy	Every 10 years	Colonoscopy provides an opportunity to visualize, sample, and/or remove significant lesions
Double-contrast barium enema	Every 5 years	All positive tests should be followed up with colonoscopy

[a] If colonoscopy is unavailable, not feasible, or not desired by the patient, double-contrast barium enema (DCBE) alone or the combination of flexible sigmoidoscopy and DCBE is an acceptable alternative. Adding flexible sigmoidoscopy to DCBE may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic exam fails to reach the cecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion or does not adequately visualize the entire colorectum.

[b] There is no justification for repeating FOBT in response to an initial positive finding.

FOBT = Fecal occult blood test

Adapted with permission from Smith RA, von Eschenbach AC, Wender R, et al: CA Cancer J Clin 53:27-43, 2003.

TABLE 4: American Cancer Society guidelines on screening and surveillance for the early detection of colorectal adenomas and cancer—Increased or high risk

Risk category	Age to begin	Practice
Increased risk		
A single, small (< 1 cm) adenoma	3-6 years after initial polypectomy	Colonoscopy[a]
If the exam is normal, the patient can thereafter be screened as per average-risk guidelines.		
A large (> 1 cm) adenoma, multiple adenomas, or adenomas with high-grade dysplasia or villous change	Within 3 years after the initial polypectomy	Colonoscopy[a]
If the exam is normal, repeat examination in 3 years; if the exam is normal then, the patients can thereafter be screened as per average-risk guidelines.		
Personal history of curative-intent resection of colorectal cancer	Within 1 year after cancer resection	Colonoscopy[a]
If the exam is normal, repeat examination in 3 years; if the exam is normal then, repeat examination every 5 years.		
Either colorectal cancer or adenomatous polyps in any first-degree relative before age 60 or in two or more first-degree relatives at any age (if not a hereditary syndrome)	Age 40, or 5-10 years before the youngest case in the immediate family	Colonoscopy[a]
Every 5-10 years. Colorectal cancer in relatives more distant than first-degree relatives does not increase risk substantially above the average-risk group.		
High risk		
Family history of familial adenomatous polyposis (FAP)	12 years	Early surveillance with endoscopy and counseling to consider genetic testing
If the genetic test is positive, colectomy is indicated. These patients are best referred to a center with experience in the management of FAP.		
Family history of hereditary nonpolyposis colorectal cancer (HNPCC)	Age 21	Colonoscopy and counseling to consider genetic testing
If the genetic test is positive or if the patient has not had genetic testing, every 1-2 years until age 40, then annually. These patients are best referred to a center with experience in the management of HNPCC.		
Inflammatory bowel disease, chronic ulcerative colitis, Crohn's disease	Cancer risk begins to be significant 8 years after the onset of pancolitis or 12-15 years after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia
Every 1-2 years. These patients are best referred to a center with experience in the surveillance and management of inflammatory bowel disease.		

[a] If colonoscopy is unavailable, not feasible, or not desired by the patient, double-contrast barium enema (DCBE) alone or the combination of flexible sigmoidoscopy and DCBE is an acceptable alternative. Adding flexible sigmoidoscopy to DCBE may provide a more comprehensive diagnostic evaluation than DCBE alone in finding significant lesions. A supplementary DCBE may be needed if a colonoscopic exam fails to reach the cecum, and a supplementary colonoscopy may be needed if a DCBE identifies a possible lesion or does not adequately visualize the entire colorectum.

Adapted with permission from Smith RA, von Eschenbach AC, Wender R, et al: CA Cancer J Clin 53:27-43, 2003.

Rectum Patients with cancer of the rectum may present with a change in bowel movements; rectal fullness, urgency, or bleeding; and tenesmus.

Pelvic pain is seen at later stages of the disease and usually indicates local extension of the tumor to the pelvic nerves.

Pickhardt et al evaluated the performance characteristics of CT virtual colonoscopy for screening in 1,233 average-risk asymptomatic adults. The sensitivity of virtual colonoscopy for adenomatous polyps was 93.8% for polyps at least 10 mm in diameter, 93.9% for polyps at least 8 mm in diameter, and 88.7% for polyps at least 6 mm in diameter. The sensitivity of optical colonoscopy for adenomatous polyps was 87.5%, 91.5%, and 92.3% for the three sizes of polyps, respectively (*Pickhardt AJ, Choi JR, Hwang I, et al: N Engl J Med 349:2191-2200, 2003*).

Screening and diagnosis

Screening

Fecal occult blood testing (FOBT) Guaiac-based fecal occult blood tests are, in themselves, inexpensive but have been associated with many false-positive and false-negative results. Almost all colonic polyps and > 50% of all colorectal carcinomas go undetected because they are not bleeding at the time of the test. The newer FOBTs, including a guaiac-based product called Hemoccult SENSA and immunochemical tests for hemoglobin (HemeSelect), appear to have better sensitivity than the older tests without sacrificing specificity.

Three large randomized controlled clinical trials have demonstrated decreased colorectal cancer mortality associated with detection of earlier-stage cancer and adenomas by FOBT. Recently, results from a large trial also showed a decreased incidence of colorectal cancer associated with FOBT, largely because of increased use of polypectomy resulting from diagnostic endoscopy following positive tests.

Digital rectal examination is simple to perform and can detect lesions up to 7 cm from the anal verge.

Sigmoidoscopy Flexible proctosigmoidoscopy is safe and more comfortable than examination using a rigid proctoscope. Almost 50% of all colorectal neoplasms are within the reach of a 60-cm sigmoidoscope. Even though flexible sigmoidoscopy visualizes only the distal portion of the colorectum, the identification of adenomas can lead to colonoscopy. When we add the percentage of colorectal neoplasms in the distal 60 cm of the colorectum to the percentage of patients with distal polyps leading to complete colonoscopy, 80% of those individuals with a significant neoplasm anywhere in the colorectum can be identified.

Colonoscopy provides information on the mucosa of the entire colon, and its sensitivity in detecting tumors is extremely high. Colonoscopy can be used to obtain biopsy specimens of adenomas and carcinomas and permits the excision of adenomatous polyps. Colonoscopy is the best follow-up strategy for evaluating patients with positive guaiac-based FOBTs and the best screening modality for high-risk patients.

Limitations of colonoscopy include its inability to detect some polyps and small lesions because of blind corners and mucosal folds and the fact that sometimes

the cecum cannot be reached. A supplementary double-contrast barium enema may be needed if a colonoscopic exam fails to reach the cecum.

Some recent studies have suggested that CT virtual colonoscopy may have a sensitivity and specificity for detecting neoplastic polyps which approaches that of optical colonoscopy. Unfortunately, other studies have demonstrated clear superiority of optical colonoscopy. Until additional confirmatory studies are available, virtual CT colonoscopy should not replace routine optical colonoscopic screening.

Barium enemas can accurately detect colorectal carcinoma; however, the false-negative rate associated with double-contrast barium enemas ranges from 2% to 61% because of misinterpretation, poor preparation, and difficulties in detecting smaller lesions. A supplementary colonoscopy may be needed if double-contrast barium enema does not adequately visualize the entire colon or to obtain histopathology or perform polypectomy in the event of abnormal findings.

Recommendations for average-risk individuals Adults at average risk should begin colorectal cancer screening at age 50. The American Cancer Society (ACS) guidelines on screening and surveillance for the early detection of colorectal adenomatous polyps and cancer provide five options for screening average-risk individuals (Table 3).

For those individuals who elect FOBT alone, or in combination with flexible sigmoidoscopy, a single test of a stool sample in the clinical setting (as, for instance, is often performed with the stool sample collected on the fingertip during a digital rectal examination) is not an adequate substitute for a full set of samples using the take-home card system. Because combining flexible sigmoidoscopy with FOBT can substantially increase the benefits of either test alone, the ACS regards annual FOBT accompanied by flexible sigmoidoscopy every 5 years as a better choice than either FOBT or flexible sigmoidoscopy alone. In a recent review of the current status of emerging technologies for colorectal cancer screening, the ACS modified its guidelines for FOBT to include immunochemical tests. The ACS concluded that in comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly and are likely to produce equal or better sensitivity and specificity.

The choice of colonoscopy or double-contrast barium enema for screening may depend on factors such as personal preference, cost, and the local availability of trained clinicians to perform a high-quality examination. For those who elect either colonoscopy or double-contrast barium enema for screening, there is no need for annual FOBT. Digital rectal examination should be performed at the time of the sigmoidoscopy or colonoscopy.

Recommendations for screening increased-risk and high-risk individuals Risk of colorectal cancer is even higher among individuals with hereditary syndromes. Individuals with a history of inflammatory bowel disease of significant duration are also at increased risk.

Those individuals who have been diagnosed as having adenomatous polyps or a personal history of curative-intent resection of colorectal cancer should undergo a colonoscopy to remove all polyps from the colorectum, after which a colonoscopic

exam should be repeated at an interval to be determined on the basis of the size, multiplicity, and histologic appearance of the adenoma(s) (Table 4). If colonoscopy is not available, or not feasible, flexible sigmoidoscopy followed by double-contrast barium enema may be used for surveillance.

A family history of either colorectal cancer or colorectal adenomas increases the risk of developing colorectal cancer. Risk is higher for individuals with a family history involving first-degree relatives, those family members with younger age of onset, and those with multiple affected family members. Individuals with a single first-degree relative diagnosed with colorectal cancer or an adenomatous polyp after age 60, or with affected relatives who are more distant than first-degree relatives, can be considered to be at "average risk." In general, colonoscopy is recommended 5-10 years prior to the earliest diagnosis in the family or age 40, whichever is earlier. Subsequent colonoscopy should be repeated at intervals to be determined on the basis of the initial examination. If a colonoscopy is not available or not feasible, flexible sigmoidoscopy followed by a double-contrast barium enema can be used.

Individuals at elevated risk due to the known or likely presence of FAP or HNPCC should begin surveillance at an early age with endoscopic examinations (Table 4). There is ample evidence to support endoscopic surveillance as a method of early detection. A program of biennial colonoscopy starting at age 20 to 25 years is recommended for HNPCC carriers. For those with FAP, it is recommended that regular sigmoidoscopy start at the age of 12 years and continue at 2-year intervals. DNA testing of at-risk individuals provides the opportunity to identify those who should undergo intensive surveillance.

Individuals with a history of extensive inflammatory bowel disease affecting the colon should begin colonoscopic surveillance with biopsy for dysplasia every 1-2 years after 8 years of symptoms. Prophylactic colectomy should be considered in the presence of persistent dysplasia.

Diagnosis

Initial work-up An initial diagnostic work-up for patients suspected of having colorectal tumors should include:

- digital rectal examination and FOBT
- colonoscopy
- biopsy of any detected lesions.

Adequate staging prior to surgical intervention requires:

- chest x-ray
- CT scan of the abdomen and pelvis
- CBC with platelet count
- liver and renal function tests
- urinalysis
- measurement of carcinoembryonic antigen (CEA) level.

TABLE 5: TNM staging of colorectal cancer

TNM stage	Primary tumor[a]	Lymph node metastasis[b]	Distant metastasis[c]	Modified Astler-Coller
Stage 0	Tis	N0	M0	
Stage I	T1	N0	M0	A
	T2	N0	M0	B1
Stage IIA	T3	N0	M0	B2
IIB	T4	N0	M0	B3
Stage IIIA	T1-2	N1	M0	C1[d]
IIIB	T3-4	N1	M0	C2-3[d]
IIIC	Any T	N2	M0	C1-3[d]
Stage IV	Any T	Any N	M1	D

[a] Tis = carcinoma in situ; T1 = tumor invades submucosa; T2 = tumor invades muscularis propria; T3 = tumor invades through the muscularis propria into the subserosa or into nonperitoneal pericolic or perirectal tissues; T4 = tumor perforates the visceral peritoneum or directly invades other organs or structures

[b] N0 = no regional lymph node metastasis; N1 = metastases in one to three pericolic or perirectal lymph nodes; N2 = metastases in four or more pericolic or perirectal lymph nodes

[c] M0 = no distant metastasis; M1 = distant metastasis

[d] C1 = T2 N1, T2 N2 C2 = T3 N1, T3 N2 C3 = T4 N1, T4 N2

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th Ed. New York, Springer-Verlag, 2002.

