

GASTROINTESTINAL CANCER COMMITTEE

Gastrointestinal Committee Key Members: Christopher Willett, M.D., Chair (1999); Jaffer Ajani, M.D., Co-Chair, Medical Oncology; David Kelsen, M.D., Co-Chair, Medical Oncology; Elin Sigurdson, M.D., Co-Chair, Surgical Oncology; Ross Abrams, M.D.; Brian Berkey, M.S., Statistical Center; Mary Benetz, Research Associates Committee Liaison; Christopher Crane, M.D., Three-Dimensional Committee Liaison; Laurie Gaspar, M.D., Brachytherapy Committee Liaison; Michael D. Goodyear, M.D., Medical Oncology; Leonard Gunderson, M.D.; Michael Haddock, M.D.; John Hoffman, M.D., Surgical Oncology; Nora Janjan, M.D.; Madhu John, M.D.; Lisa Kachnic, M.D., Outcomes Committee Liaison; Richard Krieg, M.D.; Jerome Landry, M.D.; Neal Meropol, M.D.; Bruce Minsky, M.D.; Edith Mitchell, M.D.; Mohammed Mohiuddin, M.D.; John Moulder, Ph.D., Translational Research Program Liaison; Robert Myerson, M.D.; Dirk Noyes, M.D., Surgery; Thomas F. Pajak, Ph.D., Statistical Center; David Raben, M.D.; William Regine, M.D.; Tyvin Rich, M.D.; John M. Robertson, M.D.; Anthony Russell, M.D.; John Skibber, M.D., Surgery; and Paula Kim, Patient Advocacy Committee Liaison

INTRODUCTION

The RTOG Gastrointestinal (GI) Cancer Committee has provided leadership and actively participated in cooperative group clinical research of localized GI malignancies. During the current award period, major accomplishments included

1. An RTOG-led Phase III intergroup study (RTOG 94-05) examined the influence of radiotherapy (RT) dose on outcome for nonoperative esophageal cancer patients. It showed no improvement with the higher dose (64.8 Gy) vs. the moderate dose (50.4 Gy) of RT (all 236 patients received 5-fluorouracil [5-FU] plus cisplatin) suggesting that the standard of care should remain 50.4 Gy with 5-FU/cisplatin.
2. The importance of optimizing RT and chemotherapy integration in influencing local tumor control and toxicity was clarified by a Phase II study in anal carcinoma (RTOG 92-08). Results showed that minimizing treatment breaks during chemo-RT improved the therapeutic ratio.
3. Two large RTOG-led Phase III intergroup trials were activated, both attempting to improve chemotherapy-RT combinations. The first (RTOG 98-11) is comparing two different schedules of chemo-RT for anal carcinoma. The second (RTOG 97-04) is testing the role of comparing gemcitabine to 5-FU before and after conventional adjuvant chemo-RT for resected pancreatic cancer.
4. A Phase II study of a novel chemotherapy regimen with concurrent RT was completed for inoperable pancreatic cancer (RTOG 98-12). The results of this 122-patient trial will serve as a baseline for developing several lines of RTOG research for patients with inoperable pancreatic cancer.

5. The RTOG GI Cancer Committee was a major contributor to the Intergroup Gastric Cancer Trial 0116 (19% of patient entries). This study showed the superiority of adjuvant chemo-RT vs. observation after resection of gastric cancer, effecting a new standard of care.
7. The RTOG GI Committee was a major contributor to the most recent Intergroup Rectal Cancer Trial 0144 (22% of 2000 patients), which tested several schemas of modulated 5-FU with RT for resected Stage II/III rectal cancer. The results are pending.
8. In cooperation with the RTOG Translational Research Program Committee, the GI Committee established a program of testing molecular markers for prognosis in anal carcinoma (as a component of RTOG 98-11) and pancreatic carcinoma (as a component of RTOG 97-04 and 98-12).
9. In conjunction with the RTOG Cancer Control and Genitourinary Cancer Committees, the RTOG GI Cancer Committee activated a protocol studying the problem of lower GI sequelae of pelvic RT and the potential for pharmacologic treatment of this problem (RTOG 98-09).

During the next award period, the RTOG GI Cancer Committee will test three hypotheses, focusing primarily on localized carcinomas of the esophagus-gastroesophageal junction, pancreas, rectum, and anal canal:

1. Chemo-RT with contemporary, novel, and targeted chemotherapeutic agents improves the outcome of patients with common GI carcinomas.
2. Modern, image-guided and three-dimensional (3D) RT techniques will reduce the acute and late GI tract morbidity associated with aggressive contemporary chemo-RT protocols.

3. Tumor molecular markers can serve not only as prognosticators, but also as guides to therapy.

In addition, the RTOG will remain a major participant in intergroup Phase III trials testing new chemo-RT schedules for gastric, rectal, and other GI malignancies. In conjunction with the Cancer Control Committee, the GI Committee will continue to investigate strategies to decrease the toxicity and improve the quality of life for patients with GI cancer.

ENCOMPASSING VISION

Major research questions

During the current award period, the GI Cancer Committee research effort focused on five questions in the clinical research of localized (nonmetastatic) GI malignancies:

1. Influence of RT dose escalation in improving local tumor control and survival.
2. Optimizing the integration of RT and chemotherapy to improve the therapeutic index.
3. Evaluation of novel chemotherapeutic agents with RT.
4. Assessment of the efficacy of adjuvant RT and 5-FU-based chemotherapy in malignancies for which this therapy is not established.
5. Evaluation of molecular markers as potential guides to therapy.

