Role of Radiation Therapy and Fluoropyrimidines in the Treatment of Gastrointestinal Malignancies

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Background: The use of combined chemotherapy and radiation for gastrointestinal malignancies has several theoretical advantages, and clinical trials to determine the type and extent of clinical benefits have been performed.

Methods: The basic science and clinical trial data evaluating such combinations are reviewed, with an emphasis on the interactions between fluoropyrimidines and radiation.

Results: Improved outcomes from chemoradiotherapy have been demonstrated in patients with selected stages of anal, esophageal, rectal, and pancreatic cancer.

Conclusion: Despite these positive results, further work is needed to demonstrate even more effective and less toxic treatment regimens.

Introduction

In 1995, approximately 223,300 new cases of gastrointestinal (GI) malignancies were diagnosed in the United States, constituting 18% of all newly diagnosed cancer cases. GI malignancies are the second leading cause of cancer deaths. Approximately 124,000 patients die of GI cancer annually.[1] For most patients with GI malignancies, the primary modality of treatment is surgical resection. Despite the use of aggressive surgery, the outcome of treatment for several sites of gastrointestinal disease remains poor. Improvements in the control of both locoregional and systemic diseases are needed. The morbidity and functional loss resulting from surgical procedures such as esophagectomy or abdominal-perineal resection are often substantial.

One approach to improve the treatment outcome and reduce the morbidity of therapy of GI malignancies has focused on the use of combined chemoradiotherapy and radiation therapy. This combination has several theoretical advantages. Chemotherapy may enhance the local effect of radiation therapy while providing systemic therapy for micrometastases. The two modalities of treatment may interact in many ways - they may be active against different tumor cell subpopulations, and chemotherapy may inhibit the repair of sublethal damage of tumor cells after radiation exposure.[2] Chemotherapy and radiation therapy often have different toxicities, thus allowing them to be used together. However, the interactions between chemotherapy and radiation are not fully understood. For GI malignancies, the best examples of improved outcome with combined chemoradiotherapy are in the management of anal cancer, esophageal cancer, and rectal cancer. Chemoradiotherapy also has been shown to improve the survival of patients with pancreatic cancer.

Many chemotherapeutic agents have been studied for the treatment of GI cancers. One of the most active classes of drugs is fluoropyrimidines, with fluorouracil being the most commonly used drug in this class. In 1969, Moertel et al[3] from the Mayo Clinic conducted one of the earliest randomized studies of combined chemoradiotherapy for GI cancers using fluorouracil, which provided the basis for many of the subsequent studies discussed in this review. In their study, a relatively low dose of fluorouracil was given during the first three days of radiation therapy (45 mg/kg). The dose of radiation was 35 to 40 Gy in fractions of 1.5 to 2 Gy. For unresectable malignancies of the stomach, colorectum, and pancreas, an improvement in survival was seen with combined modality therapy when compared with radiation therapy alone. This review summarizes the clinical application of combined modality treatment with fluorouracil-based chemotherapy and radiation therapy in the management of carcinomas of the esophagus, pancreas, rectum, and anus.

Mechanism of Action of Fluorouracil

Fluorouracil is an analogue of uracil in which the hydrogen in the 5 position is replaced by fluorine. Its cytotoxicity is achieved through several mechanisms.[4] The active fluorouracil metabolite, 5-fluorodeoxyuridylate (5-FdUMP), is formed by conversion of fluorouracil to 5-fluoro-2'-deoxyuridine (FUDR) by thymidine phosphorylase and its subsequent phosphorylation by thymidine kinase. The 5-FdUMP binds tightly to thymidylate synthase in the presence of cofactor 5,10-methylenetetrahydrofolate, thus preventing thymidine synthesis and resulting in cell death. 5-FdUMP also may be converted to 5-fluoro-2'-deoxyuridine-5'-triphosphate (5-DUTP), which can be incorporated into DNA and can interfere with DNA stability and elongation. 5-FU may be converted to 5-fluorouridine monophosphate (5-FUMP), which is then phosphorylated to 5-fluorouridine triphosphate (5-FUTP). 5-FUTP can be integrated into RNA, thus interfering with RNA function.