FDG-PET scanning FDG(^{18}fluorodeoxyglucose)-PET scanning has emerged as a highly sensitive study for the evaluation of patients who may be candidates for resection of isolated metastases from colorectal cancer. Although not usually recommended in the evaluation of primary disease, this modality can aid in the staging of recurrence.

Pathology

Adenocarcinomas constitute 90%-95% of all large bowel neoplasms. These tumors consist of cuboidal or columnar epithelium with multiple degrees of differentiation and variable amounts of mucin.

Mucinous adenocarcinoma is a histologic variant characterized by huge amounts of extracellular mucus in the tumor and the tendency to spread within the peritoneum. Approximately 10% of colorectal adenocarcinomas are mucinous. It is more commonly seen in younger patients.

Signet-ring–cell carcinoma is an uncommon variant, comprising 1% of colorectal adenocarcinomas. These tumors contain large quantities of intracellular mucinous elements (causing the cytoplasm to displace the nucleus) and tend to in-

volve the submucosa, making their detection difficult with conventional imaging techniques.

Other tumor types Squamous cell carcinomas, small-cell carcinomas, carcinoid tumors, and adenosquamous and undifferentiated carcinomas also have been found in the colon and rectum. Nonepithelial tumors, such as sarcomas and lymphomas, are exceedingly rare.

Metastatic spread Colorectal carcinoma has a tendency for local invasion by circumferential growth and for lymphatic, hematogenous, transperitoneal, and perineural spread. Longitudinal spread is usually not extensive, with microscopic spread averaging only 1-2 cm from gross disease, but radial spread is common and depends on anatomic location.

There has been a considerable amount of debate in the literature regarding the therapeutic role of extended lymphadenectomy in the treatment of colon cancer. A recent retrospective review analyzed the number of lymph nodes removed from patients entered into an intergroup colon cancer trial. The survival rates for both lymph node-positive and lymph node-negative patients were significantly higher when higher numbers of lymph nodes were removed and examined. This study suggests that a therapeutic benefit may exist to extended lymphadenectomy for colon cancer (*Le Voyer TE, Sigurdson ER, Hanlon AL, et al: J Clin Oncol 21:2912-2919, 2003*).

By the time they are diagnosed, some 25% of colon cancers will have extended through the bowel wall, whereas cancers of the rectum will have spread through the bowel wall in 50%-70% of patients and metastasized to lymph nodes in 50%-60%.

The most common site of extralymphatic involvement is the liver, with the lungs the most frequently affected extra-abdominal organ. Other sites of hematogenous spread include the bones, kidneys, adrenal glands, and brain.

Staging and prognosis

The TNM staging classification, which is based on the depth of tumor invasion in the intestinal wall, the number of regional lymph nodes involved, and the presence or absence of distant metastases, has largely replaced the older Dukes' classification scheme (Table 5).

Pathologic stage is the single most important prognostic factor following surgical resection of colorectal tumors. The prognosis for early stages (I and II) is favorable overall, in contrast to the prognosis for advanced stages (III and IV). However, there appears to be a superior survival for patients with stage III disease whose disease is confined to the bowel wall (ie, ≤ T2, N+).

Histologic grade may be correlated with survival. Five-year survival rates of 56%-100%, 33%-80%, and 11%-58% have been reported for grades 1, 2, and 3 colorectal tumors, respectively.

Other prognostic factors (such as age at diagnosis, presurgical CEA level, gender, presence and duration of symptoms, site of disease, histologic features, obstruction or perforation, perineural invasion, venous or lymphatic invasion, ploidy status, and S-phase fraction) have not consistently been correlated with overall disease recurrence and survival. Furthermore, the size of the primary lesion

has had no influence on survival. Elevated expression of thymidylate synthase and allelic loss of chromosome 18 have been correlated with a poor prognosis.

Treatment

PRIMARY TREATMENT OF LOCALIZED DISEASE

Management of colorectal carcinoma relies primarily on resection of the bowel with the adjacent draining lymph nodes. The need for adjuvant systemic or local chemotherapy or immunotherapy, with or without concurrent irradiation, depends on tumor location (colon vs rectum) and stage of disease.

Surgery

Colon The primary therapy for adenocarcinoma of the colon is surgical extirpation of the bowel segment containing the tumor, the adjacent mesentery, and draining lymph nodes. Surgical resection can be performed by open or laparoscopic approach. The type of resection depends on the anatomic location of the tumor. Right, left, or transverse hemicolectomy is the surgical treatment of choice in patients with right, left, or transverse colonic tumors, respectively. Tumors in the sigmoid colon may be treated with wide sigmoid resection. The length of colon resected depends largely on the requirement for wide mesenteric nodal clearance.

Rectum For rectal carcinoma, the distal surgical margin should be at least 2 cm, although some investigators have suggested that a smaller but still negative margin may be adequate. The resection should include the node-bearing mesorectum surrounding the rectum. This procedure, which is termed total mesorectal excision (TME), is accomplished using a sharp dissection technique (see Figure 1). The use of TME has been associated with a significant reduction in local recurrence rates for patients with rectal cancer.

Posteriorly, the mesorectal dissection is carried out along the presacral fascia. Anteriorly, the dissection follows the posterior vaginal wall in females or Denonvilliers' fascia in males, both of which may be resected in the presence of an anterior wall rectal cancer. Reported rates of local recurrence following TME for rectal cancer have generally been < 10%, com-

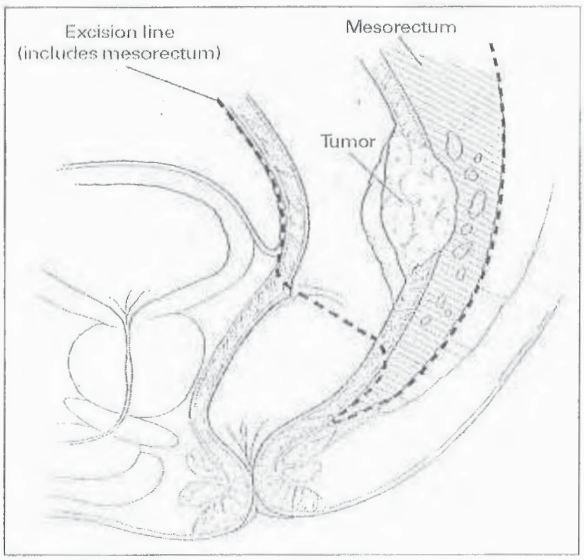

FIGURE 1: Mesorectal excision

Adapted with permission from N Engl J Med 345(9):690-692, 2001.

pared with rates of recurrence up to 30% prior to the advent of TME. Selective use of radiation therapy can improve upon the results of TME alone.

Sphincter-sparing approaches New technologies (eg, circular stapling devices) and the application of newer surgical techniques, such as coloanal anastomosis and creation of intestinal pouches, are employed to maintain anal sphincter function for tumors in the lower one-third of the rectum. If the tumor is located proximally between 6 and 15 cm from the anal verge, a low anterior resection with end-to-end anastomosis may be performed.

Abdominoperineal resection, removing the anus and sphincter muscle with permanent colostomy, may be necessary if the tumor is located in the distal rectum and other characteristics of the tumor (eg, bulky size, proximity to the sphincter musculature) preclude an oncologically adequate sphincter-sparing approach. An alternative procedure for tumors 2-5 cm from the anal verge is to resect the entire rectum, sparing the anoderm and anal sphincter musculature, and to perform a coloanal anastomosis. Either procedure can be performed with autonomic nerve preservation, minimizing bladder and sexual function morbidity.

Two prospective randomized trials involving laparoscopic colorectal resection have recently been published. A multicenter group in the United States randomized 872 patients with right, left, or sigmoid colon cancers to receive laparoscopic vs open colectomy. At 3 years of follow-up, there were no differences in recurrence rates or survival *(The Clinical Outcomes of Surgical Therapy Study Group: N Engl J Med 350:2050-2059, 2004).* A similar study randomized 403 patients with rectosigmoid carcinoma to receive laparoscopic vs open colectomy. At 5 years of follow-up, there were no differences in recurrence rates or survival *(Leung KL, Kwok SP, Lam SC, et al: Lancet 363:1187-1192, 2004).* Although the operative time for laparoscopy was longer, both studies demonstrated a reduction in postoperative hospitalization and narcotic use.

Local excision alone may be indicated for selected patients who have small (< 3-4 cm), T1, well to moderately differentiated rectal cancers without histologic evidence of lymphovascular involvement, provided that a full-thickness negative margin can be achieved. In most series, transanal excision for these good histology T1 lesions results in excellent long-term control. However, some studies with long-term follow-up demonstrated significant local recurrence rates, even with T1 lesions. For T2 or T3 tumors, the standard therapy remains a transabdominal resection because of the risk of mesorectal nodal spread. Preoperative transrectal ultrasonography is useful in defining lesions that can be resected by local excision alone. A trial sponsored by the CALGB (Cancer and Leukemia Group B) demonstrated reasonable results for patients with T2 rectal cancer undergoing negative margin local excision followed by fluorouracil (5-FU) and external-beam radiation therapy. The locoregional recurrence rate at 6 years was only 14%. Good results with local excision alone following chemoradiotherapy for rectal cancer, have been reported. The role of local excision alone in this clinical scenario awaits confirmatory studies.

Neoadjuvant therapy For rectal cancers approaching the anal sphincter, preoperative (neoadjuvant) irradiation or the combination of chemotherapy and irradiation will significantly reduce the size of the majority of tumors. This

TABLE 6: Chemotherapy regimens for colorectal adenocarcinoma

Drug/combination	Dose and schedule
Adjuvant low-dose leucovorin/fluorouracil	
Leucovorin	20 mg/m^2 IV bolus on days 1-5 immediately before fluorouracil
Fluorouracil	425 mg/m^2/d IV bolus on days 1-5
Repeat cycle at 4 weeks, 8 weeks, and then every 5 weeks for 6 cycles.	
Poon MA, O'Connell MJ, Moertel CG, et al: J Clin Oncol 7:1407–1418, 1989.	
Adjuvant high-dose leucovorin/fluorouracil	
Leucovorin	500 mg/m^2 IV infused over 2 hours every week for 6 weeks
Fluorouracil	500 mg/m^2 IV infused over 1 hour after the start of leucovorin every week for 6 weeks
Repeat cycle every 8 weeks for 6 cycles.	
Wolmark N, Rockette H, Fisher B, et al: J Clin Oncol 11:1879–1887, 1993.	
Single-agent irinotecan	
Irinotecan	125 mg/m^2 IV infused over 90 minutes weekly for 4 weeks, followed by a 2-week rest
Pitot HC, Wender DB, O'Connell MJ, et al: J Clin Oncol 15:2910–2919, 1997.	
Irinotecan	350 mg/m^2 IV infused over 90 minutes repeated every 3 weeks
NOTE: Patients with performance status of 2 or age ≥ 70 years should receive 300 mg/m^2 IV infused over 90 minutes.	
Cunningham D, Pyrhonen S, James RD, et al: Lancet 352:1413–1418, 1998.	
Irinotecan/fluorouracil/leucovorin (IFL)	
Irinotecan	125 mg/m^2 IV infused over 90 minutes once a week for 4 weeks
Fluorouracil	500 mg/m^2 IV bolus once a week for 4 weeks
Leucovorin	20 mg/m^2 IV bolus once a week for 4 weeks
Repeat cycle every 6 weeks: ie, give all of the drugs once a week for 4 weeks, followed by 2 weeks rest, and then start the cycle again.	
Saltz LB, Cox JV, Blanke C, et al: N Engl J Med 343:905–914, 2000.	
Irinotecan/fluorouracil/leucovorin (FOLFIRI)	
Leucovorin	400 mg/m^2 IV infused over 2 hours on day 1
Irinotecan	180 mg/m^2 IV infused over 90 minutes on day 1
Fluorouracil	400 mg/m^2 IV bolus on day 1
Fluorouracil	2,400 mg/m^2 46-hour IV infusion
Andre T, Louvet C, Maindrault-Goebel F, et al: Eur J Cancer 35:1343–1347, 1999.	