RT dose

The influence of RT dose in improving the outcome of patients with nonoperative esophageal cancer was examined by RTOG 9405, an intergroup Phase III trial comparing higher dose RT (64.8 Gy) and cisplatin and 5-FU chemotherapy with conventional RT (50.4 Gy) and cisplatin and 5-FU chemotherapy. This study demonstrated that patients randomized to the higher RT dose combined with concomitant and maintenance 5-FU and cisplatin in this particular trial design did not achieve improved overall survival. Patients randomized to receive higher dose RT had a lower 2-year survival rate (30%) than did patients undergoing moderate-dose RT (39%); however, the cancer-related deaths were lower in the high-dose arm at 39% vs. 50%. Although more treatment-related deaths occurred in the assigned 64.8-Gy dose arm (11 patients) than in the conventional dose arm (2 patients), this is deceptive because only 4 of the 11 patients assigned to the high-dose arm who died received RT doses greater than the conventional 50.4 Gy. Detailed analysis of this study is underway and will include issues of extended treatment delay and actual treatment delivered in both arms in relation to the outcome analyses. Until such data are available, investigations will evaluate new agents with RT for patients with nonoperative esophageal cancer, as well as alternative image-guided RT techniques for this disease.

Optimizing integration of RT and 5-FU-based chemotherapy

The importance of optimizing the integration of intensive RT and chemotherapy in improving the therapeutic ratio in

anal cancer was clarified by RTOG 92-08. This Phase II study showed that minimizing treatment breaks during chemo-RT appeared to improve the therapeutic index for patients with localized anal cancer. In the original version of this protocol, 46 patients were treated with concurrent 5-FU and mitomycin chemotherapy and 59.4 Gy RT during 9 weeks with a scheduled 2-week rest period during Weeks 5 and 6 (1, 2). Although Grade 3 and higher toxicity rates were similar to prior RTOG studies, this approach resulted in an unexpectedly high rate of colostomy (23%) and local failure. It was hypothesized that the prolonged RT treatment time may have caused this result, so the study was amended to eliminate the planned treatment break. This appears to have improved the local control rate, with only 2 of 18 assessable patients requiring colostomy. This study was followed by a large RTOG-led intergroup trial (RTOG 98-11) that is currently active. RTOG 98-11 compares conventional chemo-RT as per RTOG 92-08 vs. an innovative regimen of neoadjuvant 5-FU/cisplatin followed by concurrent 5-FU/cisplatin. This trial incorporates detailed quality-of-life measurements related to anorectal function in addition to conventional end points.

Novel chemotherapy with RT

The evaluation of novel chemotherapeutic agents with RT has primarily been in pancreatic cancer. This strategy was initiated in RTOG 98-12, a Phase II study, evaluating concurrent paclitaxel and RT for patients with locally advanced pancreatic cancer. This trial accrued 122 patients in 16 months and will serve as the starting point of an evaluation of new chemotherapeutic agents and molecular-based therapies for patients with this malignancy. One hundred thirteen patients are assessable, with an estimated 1-year survival rate of 52.4% and a median survival of 12.6 months. A complete analysis of this study is planned for spring 2001.

Also in pancreatic cancer, RTOG has activated and successfully led the Intergroup Adjuvant Pancreas Trial (RTOG 97-04), which is nearing completion of accrual. This study compares "conventional" postoperative chemo-RT (5-FU before, after, and during RT) vs. gemcitabine delivered before and after RT (with 5-FU delivered during RT). The results of this trial are expected to set the standard of care for adjuvant therapy of pancreatic cancer in the United States. The patient accrual rate exceeded the original expectations. The project will close in early 2002.

Assessment of adjuvant therapy in "new" areas

The RTOG actively participated in two intergroup Phase III studies evaluating the efficacy of adjuvant therapy for patients with malignancies for which the role of postoperative chemo-RT had not been established. The Southwest Oncology Group (SWOG) intergroup study 0116 (RTOG 90-18) randomized 603 patients (116 from RTOG institutions) with resected high-risk gastric cancer (Stage Ib-IVM0) to postoperative irradiation with 5-FU and leucovorin vs. observation only (3). The 3-year results show a statistically significant improvement in disease-free survival (treatment 49% and observation 32%, $p = 0.001$) and

overall survival (treatment 52% and observation 41%, $p = 0.03$). The results of this seminal study have established the value of adjuvant chemo-RT in the care of these patients and will lead to future studies evaluating adjuvant RT and other systemic therapies. The RTOG served as co-investigator with the North Central Cancer Treatment Group (NCCTG) on intergroup study 0130 (RTOG 92-03), a Phase III study that randomized 222 patients (57 from RTOG institutions) with resected but high-risk colon cancer to adjuvant 5-FU and levamisole or postoperative RT plus 5-FU and levamisole (4). The preliminary analysis demonstrated no survival difference between the two arms, but definitive conclusions will not be reached given the underpowered nature of the study.

Response to problems

The concerns of the last grant review of the GI Subcommittee Research Plan included slow patient accrual to Phase I and II studies, the complexity of the trials, and a lack of translational research efforts.

Slow accrual to Phase I/II studies

During the past 5 years, the number of Phase I and II studies has been reduced, and the studies have been simplified and directed at specific disease sites; the accrual to these studies has been excellent. In particular, RTOG 92-08 (anal canal) and RTOG 98-12 (inoperable pancreas) were two very successful studies. The Committee has placed a high emphasis on Phase III intergroup studies in the major disease categories (esophagus, gastric, rectal), with very successful accrual.