In vitro studies have demonstrated enhanced cytotoxicity of radiation by fluorouracil.[5-7] The combined effects of radiation and fluorouracil in controlling tumor growth is better than the additive effects of the two modalities given independently.[8] Byfield et al[9] showed that prolonged exposure of irradiated cells to fluorouracil significantly enhanced cell killing in vitro, and the result was maximized if the cells were continuously exposed to fluorouracil for 48 hours after radiation. In vitro exposure of cells to fluorouracil prior to irradiation did not result in enhanced cytotoxicity. Fluorouracil is rapidly metabolized by the liver, with a plasma half-life of six to 20 minutes. Continuous intravenous infusion provides a method whereby tumor cells may be exposed to the drug for prolonged periods.

The mechanisms of interaction between fluorouracil and radiation are not clearly understood. It has been postulated that fluorouracil may inhibit the ability of cells to...
The cytotoxicity of fluorouracil is enhanced by biochemical modulators. Leucovorin provides the reduced folate cofactor for formation of the stable covalent complex between 5-FdUMP and thymidylate synthase. Results of in vitro studies demonstrate that leucovorin potentiates the cytotoxicity and radiosensitization of fluorouracil. [12,13] Leucovorin has also been shown to enhance the therapeutic effects of fluorouracil in randomized clinical trials. [14,15] In a randomized study reported by Petrelli et al.[14] 74 patients with metastatic colorectal cancer were given fluorouracil and leucovorin, fluorouracil and methotrexate, or fluorouracil alone. Patients who received fluorouracil and leucovorin had a response rate of 48% compared with 5% and 11% for the other two groups, respectively. However, no significant improvement in survival was shown. A study by the Mayo Clinic/North Central Cancer Treatment Group[15] included 208 patients with advanced colorectal cancer and showed that treatment with fluorouracil and leucovorin resulted in an improved response rate as well as survival when compared with fluorouracil alone. The combination of levamisole and fluorouracil, when administered as adjuvant therapy, improves the survival of patients with Dukes C colon cancer. [16,17] However, the mechanisms of interaction between levamisole and fluorouracil are not clear. Although levamisole potentiates the cytotoxicity of fluorouracil in several cell lines, the doses of levamisole required for the additive cytotoxicity in vitro are at suprapharmacologic levels. [18]

**Esophageal Cancer**

In 1995, approximately 12,100 new cases of esophageal cancer were diagnosed in the United States, and the estimated number of deaths was 10,900. [1] The standard treatment for esophageal cancer has been esophagectomy. Despite a reduction in the postoperative mortality in the past decade, the long-term survival of patients remains poor. Muller et al. [19] reviewed the literature spanning 1980 to 1988 on surgical treatment of esophageal cancer. Of all patients presenting to surgeons with esophageal cancer, 56% had resectable disease, and the five-year survival was only 10%. Surgery also is associated with significant morbidity. Radiation alone has been an ineffective treatment for esophageal cancer. Earlam and Cunha-Melo [20] reviewed the results of more than 8,000 patients treated in multiple institutions and found that the five-year survival was only 6%.

Numerous studies have evaluated the feasibility of concomitant chemoradiotherapy in esophageal cancer, given either as preoperative treatment or as primary therapy. In most of these studies, the chemotherapy has included fluorouracil. In a small study, Byfield et al. [21] evaluated the efficacy of fluorouracil infusion for five days and 10 Gy of radiation in four fractions given every two weeks for a total of six cycles. Five of six patients achieved complete responses and were alive at the time of the report (range: 1-22 months). Coia and colleagues [22] reported the results of 57 patients with clinical stage I or II esophageal cancer who were treated with combined modality therapy. These patients received four days of fluorouracil infusion for two cycles, starting on days 2 and 29, and mitomycin C by injection on day 2. The dose of radiation was 60 Gy in 30 fractions. The three- and five-year actuarial survival was 29% and 18%, respectively. The disease-specific survival was 41% and 30% at three and five years, respectively.

In a pilot study [23] from Wayne State University, patients received two cycles of fluorouracil plus cisplatin and mitomycin C plus bleomycin at weeks 9 and 12. Radiation therapy was given as a split course, with 30 Gy given in the first three weeks and 20 Gy given as a boost in weeks 11 and 12. The median survival for the 22 patients was 22 months. Six patients remained disease-free at 40 to 46 months. Surgery after chemoradiotherapy did not appear to give better result than combined chemoradiotherapy.