Drug/combination	Dose and schedule
Oxaliplatin/fluorouracil/leucovorin (FOLFOX4)	
Oxaliplatin	85mg/m^2 IVPB over 2 hours on day 1only
Leucovorin	200 mg/m^2/d over 2 hours on day 1 given simultaneously with oxaliplatin
Fluorouracil	400 mg/m^2 IV bolus over 2 to 4 minutes
Fluorouracil	600 mg/m^2 continuous infusion over 22 hours on days 1 and 2 every 14 days for 12 cycles
Andre T, Boni C, Mounedji-Boudiaf L, et al: N Engl J Med 350:2343–2351, 2004.	
Oxaliplatin/fluorouracil/leucovorin (FOLFOX6)	
Leucovorin	400 mg/m^2 IV infused over 2 hours on day 1
Oxaliplatin	100 mg/m^2 IV infused over 90 minutes on day 1
Fluorouracil	400 mg/m^2 IV bolus on day 1
Fluorouracil	2,400 mg/m^2 46-hour IV infusion
Maindrault-Goebel F, Louvet C, Andre T, et al: Eur J Cancer 35:1338–1342, 1999.	
Capecitabine/oxaliplatin (CapeOx)	
Oxaliplatin	130 mg/m^2 IV infused on day 1 only followed by
Capecitabine	1,000 mg/m^2 IV orally twice daily in the evening on day 1 to the morning of day 15
Cycle repeated every 3 weeks.	
Cassidy J, Tabernero J, Twelves C, et al: J Clin Oncol 22:2084-2091, 2004.	
Fluorouracil as an irradiation enhancer—bolus	
Leucovorin	20 mg/m^2 IV bolus on days 1-5, 29-33 immediately before fluorouracil
Fluorouracil	325 mg/m^2/d IV bolus on days 1-5, 29-33
Hyams DM, Mamounas EP, Petrelli N, et al: Dis Colon Rectum 40:131–139, 1997.	
Fluorouracil as an irradiation enhancer— continuous infusion	
Fluorouracil	225 mg/m^2/d IV continuous infusion during irradiation
O'Connell MJ, Martenson JA, Wieand HS, et al: N Engl J Med 331:502–507, 1994.	
Irinotecan/fluorouracil/leucovorin (IFL) with bevacizumab	
Irinotecan	125 mg/m^2 IV once a week for 4 weeks, cycle repeated every 6 weeks
Fluorouracil	500 mg/m^2 IV once a week for 4 weeks, cycle repeated every 6 weeks
Leucovorin	20 mg/m^2 IV once a week for 4 weeks, cycle repeated every 6 weeks
Bevacizumab	5 mg/kg IV every 2 weeks
Hurwitz H, Fehrenbacher L, Novotny W, et al: N Engl J Med 350:2335–2342, 2004.	

Continued on following page

Drug/combination	Dose and schedule
Fluorouracil and leucovorin plus bevacizumab	
Leucovorin	500 mg/m^2 IV infused over 2 hours once a week for 6 weeks, then a 2-week rest period
Fluorouracil	500 mg/m^2 IV bolus slow push 1 hour after leucovorin infusion once a week for 6 weeks, then a 2-week rest period
Bevacizumab	5 mg/kg IV continuous infusion over 90 minutes every 2 weeks

Kabbinavar F, Hurwitz H, Fehrenbacher I, et al: J Clin Oncol 21:60–65, 2003.

Cetuximab with or without irinotecan	
Cetuximab	400 mg/m^2 initial dose followed by 250 mg/m^2 weekly
OR	
Irinotecan	350 mg/m^2 every 3 weeks, 180 mg/m^2 every 2 weeks, or 125 mg/m^2 weekly for 4 weeks
Cetuximab	400 mg/m^2 initial dose followed by 250 mg/m^2 weekly
Repeat cycle every 6 weeks.	

Cunningham D, Humblet Y, Siena S, et al: Proc Am Soc Clin Oncol 22:252 (abstract 1012), 2003.

Compared with 5-FU and leucovorin, capecitabine (Xeloda) provides an equivalent or superior benefit in the adjuvant treatment of resected stage III colon cancer. Patients in the capecitabine arm also experienced fewer severe toxicities, including less stomatitis and neutropenic fever/sepsis (*Cassidy J, Scheithauer W, McKendrick H, et al: Proc Am Soc Clin Oncol [abstract] 23:247S, 2004*).

approach allows for sphincter-preserving surgery in many patients. In addition, the long-term morbidity of radiation therapy for rectal cancer may be reduced if it is administered prior to surgery. The use of preoperative chemotherapy and radiation therapy is particularly important for patients presenting with locally advanced, unresectable rectal cancer, as the disease of the majority will be rendered resectable following neoadjuvant therapy. One additional role of neoadjuvant therapy may be in facilitating transanal excision of T2 and T3 rectal cancers in poor surgical risk patients. A number of investigators have reported good results with transanal excision of T2 and T3 tumors following a complete response to neoadjuvant therapy. However, this approach cannot be considered the current standard of care.

Laparoscopic colonic resection The use of laparoscopic colonic resection is becoming an oncologically acceptable method of treating cancers of the colon. The potential advantages include a shorter hospital stay, reduced postoperative ileus, decreased time away from work, fewer adhesive complications, and a lower risk of hernia formation. The potential disadvantages compared with open transabdominal resection include longer operative time, higher operative costs, and technical considerations related to operative skill.

Patterns of failure

The natural history and patterns of failure following "curative" resection are different for colon and rectal carcinomas. Locoregional failure as the only or major site of recurrence is common in rectal cancer, whereas colon cancer tends to recur in the peritoneum, liver, and other distant sites, with a lower rate of local failure. As a result, local therapy, such as irradiation, may play a significant role in the treatment of rectal tumors but is not used routinely for colon cancers.

ADJUVANT THERAPY FOR COLON CANCER

Approximately 75% of all patients with colorectal carcinoma will present at a stage when all gross carcinoma can be surgically resected. Nevertheless, despite the high resectability rate, almost half of all patients with colorectal adenocarcinoma die of metastatic disease, primarily because of residual disease that is not apparent at the time of surgery. These individuals are candidates for adjuvant local or systemic therapies.

Systemic chemotherapy

Systemic combined chemotherapy is the principal adjuvant therapy for colon cancer (Table 6). The administration of single-agent 5-FU or floxuridine (fluorodeoxyuridine [FUDR]) in patients with stage II or III tumors following surgical resection has failed to show a survival advantage over postoperative observation.

5-FU plus levamisole (Ergamisol) 5-FU combined with levamisole, an antihelminthic agent with nonspecific immunostimulating properties, was the first adjuvant regimen to demonstrate a decrease in the recurrence rate and an increase in disease-free and overall survival in patients with stage III colon cancer. This combination is given over 1 year. It has largely been replaced by 5-FU and leucovorin, a combination with equivalent activity that can be given over 6 months.

5-FU plus leucovorin Studies have demonstrated the benefits of 5-FU plus leucovorin (folinic acid) in the adjuvant treatment of colon carcinomas. Acceptable adjuvant regimens of 5-FU plus leucovorin for colon cancer include:

- a "low-dose" leucovorin (Mayo Clinic) regimen, consisting of leucovorin (20 mg/m^2) immediately followed by 5-FU (425 mg/m^2), both given by rapid IV injections daily for 5 consecutive days, with courses repeated every 4 weeks for 6 months
- a "high-dose" weekly leucovorin regimen, consisting of 5-FU (500 mg/m^2) by rapid IV injection given at 1 hour during a 2-hour infusion of leucovorin (500 mg/m^2) weekly for 6 weeks, with courses repeated every 8 weeks for 6 cycles. More recently, completed randomized trials by the National Surgical Adjuvant Breast and Bowel Project (NSABP) have used three rather than six cycles of therapy

An analysis of survival data from patients with stage II or III disease treated in four consecutive NSABP adjuvant chemotherapy trials showed similar relative

reductions in disease recurrence and mortality as well as similar improvements in overall survival in patients with stage II and III disease.

5-FU and leucovorin plus other agents The addition of other agents to 5-FU and leucovorin is currently being assessed.

Monoclonal antibody 17 1A (edrecolomab) A randomized study of 17 1A antibody in patients with stage III colon cancer showed it to be inferior to 5-FU and leucovorin. Its addition to 5-FU and leucovorin did not improve disease-free or overall survival. A trial of the antibody in stage II colon cancer recently completed accrual. No results are yet available from this trial.

Irinotecan (CPT-11, Camptosar) The addition of irinotecan to 5-FU and leucovorin is being assessed in a phase III trial. (See discussion of irinotecan under treatment of advanced colon cancer.) A recent letter to investigators involved in the phase III trial of bolus 5-FU and leucovorin with or without irinotecan reported no benefit to the addition of irinotecan. Until further details are provided, irinotecan should not be used in the adjuvant setting outside a clinical trial.

Oxaliplatin (Eloxatin) has been approved by the FDA for first-line therapy of advanced colorectal cancer and has been evaluated for resected stage II and III colon cancer in a phase III trial from Europe (MOSAIC). The use of FOLFOX compared with the same infusional regimen without oxaliplatin led to a higher 3-year disease-free survival rate in those receiving FOLFOX. This clinical trial led to the recent approval of oxaliplatin for adjuvant therapy in Europe. (See further discussion about oxaliplatin in the first-line setting under treatment of advanced colon cancer.)

Radiation therapy

Postoperative irradiation to the tumor bed should be considered in patients with T3 node-positive and T4 (B3 or C3) tumors located in retroperitoneal portions of the colon because more than 30% of these patients develop a local recurrence. Retrospective studies suggest improved local control with irradiation, particularly in patients with positive resection margins. However, an underpowered intergroup trial failed to show a benefit to adjuvant chemotherapy and irradiation compared with adjuvant chemotherapy alone in selected patients with T3 node-positive and T4 disease. The 5-year disease-free survival in both groups was 51%.

ADJUVANT THERAPY FOR RECTAL CANCER

Local recurrence alone or in combination with distant metastases occurs in up to 50% of patients with rectal carcinoma. Nodal metastases and deep bowel wall penetration are significant risk factors for locoregional failure.

In the absence of nodal metastases, the rate of local recurrence may be as low as 5%-10% for stage I rectal cancer and 15%-30% for stage II tumors. In stage III disease, the incidence of pelvic failure increases to 50% or more. The use of TME significantly reduces this risk of local recurrence; however, local recurrence remains a concern in patients with stages II and III disease.