Trial complexity

In the current grant cycles, RTOG GI studies have been designed and executed to answer important scientific questions efficiently. Three examples of such studies include (1) RTOG 94-05, a large Phase III study testing a higher RT dose for nonoperative esophageal cancer; (2) RTOG 97-04, a large Phase III study comparing maintenance gemcitabine with 5-FU for patients undergoing adjuvant therapy for pancreatic cancer; and (3) RTOG 98-11, a Phase III study comparing RT with cisplatin and 5-FU chemotherapy or mitomycin-C and 5-FU chemotherapy in the treatment of patients with anal cancer. These RTOG-directed intergroup studies are addressing simple but important questions in the treatment of patients with localized GI malignancies.

Lack of translational efforts

In the current anal cancer trial (RTOG 98-11), a translational component of the study will seek to confirm the prognostic importance of p53 status in a large number of patients. It will also evaluate two other tumor markers, human papilloma virus and enzyme marker HAP1.

Correlative studies of p53 and p16 activity were a component of RTOG 98-12, a Phase II study assessing the results of irradiation with paclitaxel for patients with unresectable pancreatic cancer.

In RTOG 97-04, serum CA19-9 levels will be measured on all resected pancreatic cancer patients before initiation of postoperative chemo-RT and assayed again at the follow-up

visits. The correlation of outcome with serum CA19-9 levels in this large Phase III trial will provide invaluable data in assessing the true prognostic value of this marker.

Efforts to identify phenotypic variations in critical enzymes of 5-FU metabolism to aid in future trial design have been proposed for rectal cancer. This may lead to the development of protocols using chemo-RT protocols based on phenotype vs. fixed regimen-based approaches.

Studies to assess the prognostic importance of biomarkers in esophageal cancer will be pursued. Given RTOG's success in accrual and completion of esophageal studies, this represents a unique opportunity to initiate translational research in this disease. Three types of genetic markers will be evaluated: cell proliferation (PCNA or Ki-67 staining), cell apoptosis (terminal deoxy nucleotidyl transferase-mediated dUTP-biotin nick end labeling [TUNEL] staining), and genetic alterations (oncogene activation, tumor suppressor gene inactivation, and microsatellite instability). It is proposed that tumor samples from patients entering through RTOG institutions should be prospectively analyzed for these markers and correlated with outcome.

Future directions

Under the leadership of Dr. Michael O'Connell, the GI Intergroup Committee has been restructured into five task forces for each of the major categories of GI malignancy (esophageal, gastric, pancreatic, colon, and rectal neoplasms). The goal of each task force is to facilitate the design, implementation, and coordination of Phase III studies within each disease category among the cooperative groups. Each task force is composed of a chair (the GI Chair from each cooperative group), two representatives from each of the cooperative groups, and a statistician from a cooperative group who works on GI studies. RTOG is actively participating in all task forces and has designated representatives. Dr. Willett is serving as Chair of the esophageal cancer task force, and Dr. Pajak as the statistical representative. All Phase III studies will be run through the intergroup mechanism.

During the next award period, RTOG Phase II and III clinical studies will test three hypotheses in the treatment of localized GI malignancies: (1) chemo-RT with contemporary, novel, and targeted chemotherapeutic agents improves the outcome of patients with esophageal, gastric, pancreatic, rectal, and anal carcinoma; (2) conformal 3D RT techniques reduces the acute and late GI tract morbidity associated with aggressive contemporary chemo-RT protocols; and (3) tumor molecular markers can serve not only as prognostic markers of outcome but as guides to therapy selection.

Hypothesis 1: Chemo-RT with contemporary, novel, or targeted chemotherapeutic agents improves the outcome of patients with GI cancer

Esophageal cancer

Nonoperative esophageal cancer. As previously discussed, no survival benefit was seen for patients with nonoperative esophageal cancer randomized to receive higher dose RT

(64.8 Gy) with 5-FU and cisplatin vs. moderate-dose RT (50.4 Gy) initially with 5-FU and cisplatin (RTOG 94-05). Given this result, the focus of investigation will shift to the evaluation of new agents with RT for these patients. As a replacement study to RTOG 94-05 for patients with nonoperative esophageal cancer, a randomized Phase II study (RTOG 01-13) evaluating two paclitaxel-based regimens has been written and approved by the National Cancer Institute in December 2000. Single-institution Phase I and II studies have reported high pathologic response rates and survival with the use of paclitaxel-based regimens and RT. RTOG 01-13 will assess the 1-year survival and frequency of major acute and late toxicities of 78 assessable patients undergoing induction chemotherapy (2 cycles of 5-FU, cisplatin, and paclitaxel) followed by moderate-dose RT (50.4 Gy) plus concurrent continuous infusion 5-FU and weekly paclitaxel or induction chemotherapy (2 cycles with paclitaxel and cisplatin) followed by moderate-dose RT (50.4 Gy) with concurrent infusion paclitaxel and weekly cisplatin. The goal of this study is to identify the experimental arm in a future Phase III study to be compared with the standard treatment of moderate-dose RT (50.4 Gy) plus 5-FU and cisplatin.

Operative esophageal cancer. Currently, no Phase III study is available for patients with operative esophageal cancer in the United States. RTOG is exploring the feasibility of a Phase III study comparing chemo-RT with surgery reserved for salvage vs. induction chemotherapy, chemo-RT, and surgery.