In a recent report, Burmeister et al. [24] treated 137 patients with 60 Gy of radiation over six weeks and two courses of cisplatin and fluorouracil infusion in weeks 1 and 4. The three-year actuarial survival was 43%. In a second protocol, 78 patients received preoperative chemotherapy with the same regimen and 30 to 35 Gy of radiation prior to surgical resection. The three-year actuarial survival for this group was 40%, which was similar to those treated with chemoradiotherapy.

In a randomized intergroup trial, [25] patients with localized esophageal cancer were given either 64 Gy of radiation therapy alone or four courses of fluorouracil and cisplatin plus 50 Gy of radiation therapy. The trial was terminated after accrual of 121 patients because of a significant survival benefit in the combined modality group. The 24-month survival was 38% in the chemoradiotherapy arm compared with 10% in the radiation-alone arm (P=0.001). In an update of the study with additional follow-up, the three-year survival was 31% in the chemoradiotherapy arm, whereas there were no three-year survivors in the radiation-only arm. [26] The local failure rate was 44% in the combined-modality arm compared with 65% in the radiation-only arm (P<0.001). Within 12 months, the rate of distant metastasis was 22% in the combined-modality arm compared with 38% in the radiation-only arm (P=0.005), and more toxicity was associated with the combined-modality treatment. In addition, 44% of patients in the combined-modality arm had severe side effects and 20% had life-threatening side effects compared with 25% and 3%, respectively, in the radiation-only arm.

The results of the intergroup trial are consistent with the concept of radiosensitization since a lower dose of radiation in the combined-modality group improved local control compared with the radiation only group. The chemoradiotherapy also reduced the risk of micrometastasis. Despite the better outcome with chemoradiotherapy, the overall prognosis of these patients remains poor. Although there have been no randomized trials comparing chemoradiotherapy with esophagectomy, it appears that chemoradiotherapy provides a reasonable alternative to esophagectomy in selected patients.

**Pancreatic Cancer**

The number of new cases of pancreatic cancer in the United States was estimated to be 27,000 cases in 1995. Pancreatic cancer was the fifth leading cause of cancer death, resulting in 24,000 deaths annually. [1] Most patients have extensive locoregional disease or distant metastases at the time of diagnosis, making surgical resection impossible. Results of treatment have been disappointing. Connolly et al. [27] reported three-year survival of 2.5% for 912 patients. The recent National Cancer Data Base Report included 17,490 cases from 1985 to 1991. [28] Only 14.2% of the patients had pancreatectomy. For patients with resectable tumor, the three-year survival was 17%, and for patients with unresectable pancreatic cancer, the outcome was uniformly fatal. Radiation alone does not result in long-term survival for these patients. Even at doses of up to 68 Gy, the median survival was only 10 months, and 67% of the patients had locoregional recurrence at the time of death. [29] Fluorouracil has been the mainstay of chemotherapy for this disease. It has been used alone or in combination with various other chemotherapeutic agents, with a response rate of 4% to 29%. [30-32] The addition of doxorubicin and mitomycin C to fluorouracil in one randomized study did not improve the treatment outcome compared with fluorouracil alone. [30]