Local recurrence in the pelvis is complicated by involvement of contiguous organs, soft and bony tissue, and deep nodal disease. Presenting symptoms vary from vague pelvic fullness to sciatica related to mass effect in the fixed space of the bony pelvis and invasion of the sciatic nerve.

Because local recurrence in the absence of metastatic disease is more common in rectal cancer than in colon cancer, aggressive resections, such as pelvic exenteration (anterior and posterior), sacral resection, and wide soft-tissue and pelvic floor resection, have been employed to treat these recurrences. Modern techniques of pelvic floor reconstruction, creation of continent urinary diversion, and vaginal reconstruction may be required for functional recovery.

The recent findings of the NSABP R-02 trial indicated postoperative adjuvant chemotherapy resulted in similar survival rates to those of postoperative chemoradiation therapy but was associated with a significantly higher rate of locoregional failure.

Radiation therapy alone

Radiation therapy has been used to reduce the locoregional recurrence rate of rectal tumors. Preoperative radiation therapy has been demonstrated to reduce local tumor recurrence, even in patients undergoing TME surgery. However, with the exception of one recent study, preoperative therapy has not affected overall survival in patients with stage II or III rectal cancer. An improvement in local control also has been observed with postoperative irradiation, but again with no benefit with regard to disease-free or overall survival.

Chemoradiation therapy

Postoperative chemoradiation therapy Clinical trials of surgical adjuvant treatment indicate that postoperative radiation therapy with concurrent chemotherapy (chemoradiation therapy) is superior to postoperative radiation therapy alone or surgery alone. Postoperative chemoradiation therapy is a standard of care for patients with stage II or III rectal cancer based largely on the findings of the North Central Cancer Treatment Group (NCCTG) and Gastrointestinal Tumor Study Group (GITSG) trials. A summary of the 5-year survival results of the Patterns of Care Study (PCS) of the American College of Radiology and the results of the National Cancer Data Base (NCDB), both of which are representative of American national averages, is shown in Table 7.

The most effective combination of drugs, optimal mode of administration, and sequence of irradiation and chemotherapy still need to be determined. Radiation doses of 45-55 Gy are recommended in combination with 5-FU–based chemotherapy. Postoperative bolus 5-FU administration with irradiation is inferior to protracted venous infusion, resulting in lower 3-year rates of both overall survival (68% vs 76%) and disease-free survival (56% vs 67%).

An adjuvant treatment combining chemotherapy and pelvic irradiation in patients with stage II or III disease used the following regimen: 5-FU, 500 mg/m^2/d administered as a rapid IV infusion on days 1-5 and 450 mg/m^2/d on days 134-138 and days 169-173. Patients received a protracted IV infusion of 5-FU,

TABLE 7: Five-year overall survival in Patterns of Care Study (PCS) vs the National Cancer Data Base (NCDB), Gastrointestinal Tumor Study Group (GITSG), and Mayo/North Central Cancer Treatment Group (Mayo/NCCTG) studies

Study	5-year survival	
Bimodality vs trimodality	**S + RT**	**S + RT + CT**
Stage II		
PCS	61%	81%
NCDB	55%	62%
Stage III		
PCS	33%	65%
NCDB	39%	42%
Postop CRT vs postop RT	**Postop RT**	**Postop CRT**
GITSG (7175)	52%	59%
Mayo/NCCTG (7945)	48%	57%
PCS	50%	69%

S = surgery; RT = radiation therapy; CT = chemotherapy; CRT = concurrent irradiation therapy and chemotherapy

Adapted from Coia LR, Gunderson LL, Haller D, et al: Cancer 86:1952–1958, 1999.

225 mg/m^2/d, by portable ambulatory infusion pump during the entire period of pelvic irradiation. Pelvic radiation therapy began on day 64 with a multiple-field technique to the tumor bed and nodal groups. A total of 4,500 cGy in 180-cGy fractions was administered over a 5-week period. Patients received a minimal boost dose of 540 cGy to the entire tumor bed, adjacent nodes, and 2 cm of adjacent tissue. A second boost dose of 360 cGy was allowed in selected patients with excellent displacement of the small bowel.

Preoperative vs postoperative chemoradiation therapy Preoperative chemoradiation therapy may be preferred to postoperative adjuvant treatment, particularly in patients with T3 or T4 lesions. Such treatment may enhance resectability and may be associated with a lower frequency of complications compared with postoperative treatment. In a recent report of a randomized trial conducted by the German Rectal Cancer Study, Sauer et al found that compared with postoperative chemoradiotherapy, preoperative chemoradiotherapy significantly decreased local failure (7% vs 11%, $P = .02$) and sphincter preservation in low-lying tumors (39% vs 19%, $P < .004$). In addition, the incidence of chronic anastomotic recurrence was also lowest in the preoperative chemoradiotherapy group (2.7% vs 8.5%, $P = .001$).

TREATMENT OF ADVANCED COLON CANCER

Surgery

Local recurrences from colon cancers usually occur at the site of anastomosis, in the resection bed, or in the contiguous and retroperitoneal (para-aortic, para-

caval) lymph nodes. Anastomotic recurrences heralded by symptoms are the most curable, followed by local soft-tissue recurrences. Regional and retroperitoneal lymph node recurrences portend a poor prognosis and systemic disease.

Metastasectomy Metastases to the liver and lungs account for most cases of non-nodal systemic disease in colorectal cancer. Resection of metastases, or metastasectomy, has gained recognition as a viable treatment. Resection of liver metastases results in cure rates of 5%-60%, depending on the number of metastases and stage of disease. Resection of solitary metastases in patients with stage I or II disease results in a 5-year survival rate of ~40%.

Adjuvant therapy after resection of hepatic metastases has been assessed in several randomized trials. Intra-arterial administration of floxuridine, using a hepatic artery catheter, alternating with systemic 5-FU and leucovorin, improves overall survival and reduces the risk of recurrence within the liver.

Chemotherapy The development of chemotherapy for colorectal cancer has become a very active field (Table 6). After decades of 5-FU–based treatment, and of little clinical gains, the arrival of new, effective agents has significantly changed the way this cancer is treated. Although 5-FU remains the backbone of most regimens, the new agents irinotecan and oxaliplatin are rapidly becoming an important part of front-line treatment of this disease in the United States and abroad. The rapid development of newer agents, such as the molecular-targeted agents, holds the promise that progress will continue in chemotherapy for colorectal cancer.

5-FU, synthesized by Heidelberger in 1957, remains an important agent in the treatment of advanced colon carcinoma. 5-FU may be administered as a bolus injection either weekly or daily for 5 days, every 4-5 weeks. With these regimens, response rates have been approximately 10%-15%. The development of permanent venous access devices and portable infusion pumps has permitted the continuous infusion of 5-FU on an outpatient basis. Commonly used continuous infusion regimens of 5-FU are 750-1,000 mg/m^2/d for 5 days. Protracted infusions have administered 5-FU at 200-400 mg/m^2/d for up to 12 weeks.

The pattern of 5-FU toxicity differs depending on whether it is administered as a bolus or continuous infusion than by other methods. Bolus administration has pronounced myelotoxic effects, whereas the dose-limiting toxic effects of continuous infusion 5-FU are mucositis and diarrhea. Palmar-plantar erythrodysesthesia (hand-foot syndrome) has been reported with protracted infusions.

Overall, the incidence of side effects is significantly lower when 5-FU is delivered by continuous infusion. A meta-analysis of more than 1,200 patients treated with either continuous infusion or bolus regimens of 5-FU demonstrated superior response rates and a small survival advantage for the continuous infusion regimens.

A randomized phase III trial of the anti-VEGF antibody bevacizumab, combined with IFL, resulted in a significantly higher median survival, disease progression-free survival, and overall response rate compared with bevacizumab plus placebo *(Hurwitz H, Fehrenbacher L, Novotny W, et al: N Engl J Med 350:2335-2342, 2004).*

TABLE 8: NCCN recommendations for post-treatment surveillance/monitoring*

- History and physical examination every 3 months for 2 years, then every 6 months for a total of 5 years
- CEA level evaluation every 3 months for 2 years, then every 6 months or years 2-5 for T2 or greater lesions
- Colonoscopy in 1 year, repeat in 1 year if results are abnormal or at least every 2-3 years if results are negative for polyps. If no preoperative colonoscopy has been performed due to an obstructing lesion, colonoscopy in 3-6 months
- Abdominal/pelvic CT scan in addition to chest x-ray or chest CT for patients with resected stage IV disease only:

  Every 6 months for 2 years, then every 6-12 months for a total of 5 years

* http://www.nccn.org

CEA = carcinoembryonic antigen; NCCN = National Comprehensive Cancer Network

Two large randomized trials demonstrated improved response rates and overall survival for the combination of 5-FU plus leucovorin and irinotecan (discussed later in this chapter).

Biochemical modulation of 5-FU Interest in the biochemical modulation of 5-FU by leucovorin is based on preclinical studies demonstrating that leucovorin raises the level of N_5,N_{10}-methylenetetrahydrofolate and, thus, forms a stable tertiary complex of thymidylate synthase (TS), the folate coenzyme, and 5-FU (in the form of 5-fluorodeoxyuridine). The use of 5-FU with leucovorin results in higher response rates than 5-FU alone and may prolong survival.

Although there is no agreement as to the optimal dose of leucovorin, two dosing schedules have been approved by the FDA:

- "low-dose" leucovorin regimen, consisting of leucovorin, 20 mg/m^2/d, immediately followed by 5-FU, 425 mg/m^2/d
- "high-dose" leucovorin regimen, consisting of leucovorin, 200 mg/m^2/d, immediately followed by 5-FU, 370 mg/m^2/d

With both schedules, leucovorin and 5-FU are administered by rapid IV injections daily for 5 consecutive days. Courses of both schedules are repeated at 4 weeks, 8 weeks, and every 5 weeks thereafter. There is no survival difference between these two regimens.

Irinotecan, a novel topoisomerase I inhibitor synthesized from *Camptotheca acuminata,* a tree that is native to China, has significant clinical activity in metastatic colorectal cancer patients whose disease has recurred or spread after standard chemotherapy. Its FDA approval was based on two phase III trials showing that irinotecan (350 mg/m^2 once every 3 weeks) significantly increased survival, compared with best supportive care and infusional 5-FU, respectively, in patients with recurrent or progressive cancer following first-line 5-FU therapy.

TABLE 9: TNM classification of anal canal tumors

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 2 cm in greatest dimension
T2	Tumor > 2 cm but not > 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor of any size that invades adjacent organs (eg, vagina, bladder, urethra, bladder)[a]
Regional lymph nodes (N)	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in perirectal lymph node(s)
N2	Metastasis in unilateral internal iliac and/or inguinal lymph node(s)
N3	Metastasis in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes
Distant metastasis (M)	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Grade (G)	
Gx	Grade of differentiation cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Stage groupings			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
	T3	N0	M0
Stage IIIA	T1-3	N1	M0
	T4	N0	M0
Stage IIIB	T4	N1	M0
	Any T	N2-3	M0
Stage IV	Any T	Any N	M1

[a] Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th Ed. New York, Springer-Verlag, 2002.

Irinotecan increased the median survival by 27% and 41%, respectively, in the two trials.

Irinotecan is active in patients whose disease progressed while receiving 5-FU. Reproducible 15%-20% response rates in this patient population led to the approval of irinotecan for use in patients with 5-FU–refractory disease. The dosage schedules most commonly used are 125 mg/m^2 weekly for 4 weeks, followed by a 2-week rest period (United States), and 350 mg/m^2 every 3 weeks (Europe).