The end points will include local control, disease-free survival, survival, and quality of life. Dr. Robert Ginsberg has circulated a survey to the thoracic surgical community to assess the interest in this study. The results indicate significant enthusiasm. It is hoped that by 2003, an intergroup study will be in place in an effort to improve the outcome in this poor-prognosis disease.

Gastric cancer

Induction therapy. RTOG 99-04, a Phase II study, evaluates an induction approach of chemotherapy (2 cycles of 5-FU, leucovorin, and cisplatin) followed by 45 Gy of RT with concurrent 5-FU and paclitaxel, and surgery for 49 patients with potentially resectable gastric cancer. The end points of this study are the determination of the feasibility of preoperative chemo-RT for patients with potentially resectable gastric cancer and the pathologic response rate, curative resection rate, survival, and tolerance of this approach. This study is innovative in that a neoadjuvant approach is being used where postoperative trials have dominated the clinical investigation of this disease. It is especially timely given the important results of Intergroup 0116 showing the benefit of adjuvant RT plus concurrent and maintenance 5-FU and leucovorin. This study has had relatively slow accrual, but accrual is expected to increase once the results of the intergroup postoperative trial become more widely disseminated, increasing the level of interest in chemotherapy for this disease. Plans for a future follow-up Phase II and/or Phase III trial will depend on the results of this study.

Adjuvant therapy. As a replacement study to the Gastric Intergroup 0116 study that established the efficacy of adjuvant postoperative RT and chemotherapy for patients with resected high-risk gastric cancer, the RTOG has developed a randomized Phase II study (RTOG 0114) that will use the same two paclitaxel regimens used in the nonoperative esophageal adjuvant study for patients with resected gastric cancer. After surgery, patients will undergo induction chemotherapy (2 cycles of 5-FU, cisplatin, and paclitaxel) followed by moderate-dose RT (50.4 Gy) with concurrent continuous infusion 5-FU and weekly paclitaxel or induction chemotherapy (2 cycles with paclitaxel and cisplatin) followed by moderate-dose RT (50.4 Gy) with concurrent infusion paclitaxel and weekly cisplatin. The goal of this study is to identify an experimental treatment arm in a future Phase III study to compare with the "standard" treatment of postoperative RT with concurrent and maintenance 5-FU and leucovorin. This study was approved by the National Cancer Institute in January 2001.

Pancreatic cancer

Adjuvant therapy. RTOG 97-04, a Phase III intergroup study, assesses the efficacy of gemcitabine vs. 5-FU as maintenance therapy for patients with resected pancreatic cancer undergoing postoperative RT with continuous infusion 5-FU. Gemcitabine, a deoxycytidine analog resembling cytosine arabinoside, is one of the most active agents against pancreatic cancer. In a Phase III multicenter randomized trial, gemcitabine was compared with 5-FU for patients with advanced or metastatic pancreatic cancer (5). This study showed that patients receiving gemcitabine had a statistically significant improvement in clinical benefit, tumor response, and survival compared with patients receiving 5-FU. RTOG 97-04 extends this question (gemcitabine vs. 5-FU) to the adjuvant setting in establishing the optimal maintenance chemotherapy (3 cycles of weekly gemcitabine vs. 3 cycles of infusion 5-FU) for patients with resected pancreatic cancer undergoing postoperative irradiation plus protracted venous infusion 5-FU. This trial is accruing extremely well with 243 (as of October 1, 2000) of 330 targeted patients on study, and it is anticipated that this trial will close in 2001.

A Phase I and II study is currently being written that will determine the optimal dose of gemcitabine during external beam RT preceded and followed by gemcitabine in this context; determine the optimal dose of R115777, a farnesyl transferase inhibitor, that can be given during this gemcitabine-based chemotherapy and chemo-RT in this context; and estimate the survival and tolerance associated with this treatment program. This study may become the experimental arm in a future Phase III study that would compare the best arm from RTOG 97-04 against a regimen that incorporates concurrent gemcitabine and/or a farnesyl transferase inhibitor. See the section "Locally advanced disease" below for discussion of R115777.

Locally advanced disease. Building on the experience with RT and paclitaxel for patients with locally advanced pancreatic cancer (RTOG 98-12), the next study for this group

of patients will evaluate the combination of concurrent weekly paclitaxel and gemcitabine with RT followed by the farnesyl transferase inhibitor R115777. A randomized Phase II study will be undertaken in which patients will be randomized to paclitaxel, gemcitabine, and 50 Gy of external beam RT with or without sequential R115777. Like paclitaxel, gemcitabine has been shown to be a potent radiosensitizer during *in vitro* investigations. The combination of paclitaxel and gemcitabine, when administered with RT, may enhance the local response of locally advanced pancreatic cancer and lower the systemic risks. In the Phase II studies of paclitaxel and RT by Brown University and the RTOG, locoregional toxicities from paclitaxel plus RT, such as enteritis, nausea, and abdominal pain, have been uncommon, occurring in <10% of patients (6). In a step-wise fashion, gemcitabine has been added to paclitaxel and RT to determine the maximal tolerated dose of the addition of gemcitabine. The Brown University Oncology Group performed a Phase I study combining paclitaxel, gemcitabine, and RT. Patients with locally advanced pancreatic cancer received 50.4 Gy RT, paclitaxel 40 mg/m²/wk, and escalating doses of gemcitabine. Six patients were treated at gemcitabine dose level 1 (75 mg/m²/wk). No Grade 3–4 toxicities were observed. Four of six patients responded, including 1 patient who underwent resection after chemo-RT and had a pathologically complete response. Three patients were treated at the second gemcitabine dose level of 150 mg/m²/wk; Grade 3 GI toxicity developed in all 3 patients and 1 also had Grade 3 myelosuppression. An intermediate dose level of gemcitabine, 110 mg/m², has also been investigated; however, Grade 3 toxicities were encountered. Therefore, because the dose level of 75 mg/m²/wk of gemcitabine, paclitaxel 40 mg/m²/wk, and 50.4 Gy concurrent RT was well tolerated with promising activity, this dose level will be investigated in this Phase II study.