Retroverspective studies suggest that adjuvant irradiation may improve local control after surgery. However, adjuvant irradiation alone has no proven benefit on survival. [33] Combined chemoradiotherapy may improve the survival of patients compared with no adjuvant treatment. In a Gastrointestinal Tumor Study Group (GITSG) trial, patients were randomized to adjuvant chemoradiotherapy or to observation after complete resection. [34] Radiation was given in two courses of 20 Gy each, separated by an interval of two weeks, for a total dose of 40 Gy. Fluorouracil was administered for three consecutive days at the beginning of each radiation course and was continued once weekly for two years. Despite the small number of patients evaluated, the study suggested a significant survival benefit for the combined treatment group compared with the control group (median survival: 20 months vs 11 months, respectively). Unfortunately, 71% of the treatment group and 86% of the control group developed recurrent disease. Additional patients were given the adjuvant therapy without being randomized and the updated results were similar to the initial study. [35] Nonrandomized studies from other institutions treating patients adjuvantly with fluorouracil-based chemotherapy and radiation after surgical resection also suggest improved survival when compared with surgery only. [33,36]
Although the outcome of patients with unresectable localized pancreatic cancer is dismal, randomized studies suggest that combined chemotherapy and radiation therapy results in improved survival when compared with radiation therapy or chemotherapy alone. In a Mayo Clinic study, fluorouracil and radiation resulted in better survival compared with radiation alone. The GITSG randomized 194 patients to receive 60 Gy of radiation alone, 40 Gy of radiation plus fluorouracil, or 60 Gy radiation plus fluorouracil.[37] The median time to progression was 12.6 weeks for the radiation group and 30 to 34 weeks for the combined-modality groups. The median survival for radiation-alone group was 5.5 months compared with 10 months for the combined-modality group. Although the median survival of patients receiving 60 Gy was slightly better than those who received 40 Gy, the difference was not significant. In another GITSG study,[38] patients with locally unresectable pancreatic cancer were randomized to multitid chemotherapy (streptozotocin, mitomycin C, and fluorouracil) or to 54 Gy of radiation plus fluorouracil followed by the same three-drug chemotherapy regimen. Overall survival for the combined chemoradiotherapy group was 41% at one year compared with 19% for the chemotherapy group.

More research is needed to improve the treatment outcome of pancreatic cancer. The optimal dose of radiation remains to be defined. Escalation of radiation dose without increasing the side effects significantly may be feasible with three-dimensional conformal radiation treatment. The role of continuous-infusion fluorouracil with or without biochemical modulators during radiation warrants research. More effective chemotherapeutic agents need to be developed.

Rectal Cancer

Patients with rectal cancers that have penetrated through the rectal wall or have metastasized to the regional lymph nodes are at substantially higher risk of recurrent disease and death compared with those whose diseases are confined within the rectal wall. Adjuvant therapy with radiotherapy, fluorouracil-based chemotherapy, or combined chemoradiotherapy have been extensively studied for these patients (Table 1). Postoperative radiation alone has not been shown to improve the treatment outcome of patients in randomized studies.[39,40] In the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol R-01, adjuvant chemotherapy with fluorouracil, semustine, and vincristine was found to improve the disease-free survival and overall survival in patients with surgically resected Dukes B and C rectal cancer.[39]

The GITSG published the first randomized trial that showed the benefit of combined chemoradiotherapy as adjuvant treatment for rectal cancer.[41] In this study, patients with resected Dukes B2 or C rectal cancer were randomized to one of four arms: (1) no adjuvant therapy, (2) postoperative radiotherapy of 40 to 48 Gy, (3) postoperative chemotherapy with fluorouracil and semustine, or (4) combined chemoradiotherapy and radiotherapy. Of the original 227 patients, data were analyzed from a total of 202 patients. In the combined chemoradiotherapy group, fluorouracil was given at a dose of 500 mg/m^2 on the first three days and the last three days of radiotherapy. At seven years, the survival was 56% for the combined treatment group compared with 32% for the control group (P=0.005).[42] Although both locoregional and distant recurrence decreased, the principal benefit was improvement in locoregional control. The administration of chemotherapy alone or radiotherapy did not improve local control or survival significantly.

The Mayo Clinic/North Central Cancer Treatment Group conducted a randomized study[43] in which patients with resected rectal cancer and tumor penetration through the rectal wall or with metastatically involved lymph nodes were assigned to postoperative radiation alone (45 to 50.4 Gy) or to two cycles of chemotherapy with fluorouracil and semustine followed by concomitant fluorouracil and radiotherapy and two additional cycles of chemotherapy. At five years, the recurrence-free survival was 37% for the radiation group compared with 58% for the combined-modality group (P=0.0016). The overall survival was 44% for the radiation group and 57% for the combined-modality group (P=0.025). The incidence of severe late complications was similar between the two treatment groups.

Semustine has been found to increase the risk of leukemia significantly. Boice et al[44] reported that the relative risk of developing leukemia for patients who received semustine as adjuvant therapy for GI cancers was 12.4, which increased significantly with time after treatment. In a GITSG study,[45] the contribution of semustine to the efficacy of the adjuvant therapy was evaluated. Patients were randomized to receive adjuvant treatment with radiation therapy plus fluorouracil and semustine, or radiotherapy and escalating doses of fluorouracil. At a median follow-up time of 5.8 years, no difference in overall survival and disease-free survival was found between the treatment groups. It was therefore concluded that semustine is not an essential component of the adjuvant chemotherapy regimen.