The primary toxicities of irinotecan are diarrhea and neutropenia. Intensive loperamide is important in the management of the former complication. An initial 4-mg loading dose is given at the first sign of diarrhea, followed by 2-mg doses every 2 hours until diarrhea abates for at least a 12-hour period.

5-FU plus leucovorin and irinotecan The results of two large randomized trials comparing the combination of 5-FU plus leucovorin and irinotecan vs 5-FU plus leucovorin in the first-line treatment of metastatic colorectal cancer have been reported. Both trials demonstrated improved response rates and overall survival for the three-drug combination. The two trials used different schedules and were conducted in different locations, yet their results were remarkably consistent. The response rates for the three-drug combination ranged from 35%-40%, and the median time to disease progression was approximately 7 months.

This combination of irinotecan, 5-FU, and leucovorin is one option for patients with metastatic colorectal cancer. Based on its superior activity, compared with 5-FU and leucovorin, the FDA approved this combination as first-line treatment for patients with metastatic colorectal cancer in 2000.

A portion of patients receiving bolus infusions of irinotecan, 5-FU, and leucovorin will develop severe and life-threatening diarrhea and neutropenia shortly after the initiation of therapy. Careful monitoring and prompt intervention are essential with the initiation of this combination.

Capecitabine (Xeloda) is an oral fluorinated pyrimidine FDA approved for use in advanced colon cancer. It is converted to 5-FU through a three-step process after ingestion. In a phase III trial of previously untreated patients with metastatic colon cancer, capecitabine produced higher response rates than 5-FU and leucovorin. Overall survival and time to disease progression were similar (noninferior) to those with 5-FU and leucovorin. The recommended dose of capecitabine is 2,500 mg/m^2 each day, given as a twice-daily dose, for 14 days followed by a 1-week rest period. The side effects of capecitabine tend to be similar to those seen with prolonged infusion of 5-FU, with hand-foot syndrome being the most common.

Oxaliplatin is a new diaminocyclohexane platinum that has undergone clinical investigation in Europe and the United States. Oxaliplatin has demonstrated activity in patients with pretreated, 5-FU–resistant colorectal cancer when used alone (10% response rate) or in combination with 5-FU (45% response rate). In patients with untreated metastatic colon cancer, response rates of 27% have been reported with oxaliplatin alone, and rates as high as 57% have been noted

when the drug is combined with 5-FU. Patients receiving oxaliplatin, infusional 5-FU, and leucovorin have achieved overall survivals of > 20 months in several reported trials. However, many of these patients have received second- and even third-line therapies at the time of disease progression. Oxaliplatin's toxicity profile includes nausea/vomiting and cumulative, reversible peripheral neuropathy. Patients may also develop a reversible, cold-induced, acute pharyngolaryngeal neuropathy.

Oxaliplatin combined with infusional 5-FU and leucovorin was approved by the FDA in 2002 as second-line therapy for patients with disease progression after treatment with irinotecan, 5-FU, and leucovorin. This approval was based on an improved time to disease progression compared with that of either oxaliplatin alone or infusional 5-FU and leucovorin.

A multicenter, randomized phase III study (ASCO 2002, 2003) showed improved outcome with regard to response rate, time to disease progression, and overall survival for patients receiving first-line therapy for metastatic colorectal cancer with oxaliplatin, infusional 5-FU, and leucovorin, compared with irinotecan, 5-FU, and leucovorin. At the time of the 2003 presentation, the time to disease progression for the oxaliplatin combination was 8.7 months, compared with 6.9 months for the irinotecan combination. The oxaliplatin regimen also had a significantly better overall survival (19.5 vs 14.8 months) and response rate (45% vs 31%). Based on the results of this trial, in January 2004, the FDA approved oxaliplatin with infusional 5-FU and leucovorin as first-line therapy.

Molecular-targeted agents A variety of monoclonal antibodies and small molecules are being evaluated in clinical trials and preclinical studies. Two of these agents (cetuximab [Erbitux] and bevacizumab [Avastin]) have been FDA approved for use.

Cetuximab is a human/mouse chimeric antibody directed against the epithelial growth factor receptor (EGFR). In a randomized trial of patients with colorectal cancer refractory to irinotecan, patients were randomized to receive either cetuximab and irinotecan or cetuximab alone. The addition of cetuximab to irinotecan led to a significantly higher response rate compared with cetuximab alone. The median survival for those receiving cetuximab and irinotecan was also longer. Based on the results of this study, cetuximab has been approved by the FDA for use in patients whose disease is refractory to irinotecan with tumors expressing EGFR.

Bevacizumab is a humanized monoclonal antibody that binds circulating vascular endothelial growth factor (VEGF). When given with either 5-FU and leucovorin or irinotecan, 5-FU, and leucovorin (IFL) as first-line therapy in patients with metastatic colorectal cancer, bevacizumab led to improved outcome. The addition of bevacizumab to 5-FU and leucovorin resulted in significant improvement in disease progression-free survival. Even better results were seen with IFL. The addition of bevacizumab to IFL resulted in significant improvement in overall survival and response rate. These studies led to the FDA approval of bevacizumab. It is indicated for use in first-line therapy for metastatic colorectal cancer when combined with 5-FU–based chemotherapy.

Intrahepatic floxuridine administration Renewed interest in regional delivery of floxuridine into the liver has followed the introduction of effective implantable infusion pumps. These pumps allow chemotherapeutic agents to be delivered in higher concentration directly into the hepatic artery.

Randomized trials have shown a considerably higher therapeutic response rate with intrahepatic administration (IA) of floxuridine than with systemic therapy. A meta-analysis of studies comparing IV vs IA fluorinated pyrimidines in patients with unresectable, liver-confined, metastatic disease has indicated a small advantage for IA therapy.

Intrahepatic chemotherapy is costly and associated with gastroduodenal mucosal ulceration, hepatitis, and sclerosing cholangitis. The addition of dexamethasone to floxuridine infusions appears to decrease biliary sclerosis.

TREATMENT OF ADVANCED RECTAL CANCER

Radiation therapy

Radiation therapy is moderately effective in palliating advanced rectal cancer symptoms. Pain is decreased in 80% of irradiated patients, although only 20% report complete relief. Bleeding can be controlled in more than 70% of patients. Obstruction cannot be reliably relieved by irradiation, and diverting colostomy is recommended. Only 15% of patients with recurrent rectal cancers achieve local disease control with irradiation, and median survival is < 2 years.

Chemoradiation therapy may be useful to convert fixed unresectable lesions into resectable lesions. These regimens have generally used protracted infusions of 5-FU (200-250 mg/m^2/d) delivered via a portable infusion pump during pelvic radiation therapy (450 cGy over 5 weeks).

Intraoperative radiotherapy (localized irradiation given to the tumor or tumor bed at the time of resection) is under active investigation in advanced and locoregionally recurrent rectal cancer.

Laser photoablation

Laser photoablation is occasionally employed for temporary relief of obstructive rectal cancer in patients who are not surgical candidates because of the presence of distant metastases, surgical comorbidity, or extensive intra-abdominal disease.

Follow-up of long-term survivors

Patients who have completed therapy for colorectal cancer require monitoring for potential treatment-related complications, recurrent disease, and new metachronous cancers. Specific follow-up recommendations for these patients are controversial. Guidelines for post-treatment surveillance/monitoring adopted by the National Comprehensive Cancer Network (NCCN), a consortium of 19 American cancer centers, are shown in Table 8.

ANAL CANAL CARCINOMA

Epidemiology, etiology, and risk factors

In the United States, about 3,990 new cases of anal canal carcinoma are diagnosed each year. Overall, it is slightly more common in women than men. More than 80% of anal canal tumors occur in individuals > 60 years of age. Recent epidemiologic studies suggest that receptive anal intercourse is strongly related to anal cancer.

The incidence rate of anal cancer for single men is reported to be six times that for married men. In people < 35 years old, anal carcinoma is more common in men than women. A history of genital warts has been observed, suggesting that papillomavirus may be an etiologic factor.

Signs and symptoms

The diagnosis of anal canal carcinoma is usually delayed because the symptoms (bleeding, pain, and sensation of mass) are so often attributed to benign anorectal disorders, such as hemorrhoids or anal fissures.

Diagnosis

Evaluation should include a careful rectal examination, endoscopic examination with description of lesion size, and assessment of whether there is invasion of disease into adjacent organs (vagina, urethra, or bladder). Reexamination under general anesthesia may be necessary. A diagnostic incisional biopsy is required.

Pelvic CT is suggested to evaluate pelvic nodes. Although distant metastases are uncommon at diagnosis, a chest x-ray and liver function tests are recommended. Suspicious inguinal nodes discovered on physical examination must be assessed pathologically. The incidence of inguinal nodal metastases at diagnosis varies from 13% to 25%. The presence of perirectal, inguinal, and pelvic lymph node involvement correlates with tumor size and is unusual for tumors < 2 cm in diameter. Formal groin dissection is not advised; needle aspiration should be performed, with limited surgical biopsy if results of aspiration are inconclusive.

Pathology

Squamous cell carcinomas Most anal canal malignancies are squamous cell carcinomas. They have been classified as cloacogenic carcinomas, basaloid carcinomas, transitional cell carcinomas, or mucoepidermoid carcinomas. However, there is little difference in the natural history of these various types.

Unusual tumors arising in the anal canal include small-cell carcinomas, anal melanomas, and adenocarcinomas.

Small-cell carcinomas of the anal canal are aggressive neoplasms similar in natural history to bronchogenic small-cell carcinomas. If such a histology is identified, the clinician should be alerted to the possibility of early distant metastases, and treatment should include chemotherapeutic regimens used in bronchogenic small-cell carcinomas.

Anal melanomas Although advanced anal melanomas generally are associated with a dismal survival, prognosis may be related to the depth of disease penetration. Early anal melanomas < 2.0 mm in depth can be cured with wide excision. More advanced disease can be treated with local excision and external-beam irradiation with excellent local control. Abdominoperineal resection is indicated only rarely in the management of anal melanoma.

Adenocarcinomas are uncommon cancers associated with a poor prognosis. Treatment should be aggressive and based on a multimodality approach. The rarity of this tumor precludes the development of specific clinical trials.

Staging

Size of the primary tumor is the most important clinical predictor of survival for patients with anal carcinomas. Both the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC) have agreed on a unified staging system (Table 9). The TNM classification distinguishes between anal canal carcinoma and anal margin tumors, since the latter exhibit biologic behavior similar to that of other skin cancers and are staged as skin cancers.

Treatment

Surgery

In selected individuals with small superficial tumors, local excision has achieved adequate local control and survival. However, most studies of local excision have been retrospective, with small numbers of patients. Prior to the advent of primary radiotherapy and combined-modality treatment (see later in this chapter), abdominoperineal resection was considered to be the conventional treatment for patients with invasive anal canal cancer. Unfortunately, even with radical surgical procedures, local recurrences are frequent. Currently, radical extirpative surgery is indicated only after the failure of combined-modality treatment.

Radiation therapy

Trials of primary external-beam radiotherapy in patients with anal canal carcinomas have used doses varying between 4,500 and 7,550 cGy. Local control rates of 60%-90%, with 5-year survival rates of 32%-90%, are similar to the results of surgical series when the trials are controlled for tumor size.

Interstitial radiation therapy alone has been used primarily in Europe for early-stage lesions. A relatively high radiation dose is delivered to a small volume.