In addition to the inclusion of gemcitabine with paclitaxel and RT, the other critical component of this study is the addition of the farnesyl protein transferase (FPTase) inhibitor R115777 after chemo-RT (7–13). FPTase inhibitors were developed after 2.5 decades of investigation of the ras oncogenes and the proteins they encode. The ras genes encode low molecular weight proteins, called Ras. Ras, after several posttranslational modifications localizes itself to the inner surface of the plasma membrane. In normal cells, Ras proteins cycle between guanosine diphosphate (GDP)-bound (inactive) and guanosine triphosphate (GTP)-bound (active) forms to regulate cellular proliferation and differentiation. When certain growth factors bind to their cellular receptors, this causes activation of the GDP-bound Ras protein that exchanges its bound GDP for GTP. This activated form of the Ras protein subsequently triggers a cascade of events that ultimately lead to cell proliferation. The GTPase activity of Ras then turns off the biologic event, Ras returns to its inactive (GDP-bound) form and the cycle is thus closed. Ras then remains in an inactive form until a new growth signal arrives. A single point mutation changing an amino acid is responsible for altering the wild-type

ras gene into an oncogene that efficiently induces neoplastic transformation. The mutations in ras genes that are frequently found in cancer inhibit GTPase activity of the Ras protein; thus, Ras remains bound to GTP and permanently activated. This results in the active Ras protein constitutively stimulating cell growth and proliferation. Mutations of the ras gene are found in 90% of pancreatic tumors. Thus, inhibition of ras gene function is a rational target in pancreatic cancer. Recent progress at blocking ras-induced cell-transforming activity has centered on inhibiting the enzyme FPTase. Membrane localization of Ras is essential for its normal function and the cell-transforming activity of its mutated, oncogenic form. Membrane anchoring of Ras is achieved through a series of posttranslational modifications. The first and most critical modification is farnesylation of its carboxyl-terminal motif, catalyzed by FPTase. Inhibition of the farnesylation reaction by synthetic FPTase inhibitors nullifies ras membrane anchorage and therefore inhibits Ras protein function and its cell transforming capability. Recent evidence suggests that inhibition of farnesylation of other proteins, not ras, may be responsible for a substantial amount of the antitumor effect of farnesyl transferase inhibitors. R115777 is a potent and selective inhibitor of FPTase both *in vitro* and *in vivo*. Phase I and II trials have established feasible and well-tolerated schedules.

More active chemo-RT may improve locoregional control and more effectively palliate symptoms. However, at the low doses used for radiosensitization, it is unlikely that conventional chemotherapy agents have substantial systemic activity to prevent the growth of micrometastases. This protocol will also evaluate the FPTase inhibitor R115777 after paclitaxel plus gemcitabine plus RT. The objectives of this study are to determine the toxicity and locoregional activity of paclitaxel, gemcitabine, and RT; feasibility and tolerance of prolonged administration of R115777 after paclitaxel, gemcitabine, and RT for pancreatic cancer; and progression-free and overall survival after paclitaxel, gemcitabine, and concurrent RT followed by R115777 in locally advanced pancreatic cancer patients.

Rectal cancer

Preoperative therapy. In the past 15 years in the United States, interest has been increasing in the use of preoperative chemo-RT and surgery protocols for patients with clinical T3 and T4 rectal cancer. Single-institution Phase I and II studies have reproducibly demonstrated the safety and potential efficacy of preoperative pelvic RT (45–50.4 Gy in 25–28 fractions) with concurrent and maintenance 5-FU-based chemotherapy followed by surgery 4 to 8 weeks later for these patients (14). As a next step in the evolution of preoperative chemo-RT and surgery protocols for patients with rectal cancer, investigators are now combining new agents, such as irinotecan, with 5-FU and RT in neoadjuvant studies. Others have evaluated the use of hyperfractionated irradiation plus concomitant infusion 5-FU as a means to improve the complete pathologic response rates with lower rates of toxicity compared with conventionally fractionated RT.

Investigators from Thomas Jefferson University Hospital have reported their preliminary results in 46 patients with rectal cancer treated by the combination of preoperative weekly Irinotecan (CPT-11), continuous infusion 5-FU, RT, and surgery (15). This therapy has been well-tolerated, with acceptable Grade 3 or 4 toxicity. The pathologic complete response rate of these patients was 39%.

RTOG 0012 is a randomized Phase II study that will build on the infusion 5-FU plus CPT-11 pilot data generated at Jefferson and the twice-daily RT plus infusion 5-FU data from the University of Kentucky. One hundred patients with clinical T3 or T4 rectal cancer will be randomized to either standard RT (pelvis, 45 Gy at 1.8 Gy/day and boost to tumor, 5.4 Gy for T3 and 9 Gy for T4) with infusion 5-FU and weekly irinotecan or hyperfractionated RT (pelvis, 45.6 Gy at 1.2 Gy twice daily and boost to tumor, 9.6 Gy for T3 and 14.4 Gy for T4). The primary end points of this study are the determination of the pathologic complete response rates. The secondary end points include acute and late normal tissue tolerance, patterns of failure, and complete resection rates. The results of RTOG 0012 may be used to help generate a subsequent Phase III trial in the treatment of clinical Stage T3–4 rectal cancer requiring preoperative therapy.