A recently published intergroup trial demonstrated the benefit of protracted fluorouracil infusion when given concomitantly with radiation.[46] In this study, 660 patients with stage II or stage III rectal cancer were given an initial nine-week course of chemotherapy followed by radiation and concomitant fluorouracil, and then a second course of chemotherapy. Patients were randomized to four treatment arms. They received either fluorouracil alone or fluorouracil plus semustine before and after the radiation therapy. During radiation therapy, fluorouracil was given either as bolus administration for three days during weeks 1 and 5 of radiation or as protracted continuous infusion during the entire period of radiation. Patients who received protracted fluorouracil infusion during radiation had a significant decrease in recurrence (from 47% to 37%) and distant metastasis (from 40% to 31%) compared with those who received bolus fluorouracil. Survival was better in patients treated with protracted venous infusion of fluorouracil. Patients in the protracted fluorouracil group had a higher incidence of severe diarrhea, whereas the bolus fluorouracil group had more severe leukopenia. There was no difference in the overall survival and relapse-free survival for patients who received fluorouracil alone compared with those who received fluorouracil and semustine as the preradiation and postradiation chemotherapy regimen. This study confirmed the finding of the GITSG trial that semustine does not provide additional benefit over fluorouracil alone.

The effect of adding leucovorin and levamisole in the adjuvant regimen was studied in another intergroup trial. Although the difference was not significant. All patients received two cycles of fluorouracil-based chemotherapy, without biochemical modulators during radiation warrants research. More effective chemotherapeutic agents need to be developed.
Arsenal report on the long-term adverse effects on the bowel function after postoperative chemoradiotherapy for rectal cancer was recently published by investigators from the Mayo Clinic.[47] Patients who received adjuvant chemoradiotherapy had more bowel movements per day, more nocturnal bowel movements, and more fecal incontinence than those without adjuvant treatment. More research is needed to identify methods to reduce the long-term bowel complications after adjuvant treatment. Preoperative chemoradiotherapy may be one way to achieve this. However, the value of chemoradiotherapy and radiation given before surgery has not been clearly defined. Preoperative treatment has not been shown to improve survival in randomized, prospective trials. Additional information may be available with the recently developed intergroup trial sponsored by the Radiation Therapy Oncology Group that compares preoperative and postoperative chemoradiotherapy.

Until results of other randomized studies are available, the standard adjuvant therapy for patients with stage II and stage III rectal cancer should be two cycles of fluorouracil followed by a course of protracted infusion of fluorouracil and radiotherapy, and two additional cycles of fluorouracil, based on the results of the intergroup study (Fig 3).[46] Despite the progress made in recent years, further improvements in the treatment outcome and reduction in the treatment complication are needed. All physicians should encourage eligible patients to enroll in well-designed prospective studies.

**Anal Cancer**

The incidence of anal cancer is lower than colorectal cancer and accounts for approximately 1% to 2% of all large bowel cancer. In the past two decades, significant progress has been made in the management of this disease. Combined chemoradiotherapy has replaced abdominal-perineal resection (APR) as the standard treatment, despite the lack of randomized trials comparing the two modalities of treatment. Combined chemoradiotherapy has achieved results that are similar or superior to surgery, with acceptable toxicity and with preservation of anal sphincter function. In many retrospective, nonrandomized studies, radiation alone was used for the treatment of anal cancer.[56] In 1974, Nigro et al.[48] at Wayne State University reported the use of 30 Gy of preoperative radiation plus chemotheraphy (fluorouracil and mitomycin C) as preoperative treatment with the intent to reduce the tumor bulk and to allow more effective surgery. All three patients had a complete response after the chemoradiotherapy, and no residual tumor was found in the two patients who underwent the planned APR. Subsequent reports with more patients confirmed the initial results, with 84% having complete responses after the preoperative treatment.[49] APR was deemed unnecessary for patients whose tumor was eradicated by the preoperative treatment. The Wayne State regimen consisted of two cycles of fluorouracil infusion given on days 1 to 4 and on days 29 to 32 at a dose of 1000 mg/m² per day, and mitomycin C at a dose of 15 mg/m² on day 1. Radiation was delivered at 2 Gy per day for a total dose of 30 Gy. Studies from other institutions using variations of this regimen showed similar results, with overall five-year survival rates of 70% to 90% and preservation of anal sphincter function in over two thirds of the patients (Table 2).[50-54] One series from the Memorial Sloan-Kettering Cancer Center appeared to give inferior results compared with other studies (complete response rate of 45%).[54] However, the dose of fluorouracil was lower in this study, and chemoradiotherapy and radiotherapy were delivered sequentially instead of concurrently.