TABLE 10: Chemotherapy regimens for anal canal cancer

Drug/combination	Dose and schedule
Fluorouracil/mitomycin/radiation therapy	
Fluorouracil	1 g/m^2/d IV infused continuously on days 1-4 and 29-32
Mitomycin	15 mg/m^2 IV on day 1
Irradiation	200 cGy/d for 5 days per week (total dose, 3,000 cGy)
Give chemotherapy concurrently with irradiation; start both modalities on the same day.	
Leichman L, Nigro ND, Vaitkevicius VK, et al: Am J Med 78:211–215, 1985.	
Fluorouracil/cisplatin/radiation therapy	
Fluorouracil	1 g/m^2/d IV infused continuously for 4 days
Cisplatin	25 mg/m^2/d IV on days 2-5 following standard hydration
Give chemotherapy concurrently with irradiation, except in elderly or frail patients.	
Wagner JP, Mahe MA, Romestaing P, et al: Int J Radiat Oncol Biol Phys 29:17–23, 1994.	

Table prepared by Ishmael Jaiyesimi, DO

This modality carries a high potential for radiation necrosis and fails to incorporate treatment of the inguinal nodes.

Combined-modality treatment

Chemotherapy given concurrently with irradiation is the preferred therapy for most patients with anal canal cancer (Table 10). Investigators from Wayne State University pioneered the use of simultaneous pelvic irradiation and chemotherapy in the treatment of patients with anal canal carcinomas. They demonstrated that the majority of such patients could be treated with this combination, obviating the need for an abdominoperineal resection. The original study design used 3,000 cGy over 3 weeks with 5-FU (1,000 mg/m^2/d) as a continuous infusion on days 1-4 and then repeated on days 29-32. Mitomycin (Mutamycin), 15 mg/m^2, was administered as an IV bolus on day 1. A total of 4 to 6 weeks after the completion of therapy, patients had a deep muscle biopsy of the anal canal scar.

An updated analysis of this experience demonstrated that 38 of 45 patients (84%) were rendered disease free after chemotherapy and irradiation. Individuals who had positive biopsies underwent an abdominoperineal resection.

Because of the success of this experience, other investigators have attempted to implement infusional 5-FU and mitomycin with irradiation as definitive therapy. Most studies have used similar schedules of 5-FU and mitomycin but have used higher doses of pelvic irradiation (4,500-5,700 cGy). Five-year survival rates > 70% have been reported.

A randomized trial from the Radiation Therapy Oncology Group (RTOG) showed that the use of mitomycin with irradiation and 5-FU increased complete tumor regression and improved colostomy-free survival over irradiation

and 5-FU alone. At 4 years, the colostomy-free survival rate was higher in the mitomycin arm than in the 5-FU–alone arm (71% vs 59%), as was the disease-free survival rate (73% vs 51%).

Several investigators have compared the results of irradiation alone vs irradiation plus chemotherapy. Cummings et al found that with identical irradiation doses and techniques, the local control rate for cancers > 2 cm rose from 49% with radiation therapy alone to 85% when 5-FU and mitomycin were combined with irradiation. Papillon and Montbarbon found an increase in the rate of local control with a combined-modality approach, as compared with pelvic irradiation alone (81% vs 66%). Two recent randomized studies have shown improved local control with chemoradiation therapy over irradiation.

A complete response to combined chemotherapy and radiation therapy is expected in 80%-90% of patients with anal cancer. It is important to evaluate the response of therapy with a careful examination and biopsy of the anal canal after treatment. Anal canal cancers can continue to regress for up to 3 or more months after completion of treatment. For this reason, it is recommended that a biopsy be performed no sooner than 3 months after the completion of treatment. If localized persistent disease is identified after initial treatment, or if subsequent recurrence is diagnosed, abdominoperineal resection is expected to yield long-term disease control and survival in 40%-60% of patients.

Chemotherapy

Reports of other chemotherapeutic agents in anal cancer have been relatively anecdotal, with limited phase II studies. Because of the activity of cisplatin in other squamous cell carcinomas, this agent has been employed as a single agent or combined with infusional 5-FU in advanced disease.

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CHAPTER 19

Urothelial and kidney cancers

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UROTHELIAL CANCER

In the year 2005, an estimated 63,210 new cases of bladder cancer will be diagnosed in the United States, and approximately 13,180 patients will die of this disease.

Urothelial cancers encompass carcinomas of the bladder, ureters, and renal pelvis; these cancers occur at a ratio of 50:3:1, respectively. Cancer of the urothelium is a multifocal process. Patients with cancer of the upper urinary tract have a 30%-50% chance of developing cancer of the bladder at some time in their lives. On the other hand, patients with bladder cancer have a 2%-3% chance of developing cancer of the upper urinary tract. The incidence of renal pelvis tumors is decreasing.

Epidemiology

Gender Urothelial cancers occur more commonly in men than in women (3:1) and have a peak incidence in the seventh decade of life.

Race Cancers of the urothelial tract are also more common in whites than in blacks (2:1).

Etiology and risk factors

Cigarette smoking The major cause of urothelial cancer is cigarette smoking. A strong correlation exists between the duration and amount of cigarette smoking and cancers at all levels of the urothelial tract. This association holds for both transitional cell and squamous cell carcinomas.

Analgesic abuse Abuse of compound analgesics, especially those containing phenacetin, has been associated with an increased risk of cancers of the urothelial tract. This risk appears to be greatest for the renal pelvis, and cancer at this site is usually preceded by renal papillary necrosis. The risk associated with analgesic abuse is seen after the consumption of excessive amounts (5 kg).

Chronic urinary tract inflammation also has been associated with urothelial cancers. Upper urinary tract stones are associated with renal pelvis cancers.

Chronic bladder infections can predispose patients to cancer of the bladder, usually squamous cell cancer.

Occupational exposures have been associated with an increased risk of urothelial cancers. Workers exposed to arylamines in the organic chemical, rubber, and paint and dye industries have an increased risk of urothelial cancer similar to that originally reported for aniline dye workers.

Balkan nephropathy An increased risk of cancer of the renal pelvis and ureters occurs in patients with Balkan nephropathy. This disorder is a familial nephropathy of unknown cause that results in progressive inflammation of the renal parenchyma, leading to renal failure and multifocal, superficial, low-grade cancers of the renal pelvis and ureters.

Genetic factors There are reports of families with a higher risk of transitional cell cancers of the urothelium, but the genetic basis for this familial clustering remains undefined.

Signs and symptoms

Hematuria is the most common symptom in patients presenting with urothelial tract cancer. It is most often painless, unless obstruction due to a clot or tumor and/or deeper levels of tumor invasion have already occurred.

Urinary voiding symptoms of urgency, frequency, and/or dysuria are also seen in patients with cancers of the bladder or ureters but are uncommon in patients with cancers of the renal pelvis.

Vesical irritation without hematuria can be seen, especially in patients with carcinoma in situ of the urinary bladder.

Symptoms of advanced disease Pain is usually a symptom of more advanced disease, as is edema of the lower extremities secondary to lymphatic obstruction.

Diagnosis

Initial work-up The initial evaluation of a patient suspected of having urothelial cancer consists of excretory urography, followed by cystoscopy. In patients with upper tract lesions, retrograde pyelography can better define the exact location of lesions. Definitive urethroscopic examination and biopsy can be accomplished utilizing rigid or flexible instrumentation.

At the time of cystoscopy, urine is obtained from both ureters for cytology, and brush biopsy is obtained from suspicious lesions of the ureter. Brush biopsies significantly increase the diagnostic yield over urine cytology alone. Also, at the time of cystoscopy, a bimanual examination is performed to determine whether a palpable mass is present and whether the bladder is mobile or fixed.

Evaluation of a primary bladder tumor In addition to biopsy of suspicious lesions, evaluation of a bladder primary tumor includes biopsy of selected mucosal sites to detect possible concomitant carcinoma in situ. Biopsies of the

primary lesion must include bladder wall muscle to determine whether there is invasion of muscle by the overlying carcinoma.

CT For urothelial cancers of the upper tract or muscle invasive bladder cancers, a CT scan of the abdomen/pelvis is performed to detect local extension of the cancer and involvement of the abdominal lymph nodes.

Bone scan For patients with bone pain or an elevated alkaline phosphatase level, a radioisotope bone scan is performed.

A chest x-ray completes the staging evaluation.

Pathology

Transitional cell carcinomas constitute 90%-95% of urothelial tract cancers.

Squamous cell cancers account for 3%-7% of urothelial carcinomas and are more common in the renal pelvis and ureters.

Adenocarcinomas account for a small percentage (< 3%) of bladder malignancies and are predominantly located in the trigone region. Adenocarcinomas of the bladder that arise from the dome are thought to be urachal in origin.

Carcinoma in situ In approximately 30% of newly diagnosed bladder cancers, there are multiple sites of bladder involvement, most commonly with carcinoma in situ. Although carcinoma in situ can occur without macroscopic cancer, it most commonly accompanies higher disease stages.

When carcinoma in situ is associated with superficial tumors, rates of recurrence and disease progression (development of muscle invasion) are higher (50%-80%) than when no such association is present (10%). Carcinoma in situ involving the bladder diffusely without an associated superficial tumor is also considered an aggressive disease. Most patients with this type of cancer will develop invasive cancers of the bladder.

Staging and prognosis

Staging system Urothelial tract cancers are staged according to the American Joint Committee on Cancer (AJCC) TNM classification system (Table 1). Superficial bladder cancer includes papillary tumors that involve only the mucosa (Ta) or submucosa (T1) and flat carcinoma in situ (Tis). The natural history of superficial bladder cancer is unpredictable, and recurrences are common. Most tumors recur within 6-12 months and are of the same stage and grade, but 10%-15% of patients with superficial cancer will develop invasive or metastatic disease.

Prognostic factors For carcinomas confined to the bladder, ureters, or renal pelvis, the most important prognostic factors are T stage and differentiation pattern. The impact of associated carcinoma in situ on Ta and T1 lesions is discussed above (see section on "Pathology"). Less-differentiated Ta-T1 lesions also are associated with higher recurrence and progression rates. Patients with well-differentiated Ta lesions without carcinoma in situ have a 95%

TABLE 1: TNM staging of urothelial tract cancers

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Ta		Noninvasive papillary tumor
Tis		Carcinoma in situ: "flat tumor"
T1		Tumor invades subepithelial connective tissue
T2		Tumor invades muscle
	pT2a	Tumor invades superficial muscle (inner half)
	pT2b	Tumor invades deep muscle (outer half)
T3		Tumor invades perivesical tissue
	pT3a	Microscopically
	pT3b	Macroscopically (extravesical mass)
T4		Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, abdominal wall
	T4a	Tumor invades prostate, uterus, vagina
	T4b	Tumor invades pelvic wall, abdominal wall
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional node involvement
N1		Metastasis in a single node, ≤ 2 cm in greatest dimension
N2		Metastasis in a single node, > 2 cm but ≤ 5 cm in greatest dimension; or multiple lymph nodes, none > 5 cm in greatest dimension
N3		Metastasis in a lymph node, > 5 cm in greatest dimension
Distant metastasis (M)		
Mx		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping

Stage 0a	Ta	N0	M0
Stage 0is	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2a	N0	M0
	T2b	N0	M0
Stage III	T3a	N0	M0
	T3b	N0	M0
	T4a	N0	M0
Stage IV	T4b	N0	M0
	Any T	N1-N3	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

survival rate, whereas those with high-grade T1 lesions have a 10-year survival rate of 50%.

Muscle invasive carcinoma carries a 5-year survival rate of 20%-50%. When regional lymph nodes are involved, the 5-year survival rate is 0%-20%.

Treatment

TREATMENT OF LOCALIZED DISEASE

Surgical approaches to superficial bladder cancer

Transurethral resection Most patients with superficial bladder cancer can be treated adequately with transurethral resection (TUR). Such procedures preserve bladder function, entail minimal morbidity, and can be performed repeatedly. Survival rates > 70% at 5 years are expected. Although TUR removes existing tumors, it does not prevent the development of new lesions. Patients should be followed closely.