Postoperative therapy. The RTOG will participate extensively in the design and execution of the next GI Intergroup Rectal Study, which will follow the recently closed SWOG-led study. The exact design is at this time uncertain, because the SWOG study only recently closed. The potential issues to study are the incorporation of irinotecan and the determination of the need for RT for carefully selected T3N0 and T1–2N1 lesions in patients who underwent modern radical surgery.

Anal cancer

RTOG 98-11, a Phase III intergroup study, randomizes 650 patients with anal cancer to one of two treatment arms: RT with concurrent 5-FU and mitomycin-C vs. RT plus induction and concurrent 5-FU and cisplatin. This study is the first prospective randomized study to examine the potential value of an alternative regimen, 5-FU and cisplatin, to the reference standard regimen, 5-FU and mitomycin-C. Phase II studies have reported that the toxicity of RT with 5-FU and cisplatin may be less severe than RT with 5-FU and mitomycin-C (16). Furthermore, 2 cycles of induction 5-FU and cisplatin may further enhance local and distant control, sphincter preservation, and overall survival for patients with anal cancer. The accrual has improved from 3 patients monthly in 1999 to 7.5 patients monthly in 2000.

Hypothesis 2: Conformal 3D RT techniques reduce the acute and late morbidity associated with aggressive contemporary chemo-RT protocols

Esophageal cancer

As described above, RTOG 0113 serves as a replacement study to RTOG 94-05. This is a randomized Phase II study testing two paclitaxel-based regimens with conventional dose (50.4 Gy) RT. Although this study is not being run in

conjunction with the 3D Quality Assurance Center, protocol specifications mandate image-based CT-planning, which is expected to reduce the volume of normal tissue treated compared with that treated in RTOG 94-05. These guidelines have been coordinated with the Image-Guided RT Committee. This is hypothesized to result in improved acute and late tolerance to this treatment-intensive protocol. Follow-up studies to RTOG 0113 will incorporate newer 3D treatment planning, including dose–volume histogram analyses for heart, lung, and normal esophagus and, possibly, biologic imaging (e.g., positron emission tomography) to determine the target volumes.

Gastric cancer

As described under Hypothesis 1, the RTOG has developed a randomized Phase II study that will use the same two paclitaxel regimens used in the nonoperative esophageal study for an adjuvant study of patients with resected gastric cancer (RTOG 01-14). As with RTOG 0113, an important component of this study will be the use of image-based RT planning, rather than the simple two-field techniques used for most patients in Intergroup 0116. Because the target volumes for this patient population are large and irregular (gastric remnant, anastomosis, celiac/superior mesenteric nodal bed, porta hepatic nodes) and the large number of adjacent critical structures (liver, small bowel, kidneys, spinal cord), efforts to minimize the normal tissue RT by 3D techniques are imperative.

Pancreas

Although the primary research efforts of the RTOG in pancreatic cancer will focus on new chemotherapy and biologic agents, inoperable pancreatic cancer is an interesting target for dose escalation/intensification by way of 3D conformal therapy. As described in other sites (e.g., Lung Cancer), dose escalation/intensification does not simply mean increasing the number of fractions of conventional-dose RT as tested in RTOG 94-05. A dose intensification strategy in pancreatic cancer would incorporate image-guided modalities to minimize the volumes treated to the higher dose and evaluate the role of intensity-modulated RT to deliver a higher dose per fraction to gross tumor while irradiating adjacent microscopically infested regions to a moderate dose per fraction, with normal tissues receiving only very low doses of RT. In addition, concurrent and post-RT systemic therapy will be administered in a developing 3D intensity-modulated RT pancreas trial developed in concert with the Image-Guided RT Committee.

Biliary tree

The tolerance of the liver to fractionated RT is an important consideration in RT field design for patients with biliary, pancreatic, and gastric carcinoma. A joint Phase II protocol from RTOG and European Organization for Research and Treatment of Cancer will evaluate the use of preoperative chemo-RT for biliary tract carcinoma. Patients will receive 50.4 Gy preoperative external beam RT with chronomodulated infusion 5-FU (RTOG developing protocol 1020). The objective is to determine the activity of chronomodulated 5-FU infusion in combination with irra-

diation. Because of the intimate location of this malignancy with the liver, this study will also afford a unique opportunity to evaluate 3D conformal RT techniques in this anatomic location. The investigators have written guidelines for 3D techniques, and an assessment of the acute and late morbidity by these techniques will be evaluated.

Anorectal

It is expected that in the latter half of the new grant cycles, several Phase II studies will be developed in conjunction with the Image-Guided RT Committee that will integrate modern image-based RT planning and delivery. The purpose of these studies will be to assess the feasibility of sparing normal tissue (particularly small bowel) while maintaining RT dose intensity and integrating more aggressive chemotherapy into the treatment of these neoplasms. It is hypothesized that this newer RT planning will decrease the acute and late toxicity of treatment.