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<th>Number of patients</th>
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<th>Local control</th>
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<td>45</td>
<td>79</td>
<td>80%</td>
<td>NS</td>
<td>60%</td>
<td>3 years; 1-10 years</td>
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<td>42</td>
<td>57%</td>
<td>71-14</td>
<td>NS</td>
<td>3 years; 6 months</td>
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<td>2</td>
<td>18</td>
<td>43%</td>
<td>82%</td>
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<td>Miller et al.[18]</td>
<td>50</td>
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Mitomycin C can cause severe, life-threatening hematologic and pulmonary toxicity as well as hemolytic uremic syndrome. Its contribution to the efficacy of the combined modality treatment was evaluated by Cummings et al.[52] at the Princess Margaret Hospital in a series of nonrandomized protocols in which patients were treated with radiation plus fluorouracil and mitomycin C, radiation plus fluorouracil, or radiation only. The local control and cause-specific survival for patients receiving radiation and fluorouracil plus mitomycin C were significantly better than those receiving radiation and fluorouracil or radiation only. In a randomized trial by the Radiation Therapy Oncology Group (Study 87-04),[55] patients were treated with 45 Gy of radiation and two courses of fluorouracil (1000 mg/m² per day for four days on weeks 1 and 4). They were randomized to receive or not receive mitomycin C (10 mg/m² on days 1 and 29). Preliminary analysis showed significant improvements in the four-year locoregional control (82% vs 64%, respectively), colostomy-free survival (71% vs 59%, respectively), and survival without evidence of disease (73% vs 51%, respectively) for patients who received fluorouracil and mitomycin C compared with those who received only fluorouracil. The difference in overall survival was not statistically significant (76% vs 67%, respectively). Patients receiving fluorouracil and mitomycin C had a higher incidence of severe toxicities (including four fatal complications) than those receiving fluorouracil only. This study demonstrates that mitomycin C is an important component of the combined modality regimen, although it increases the toxicity of therapy.

In many retrospective, nonrandomized studies, radiation alone was used for the treatment of anal cancer.[56-59] The doses of radiation used were usually over 60 Gy. The local control rate ranged from 57% to 100%, with the majority of patients retaining anal sphincter function. An important question is whether chemoradiotherapy is necessary at all in addition to radiation. Nonrandomized studies from the Princess Margaret Hospital suggested that the addition of fluorouracil and mitomycin C improved the local control and cause-specific survival compared with radiation alone.[52] Roelofsen and colleagues[60] reported the preliminary result of a randomized trial in which patients with stage T3-4, N0-3 or T1-2, N1-3 anal cancer were given either radiation alone or radiation plus fluorouracil and mitomycin C. Significant improvements were seen in locoregional control and colostomy-free survival in the combined-modality group. It is possible that patients with early-stage anal cancer may achieve adequate local control with radiation alone. However, until results from randomized studies are available to support the use of radiation alone, combined
The combination of fluorouracil-based chemotherapy and radiation has been shown to improve treatment outcome in several GI malignancies. Its role in the adjuvant treatment of rectal cancer and unresectable pancreatic cancer has been demonstrated in randomized trials. Data also support its use in the management of esophageal cancer and unresectable pancreatic cancer. It has replaced surgery as the standard therapy for anal cancer and provides an alternative to surgery in the management of esophageal cancer. Despite this progress, continuing efforts are needed to improve the current results by well-designed randomized clinical trials. Basic research also is essential to elucidate the mechanisms of interaction between chemotherapy and radiation, to facilitate the development of more effective drugs, and to provide the framework for future clinical studies.

Conclusions

References