Laser The neodymium:yttrium-aluminum-garnet (Nd:YAG) laser has achieved good local control when used in the treatment of superficial bladder tumors. However, it has not been adopted for general use because of its limitations in obtaining material for staging and grading of tumors.

Partial cystectomy is an infrequently utilized treatment option for patients whose tumors are not accessible or amenable to TUR.

Radical cystectomy is generally not used for the treatment of superficial bladder tumors. The indications for radical cystectomy include:

- Unusually large tumors that are not amenable to complete TUR, even on repeated occasions
- Some high-grade tumors
- Multiple tumors or frequent recurrences that make TUR impractical
- Symptomatic diffuse carcinoma in situ (Tis) that proves unresponsive to intravesical therapy
- Prostatic stromal involvement.

Intravesical therapy The indications for intravesical therapy include:

- Stage T1 tumors, especially if multiple
- Multifocal papillary Ta lesions, especially grade 2 or 3
- Diffuse carcinoma in situ (Tis)
- Rapidly recurring Ta, T1, or Tis disease.

In the United States, four intravesical agents are commonly used: thiotepa, an alkylating agent; bacillus Calmette-Guérin (BCG), an immune modulator/stimulator; and mitomycin (Mutamycin) and doxorubicin, both antibiotic chemotherapeutic agents. The dose of BCG varies with the strain (50 mg [Tice] or 60 mg [Connaught]). Mitomycin doses range from 20 to 40 mg.

Although all four agents reduce the tumor recurrence rate, BCG is the most effective. For the treatment of papillary Ta and T1 lesions, BCG and mitomycin have the greatest efficacy (complete response rate, approximately 50%). For the treatment of carcinoma in situ (Tis), BCG is extremely effective.

Surgical approaches to invasive bladder cancer

Radical cystectomy Invasive bladder cancer (stage II or higher) is best treated by radical cystectomy. Candidates for radical cystectomy include:

- Patients with muscle-invasive tumor (depth of invasion is not important, merely its presence), regardless of grade
- Patients with high-grade, invasive, lamina propria tumors with evidence of lymphovascular invasion, with or without carcinoma in situ (Tis)
- Patients with diffuse carcinoma in situ or recurrent superficial cancer who do not respond to intravesical therapy.

In men, radical cystectomy includes en bloc pelvic lymph node dissection and removal of the bladder, seminal vesicles, and prostate. In women, radical cystectomy entails en bloc pelvic lymph node dissection and anterior exenteration, including both ovaries, fallopian tubes, uterus, cervix, anterior vaginal wall, bladder, and urethra.

Partial cystectomy is an infrequently utilized treatment option and should only be considered when there is a solitary lesion in the dome of the bladder and when random biopsy results from remote areas of the bladder and prostatic urethra are negative.

Urethrectomy is routinely included in the anterior exenteration performed in female patients. Urethrectomy in male patients is performed if the tumor grossly involves the prostatic urethra or if prior TUR biopsy results of the prostatic stroma are positive. Delayed urethrectomy for positive urethral cytology or biopsy is required in about 10% of male patients.

Urinary reconstruction may involve any one of the following: intestinal conduits (eg, ileal, jejunal, or colonic), continent cutaneous diversion (eg, Indiana pouch, Kock pouch), or orthotopic reconstruction (in both male and female patients).

Surgical approaches to ureteral and renal pelvic tumors

Optimal surgical management of urothelial malignancies of the ureter and renal pelvis consists of nephroureterectomy with excision of a bladder cuff. Some tumors may respond well to local resection, and tumor specifics may allow for a more conservative intervention.

Upper ureteral and renal pelvic tumors (because of similar tumor behavior and anatomic aspects) may be considered as a group, whereas lower ureteral tumors may be considered as a separate group.

Upper ureteral and renal pelvic tumors are best treated with nephroureterectomy. Solitary, low-grade upper tract tumors may be considered for seg-

mental excision or ureteroscopic surgery if close surveillance is feasible. Care should be exercised, however, as multicentricity is more probable and the risk of recurrence is greater than for lower ureteral lesions.

Lower ureteral lesions may be managed by nephroureterectomy, segmental resection, and neovesical reimplantation or by endoscopic resection. A 15% recurrence rate is seen after segmental resection or endoscopic excision. Careful follow-up is mandatory. Disease progression, the development of a ureteral stricture precluding periodic surveillance, and poor patient compliance are indications to abandon conservative management and perform nephroureterectomy.

ROLE OF RADIATION THERAPY

Radiation therapy for bladder cancer

Primary radiation or chemoradiation therapy Radiation therapy, either alone or in conjunction with chemotherapy, is the modality of choice for patients whose clinical condition precludes surgery, either because of extensive disease or poor overall status. Trials have shown that patients treated with irradiation and cisplatin with or without fluorouracil (5-FU) have improved local control, as compared with patients treated with irradiation alone.

Other studies suggest that TUR followed by radiation therapy combined with cisplatin or 5-FU chemotherapy, with cystectomy reserved for salvage, provides a survival equivalent to that achieved with initial radical cystectomy while allowing for bladder preservation in many patients. The extent of TUR and the absence of hydronephrosis are important prognostic factors in studies of bladder-conserving treatment. Updates from institutions in Europe and the United States on over 600 patients with long-term follow-up support the durability of outcomes previously reported.

A randomized phase III study of bladder preservation with or without neoadjuvant chemotherapy following TUR, conducted by the Radiation Treatment Oncology Group (RTOG), revealed no advantage to the use of MCV (methotrexate, cisplatin, and vinblastine) before radiation therapy and concurrent cisplatin. The favorable outcome without neoadjuvant chemotherapy may make bladder preservation a more acceptable option for a wider range of patients.

Preoperative irradiation may improve survival in patients undergoing radical cystectomy. Its use is limited due to concern over complications occurring with the urinary diversions currently utilized.

Radiation dose and technique Initially, a pelvic field is treated to 4,500 cGy utilizing a four-field box technique, with 180 cGy delivered daily. The bladder tumor is then boosted to a total dose of 6,480 cGy utilizing multifield techniques, with 180 cGy delivered daily.

TABLE 2: Chemotherapy regimens for bladder carcinoma

Drug/combination	Dose and schedule
M-VAC	
Methotrexate	30 mg/m^2 IV on days 1, 15, and 22
Vinblastine	3 mg/m^2 IV on days 2, 15, and 22
Adriamycin (doxorubicin)	30 mg/m^2 IV on day 2
Cisplatin	70 mg/m^2 IV on day 2

NOTE: Reduce doxorubicin dose to 15 mg/m^2 in patients who have received prior pelvic irradiation. On days 15 and 22, methotrexate (30 mg/m^2) and vinblastine (3 mg/m^2) are given only if the WBC count is > 2,500 cells/mL and the platelet count is > 100,000 cells/mL.

Repeat cycles every 28-32 days even if the interim dose is withheld due to myelosuppression or mucositis.

Loehrer PJ Sr, Einhorn LH, Elson PJ, et al: J Clin Oncol 10:1066–1073, 1992.

Paclitaxel/carboplatin	
Paclitaxel	200 mg/m^2 IV infused over 3 hours
Carboplatin	Dose calculated by the Calvert formula to an area under the curve (AUC) of 5 mg/mL/min IV infused over 15 minutes after paclitaxel

Repeat cycle every 21 days.

PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, and diphenhydramine, 50 mg IV, both 30-60 minutes prior to paclitaxel.

Redman B, Smith D, Flaherty L, et al: J Clin Oncol 16:1844–1848, 1998.

Gemcitabine/cisplatin	
Gemcitabine	1 g/m^2 IV on days 1, 8, and 15
Cisplatin	75 mg/m^2 IV on day 1

Repeat cycle every 28 days.

Kaufman D, Stadler W, Carducci M, et al: Proc Am Soc Clin Oncol 17:320a, 1998.

Radiation therapy for renal pelvic and ureteral cancers

In patients with renal pelvic and ureteral lesions who have undergone nephroureterectomy, postoperative local-field irradiation is offered if there is periureteral, perirenal, or peripelvic extension or lymph node involvement. A dose of approximately 4,500-5,040 cGy is delivered utilizing multifield techniques.

Palliative irradiation

Palliative radiation therapy is effective in controlling pain from local and metastatic disease and in providing hemostatic control. A randomized study comparing 3,500 cGy in 10 fractions vs 2,100 cGy in 3 hypofractionated treatments revealed high rates of relief of hematuria, frequency, dysuria, and nocturia with either regimen. In selected cases of bladder cancer, aggressive palliation to approximately 6,000 cGy may be warranted to provide long-term local control. Concurrent chemotherapy, such as cisplatin, should be considered.

Drug/combination	Dose and schedule
PCG	
Paclitaxel	200 mg/m^2 IV infused over 3 hours on day 1
Carboplatin	Dose calculated on AUC of 5, 15-minute IV infusion on day 1
Gemcitabine	800 mg/m^2 30-minute IV on days 1 and 8
Repeat cycle every 21 days.	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel; and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.	
Hussain M, Vaishampayan U, Du W, et al: J Clin Oncol 19:2527–2533, 2001.	
Paclitaxel/cisplatin	
Paclitaxel	135 mg/m^2 IV infused over 3 hours
Cisplatin	70 mg/m^2 IV infused over 2 hours
Repeat cycle every 3 weeks until disease progression or for a maximum of 6 cycles.	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as ranitidine, 50 mg IV, or cimetidine, 300 mg IV, prior to paclitaxel, and diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel.	
Burch PA, Richardson RI, Cha SS, et al: Proc Am Soc Clin Oncol 18:1266a, 1999.	
TCG	
Taxol (paclitaxel)	80 mg/m^2 IV infused over 1 hour on days 1 and 8
Cisplatin	70 mg/m^2 on day 1
Gemcitabine	1 g/m^2 IV on days 1 and 8
Repeat cycle every 21 days.	
PREMEDICATIONS: Dexamethasone, 20 mg PO, 12 and 6 hours prior to paclitaxel; as well as diphenhydramine, 50 mg IV, 30 minutes prior to paclitaxel, and either cimetidine, 300 mg IV, or ranitidine, 50 mg IV, 30 minutes prior to paclitaxel.	
Vaishampayan U, Smith D, Redman B, et al: Proc Am Soc Clin Oncol 18:333a (abstract 1282), 1999.	
Table prepared by Ishmael Jaiyesimi, DO	

CHEMOTHERAPY FOR ADVANCED DISEASE

Treatment of advanced metastatic urothelial cancer is palliative. Cisplatin, paclitaxel, and gemcitabine (Gemzar) have all demonstrated single-agent activity for the systemic treatment of this disease. A randomized trial showed an advantage for a regimen of M-VAC (methotrexate, vinblastine, Adriamycin [doxorubicin], and cisplatin) over cisplatin alone with regard to disease progression-free and overall survival. Combination regimens with cisplatin or carboplatin (Paraplatin), usually with paclitaxel or gemcitabine or in combination with methotrexate and vinblastine with or without doxorubicin, produce

response rates of 40%-60% in patients with advanced disease, with a median survival of 12-14 months (Table 2). In another randomized trial, the combination of gemcitabine and cisplatin exhibited equivalent survival to M-VAC in metastatic bladder cancer but was clinically better tolerated. The role of combination chemotherapy in the adjuvant treatment of resected urothelial cancer remains undetermined and an area of clinical research. A randomized trial of neoadjuvant M-VAC in locally advanced resectable bladder cancer showed a trend in survival favoring M-VAC over surgery alone, but it was not statistically significant.