Hypothesis 3: Molecular markers can serve not only as prognostic indicators of outcome to treatment but as guides to therapy selection

Esophageal cancer

Few data exist on the prognostic importance of biomarkers in esophageal cancer. Given the Committee's success in patient accrual and completion of esophageal studies, this represents a unique opportunity to initiate translational research in this disease. Three types of genetic markers could be evaluated: cell proliferation (PCNA or Ki-67 staining), cell apoptosis (TUNEL staining), and genetic alterations (oncogene activation, tumor suppressor gene inactivation, and microsatellite instability). Assays of oncogene activation would include cyclin D1 and epidermal growth factor overexpression by immunohistochemistry techniques. Tumor suppressor gene inactivation would be measured by p53 overexpression and by immunohistochemistry techniques. Microsatellite instability would be assessed by polymerase chain reaction techniques. Future RTOG studies in esophageal cancer will prospectively collect tumor samples for analysis of some of the above potential markers, the presence of which will be correlated with outcome.

Pancreatic cancer

CA19-9 levels. Several published papers have reported a dramatically worse survival in pancreatic patients with elevated CA19-9 values (17–21). The patient series from the Fox Chase Cancer Center was used for sensitivity analyses. At the 1997 Society for Surgical Oncology meeting, the Fox Chase investigators reported that the patients with 3-month postresection CA19-9 levels of 180 U/ml had significantly worse survival (21). On multivariate analysis, the 3-month postresection CA19-9 level proved to be the most prognostic factor for absolute survival and disease-free survival. This study seeks to confirm this observation in a multicenter trial and possibly refine their proposed cutpoint. Of 40 patients in the series, 20% were Lewis antigen negative, 27% had CA19-9 >180 U/ml, and 53% had CA19-9 <180 U/ml. For planning purposes, the survival of each of the groups was assumed to exponentially distributed. The treat-

ment component of the study was designed to accrue patients for 5 years, and they would be followed for an additional 1.33 years before the final analysis was undertaken, with a total of 207 deaths. Using the Fox Chase data, it is estimated that 25 patients, who were Lewis antigen negative, would be dead at the time of the final analysis. Two hundred forty-three patients have been enrolled in this study, of which 172 currently have blood samples available. On the basis of this analysis, future RTOG studies in pancreatic cancer may be able to use the CA-19-9 level as a factor in stratification and monitoring the success of treatment, similar to prostate-specific antigen in prostate cancer. *ras/FTI studies.* As described in Hypothesis 1, a major area of protocol development in the GI Committee will be the farnesyl-transferase inhibitors as an adjuvant therapy to chemo-RT for pancreatic cancer. These studies will include the collection of tumor samples for analysis of ras mutations and expression of the Ras (and related) proteins in an effort to correlate outcome with these factors.

RTOG 98-12. As a component of RTOG 98-12, p53 and p16 status will be determined from pancreatic tumor tissue samples and each characterized as a dichotomous variable and assessed for prognostic importance. One hundred twenty-two patients have been enrolled in this study, of whom 29 currently have tissue blocks available for analysis.

Molecular-guided chemo-RT for rectal cancer

Concurrent and/or maintenance 5-FU-based chemotherapy with RT forms one of the major foundations of treatment of patients with GI cancers enrolled in RTOG protocols. At present, patients receive fixed regimens of 5-FU without consideration of patient variations in the levels of critical enzymes (thymidylate synthase [TS], thymidine phosphorylase [TP], and dihydropyrimidine dehydrogenase [DPD]) involved in the metabolism of 5-FU. Differences in these enzyme levels may be important in predicting the response to 5-FU. For example, tumors that express high levels of TS are resistant to 5-FU. Drugs are now available (eniluracil, capecitabine, irinotecan, oxaliplatin) that can be alternatives to 5-FU.

In the development of future clinical studies, phenotype-based therapy vs. a fixed regimen approach of 5-FU may become increasingly important. To establish the feasibility and frequency of differences in 5-FU degradative enzymes, TS, TP, and DPD levels will be assayed by immunohistochemical techniques in the rectal cancer biopsies of patients entering RTOG 0012. As previously discussed, RTOG 0012 is a randomized Phase II study evaluating two neoadjuvant 5-FU chemo-RT therapies for patients with clinical T3 and T4 rectal cancer. The future replacement study will be a randomized Phase II trial that will expand on the theme of potential future phenotype-based therapy. Patients will be randomized to one of two arms: (1) eniluracil plus 5-FU and RT then surgery then eniluracil plus 5-FU plus irinotecan capecitabine; and (2) RT then surgery then capecitabine plus irinotecan. All randomized patients must have tissue submitted to a central facility to determine the TS, TP, and DPD levels. Outcome analyses of the pathologically com-

plete response, disease control (local and distant), and survival (overall and disease free) will be correlated with the TS, TP, and DPD levels to develop a database regarding the potential of future phenotype-based therapy.

In the future, a potential replacement study of neoadjuvant chemo-RT for rectal cancer could be based on the phenotypic differences in these enzyme levels.

RTOG 98-11 and follow-up studies of the anal canal

An analysis of the anal cancer protocol RTOG 87-04 suggested that patients with anal cancers exhibiting p53 overexpression had a poorer outcome. In the current anal cancer trial, a complementary study will seek to confirm this observation in a larger number of patients. It will also

evaluate two other tumor markers, human papilloma virus and enzyme marker HAP1. One hundred thirty-six patients have been enrolled in this study, of whom 113 currently have tissue blocks available for analysis.