KIDNEY CANCER

Approximately 36,160 new cases of renal cell carcinoma will be diagnosed in the year 2005 in the United States, with an associated 12,660 deaths. There has been a steady increase in the incidence of renal cell carcinoma that is not explained by the increased use of diagnostic imaging procedures. Mortality rates have also shown a steady increase over the past 2 decades.

Epidemiology

Gender and age This malignancy is twice as common in men as in women. Most cases of renal cell carcinoma are diagnosed in the fourth to sixth decades of life, but the disease has been reported in all age groups.

Ethnicity Renal cell carcinoma is more common in persons of northern European ancestry than in those of African or Asian descent.

Etiology and risk factors

Renal cell carcinoma occurs most commonly as a sporadic form and rarely as a familial form. The exact etiology of sporadic renal cell carcinoma has not been determined. However, smoking, obesity, and renal dialysis have been associated with an increased incidence of the disease.

Genetic factors More recently, a genetic basis has been sought for this disease.

von Hippel-Lindau disease, an autosomal-dominant disease, is associated with retinal angiomas, CNS hemangioblastomas, and renal cell carcinoma.

Chromosomal abnormalities Deletions of the short arm of chromosome 3 (3p) occur commonly in renal cell carcinoma associated with von Hippel-Lindau disease. In the rare familial forms of renal cell carcinoma, translocations affecting chromosome 3p are uniformly present. Sporadic renal cell carcinoma of the nonpapillary type is also associated with 3p deletions.

Associated malignancy Two studies from large patient databases have reported a higher-than-expected incidence of both renal cell cancer and lymphoma. No explanation for this association has been found.

Signs and symptoms

Renal cell carcinoma has been associated with a wide array of signs and symptoms. The classic triad of hematuria, flank mass, and flank pain occurs in only 10% of patients and is usually associated with a poor prognosis. With the routine use of CT scanning for various diagnostic reasons, renal cell carcinoma is being diagnosed more frequently as an incidental finding.

Hematuria More than half of patients with renal cell carcinoma present with hematuria.

Other common signs/symptoms Other commonly associated signs and symptoms of renal cell carcinoma include normocytic/normochromic anemia, fever, and weight loss.

Less common signs/symptoms Less frequently occurring, but often described, signs and symptoms include polycythemia, hepatic dysfunction not associated with hepatic metastasis, and hypercalcemia. Although not a common finding at the time of diagnosis of renal cell carcinoma, hypercalcemia ultimately occurs in up to 25% of patients with metastatic disease.

Diagnosis

Contrast-enhanced CT scanning has virtually replaced excretory urography and renal ultrasonography in the evaluation of suspected renal cell carcinoma. In most cases, CT imaging can differentiate cystic from solid masses and also supplies information about lymph nodes and renal vein/inferior vena cava (IVC) involvement.

Ultrasonography is useful in evaluating questionable cystic renal lesions if CT imaging is inconclusive.

Venography and MRI When IVC involvement by tumor is suspected, either IVC venography or MRI is needed to evaluate its extent. MRI is currently the preferred imaging technique for assessing IVC involvement at most centers.

Renal arteriography is not used as frequently now as it was in the past in the evaluation of suspected renal cell carcinoma. In patients with small, indeterminate lesions, arteriography may be helpful. It is also used by the surgeon as part of the preoperative evaluation of a large renal neoplasm.

Percutaneous cyst puncture is used in the evaluation of cystic renal lesions that are thought to be potentially malignant on the basis of ultrasonography or CT imaging. Percutaneous cyst puncture permits the collection of cyst fluid for analysis, as well as the evaluation of cyst structure via instillation of contrast medium after fluid removal. Benign cyst fluid is usually clear to straw-colored and low in protein, fat, and lactic dehydrogenase (LDH) content, whereas malignant fluid is usually bloody with high protein, fat, and LDH content.

Evaluation of extra-abdominal disease sites includes a chest x-ray. In the face of a normal chest x-ray, CT imaging of the chest adds no further helpful

information. A bone scan is required if a patient has symptoms suggestive of bone metastasis and/or an elevated alkaline phosphatase level.

Pathology

Renal cell carcinoma arises from the proximal renal tubular epithelium. Histologically, renal cell carcinoma can be of various cellular types: clear cell, granular cell, and sarcomatoid (spindle) variant. The majority of these tumors are mixtures of clear and granular cell types. Approximately 1%-6% of renal cell carcinomas are of the sarcomatoid variant, which is a more aggressive malignancy with a worse prognosis.

Staging and prognosis

Staging system The preferred staging system for renal cell carcinoma is the TNM classification (Table 3).

Prognostic factors The natural history of renal cell carcinoma is highly variable. However, approximately 30% of patients present with metastatic disease at diagnosis, and one-third of the remainder will develop metastasis during follow-up.

Five-year survival rates after nephrectomy for tumors confined to the renal parenchyma (T1/2) are > 80%. Renal vein involvement without nodal involvement does not affect survival. Lymph node involvement and/or extracapsular spread is associated with a 5-year survival of 10%-25%. Patients with metastatic disease have a median survival of 1 year and a 5-year survival of 0%-20%.

Treatment

Surgery

Radical nephrectomy is the established therapy for localized renal cell carcinoma. At surgery, the kidneys, adrenal gland, and perirenal fat (structures bound by Gerota's fascia) are removed. Also, limited regional lymph node dissection is often performed for staging purposes. Partial nephrectomy is considered in patients for whom a radical nephrectomy would result in permanent dialysis.

Since complete resection is the only known cure for renal cell carcinoma, even in locally advanced disease, surgery is considered if the involved structures can be safely removed. In the presence of metastatic disease, surgery is generally considered for palliation only. However, in patients with metastatic disease who are candidates for cytokine therapy and have a good performance status, a debulking nephrectomy may benefit survival by several months.

Radiation therapy for renal cell carcinoma

Primary radiation therapy Radiation therapy may be considered for palliation as the primary therapy for renal cell carcinoma in patients whose clinical

TABLE 3: TNM staging of renal cell carcinoma

Primary tumor (T)		
Tx		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor ≤ 7 cm in greatest dimension, limited to the kidneys
	T1a	Tumor ≤ 4 cm in greatest dimension, limited to the kidneys
	T1b	Tumor > 4 cm but not > 7 cm in greatest dimension, limited to the kidneys
T2		Tumor > 7 cm in greatest dimension, limited to the kidneys
T3		Tumor extends into major veins or invades adrenal gland or perinephric tissues but not beyond Gerota's fascia
	T3a	Tumor directly invades adrenal gland or perirenal and/or renal sinus fat but not beyond Gerota's fascia
	T3b	Tumor grossly extends into renal vein or its segmental (muscle-containing) branches or vena cava below the diaphragm
	T3c	Tumor grossly extends into the vena cava above the diaphragm or invades the wall of the vena cava
T4		Tumor invades beyond Gerota's fascia
Regional lymph nodes (N)		
Nx		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Metastasis in a single regional lymph node
N2		Metastasis in more than one regional lymph node
Distant metastasis (M)		
Mx		Distant metastasis cannot be assessed
M0		No distant metastasis
M1		Distant metastasis

Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3a	N0-N1	M0
	T3b	N0-N1	M0
	T3c	N0-N1	M0
Stage IV	T4	N0-N1	M0
	Any T	N2	M0
	Any T	Any N	M1

From Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.

TABLE 4: Biologic therapy regimens for renal cell carcinoma

Dose and schedule
High-dose IL-2
IL-2: 600,000 or 720,000 IU/kg IV infused over 15 minutes every 8 hours until toxicity develops; or 14 consecutive doses for 5 days
After a 5- to 9-day rest period, an additional 14 doses of IL-2 are administered over a 5-day period. If patients show evidence of tumor regression or stable disease, 1-2 more courses of treatment may be given.
Fyfe G, Fisher RI, Rosenberg SA, et al: J Clin Oncol 13:688–696, 1995.
Low-dose IL-2
IL-2: 72,000 IU/kg by IV bolus every 8 hours to a maximum of 15 doses every 7-10 days for 2 cycles
NOTE: The cycles represent one course of therapy. Patients who are stable or responding after one course of therapy receive a second course. Third and fourth courses are given only if patients demonstrate further tumor regression.
Yang JC, Topalian SL, Parkinson D, et al: J Clin Oncol 12:1572–1576, 1998.

Table prepared by Ishmael Jaiyesimi, DO

condition precludes surgery, either because of extensive disease or poor overall condition. A dose of 4,500 cGy is delivered, with consideration of a boost up to 5,500 cGy.

Postoperative radiation therapy is controversial. However, it may be considered in patients with perinephric fat extension, adrenal invasion, or involved margins. A dose of 4,500 cGy is delivered, with consideration of a boost.

Palliation Radiation therapy is commonly used for palliation for metastatic and local disease.

Systemic therapy for advanced disease

Metastatic renal cell carcinoma is resistant to chemotherapeutic agents. An extensive review of currently available agents concluded that the overall response rate to chemotherapy is 6%.

Interleukin-2 The only FDA-approved treatment for metastatic renal cell carcinoma is high-dose interleukin-2 (IL-2, aldesleukin [Proleukin]; Table 4).

High-dose regimen High-dose IL-2 (720,000 IU/kg IV piggyback every 8 hours for 14 doses, repeated once after a 9-day rest) results in a 15% remission rate (7% complete responses, 8% partial responses). The majority of responses to IL-2 are durable, with a median response duration of 54 months.

The major toxicity of high-dose IL-2 is a sepsis-like syndrome, which includes a progressive decrease in systemic vascular resistance and an associated decrease in intravascular volume due to a "capillary leak." Management includes judicious use of fluids and vasopressor support to maintain blood pressure and intravascular volume and at the same time to avoid pulmonary toxicity due to noncardiogenic

pulmonary edema from the capillary leak. This syndrome is totally reversible.

Other doses and schedules Because of the toxicity of high-dose IL-2, other doses and schedules have been and are being evaluated. Several trials of low-dose IL-2 (3-18 $\times$ 10^6 IU/d), either alone or combined with interferon alfa (Intron A, Roferon-A), have reported response rates similar to those achieved with high-dose IL-2. Patients should be encouraged to participate in ongoing clinical trials of metastatic renal cell carcinoma.

SU011248 and BAY 43-9006 are novel agents under development, with early reports showing activity in advanced kidney cancer. These agents block angiogenic pathways as well as pathways important in cell proliferation. Initial reports have shown partial response and prolonged disease stabilization (*Motzer RJ, Rini BI, Michaelson MD, et al: Proc Am Soc Clin Oncol [abstract] 23:381, 2004; Ratain MJ, Flaherty KT, Stadler WM, et al: Proc Am Soc Clin Oncol [abstract] 23:381, 2004*).

Immunotherapy New immunotherapeutic approaches under investigation for the treatment of advanced renal cell cancer include the use of peripheral blood stem cell transplantations, dendritic cell-based vaccines, and monoclonal antibodies. Early reports on the use of allogeneic stem cell transplantation from HLA-matched donors to invoke a graft-vs-tumor reaction have shown encouraging preliminary results that warrant further investigation. A humanized monoclonal antibody against the G250 antigen found on all clear cell, and the majority of nonclear cell, renal carcinomas is also in clinical trials.

Another area of promising therapeutic clinical research in advanced renal cell cancer is the evaluation of antiangiogenic factors. Most renal cell carcinomas are highly vascular tumors, and inhibition of tumor neovascularity holds new promise for better treatments.

SUGGESTED READING

ON UROTHELIAL CANCER

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