A potential future Phase I/II study after the completion of RTOG 98-11 may be to combine molecular theories that restore normal p53 function with conventional chemo-RT. These strategies may include local and/or systemic administration of p53 using one or more types of vectors. Alternatively, a strategy may be to deliver drugs that antagonize the genes and gene byproducts of the human papillomavirus. The exact protocols will depend on the preclinical and early clinical data available in the latter half of the new grant cycle.

Projected timeline for gastrointestinal protocols

	'01	'02	'03	'04	'05	'06	'07
Esophagus							
0113 (nonoperative)		●	→				
Phase III Nonoperative (e.g., "best" arm of 0113 vs. control from 94-05); incorporate 3D planning				●	→		
Phase III operative (intergroup)		●	→				
Gastric							
99-04 (preoperative)		●	→				
0114 (postoperative)	●	→					
Phase III adjuvant (e.g., 0114 or similar regimen vs. control from 90-18)				●	→		
Pancreas							
0020 (Nonoperative)	●	→					
Phase I/II nonoperative RT dose intensification with chemo/FTI based on 0020 (limited institution 3D dose image-guided study)			●	→			
Phase III nonoperative (based on above studies compared with "standard" chemo-RT). Incorporate 3D planning.					●	→	
Phase I/II operative (incorporate concurrent gemcitabine and/or FTI); incorporate 3D planning		●	→				
Phase III adjuvant (e.g., best arm from 97-04 with vs. without FTI); incorporate 3D planning				●	→		
Rectum							
0012 (Phase II preoperative)		●	→				
Phase II preoperative study (chemo-RT regimen based on molecular markers) incorporate 3D planning				●	→		
Phase III preoperative (e.g., best arm from above studies vs. "standard" chemo-RT); incorporate 3D planning						●	→
Phase III Intergroup postoperative rectal study		●	→				
Anal							
98-11 (Phase III study)		●	→				
Phase II (best arm from 98-11 + p53 and/or anti-HPV gene therapy); incorporate 3D planning.						●	→

REFERENCES

1. *Cancer J Sci Am* 1996;2:205-211.
2. John M, Pajak T, Kreig R, *et al.* Dose escalation without split-course chemo-RT for anal cancer: Results of a phase II RTOG study proceedings. ASTRO 97.
3. MacDonald JS, Smalley S, Benedetti J, *et al.* Postoperative combined radiation, and chemotherapy improves survival in resected adenocarcinoma of the stomach and GE junction: Results of intergroup study INT-0116 (SWOG 9008). *Proc Am Soc Clin Oncol* (ASCO) 2000;19:1a (#1).
4. Martenson J, Willett C, Sargent T, *et al.* A phase III study of adjuvant radiation therapy (RT), 5-fluorouracil (5-FU), and levamisole (LEV) vs 5-FU and LEV in selected patients with resected, high risk colon cancer: Initial results of Int 0130. *J Clin Oncol* 1999;18:235a.
5. Burriss HA, Moore MJ, Anderson J, *et al.* Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer—A randomized trial. *J Clin Oncol* 1997;15:2403-2413.
6. Safran H, King T, Choy T, *et al.* Paclitaxel and concurrent

- radiation for locally advanced pancreatic and gastric cancer: A phase I study. *J Clin Oncol* 1997;15:901–907.
7. Lowy DR, Willumsen BM. Function and regulation of Ras. *Annu Rev Biochem* 1993;62:851–891.
 8. Cox AD, Der CJ. The ras/cholesterol connection: Implications for ras oncogenicity. *Crit Rev Oncog* 1992;3:365–400.
 9. Kohl NE, Wilson FR, Mosser SC, *et al.* Protein farnesyl transferase inhibitors block the growth of ras-dependent tumors in nude mice. *Proc Natl Acad Sci USA* 1994;91:9141–9145.
 10. Kohl NE, Conner MW, Gibbs JB, *et al.* Development of inhibitors of protein farnesylation as potential chemotherapeutic agents. *J Cell Biochem* 1995;22(Suppl.):145–150.
 11. Reuveni H, Gitler A, Poradosu E, *et al.* Synthesis and biological activity of semipeptoid farnesyl transferase inhibition. *Bioorg Med Chem* 1997;5:85–92.
 12. Gibbs J, Oliff A. The potential of farnesyl transferase inhibitors as cancer chemotherapeutics. *Annu Rev Pharmacol Toxicol* 1997;37:143–166.
 13. Zhang F, Kirschmeier P, Carr D, *et al.* Characterization of Ha-Ras, N-Ras, Ki-Ras4A, and Ki-Ras4B as in vitro substrates for farnesyl protein transferase, and geranylgeranyl protein transferase type I. *J Biol Chem* 1997;15:10232–10239.
 14. Rich TA, Skibber JM, Ajani JA, *et al.* Preoperative infusional chemoradiation therapy for stage T3 rectal cancer. *Int J Radiat Oncol Biol Phys* 1995;32:1025–1029.
 15. Mitchell E, Ahmad N, Fry R, *et al.* Combined modality therapy of locally advanced recurrent adenocarcinoma of the rectum: Preliminary report of a phase I trial of chemotherapy (CT) with CPT-11, 5-FU and concomitant irradiation (RT). *J Clin Oncol* 1999;18:247a (#938).
 16. Rich TA, Ajani JA, Morrison WH, *et al.* Chemoradiation therapy for anal cancer: Radiation plus continuous infusion 5-fluorouracil with or without cisplatin. *Radiother Oncol* 1993;27:209–215.
 17. Beretta E, Malesci A, Zerbi A, *et al.* Serum CA-19-9 in the postsurgical follow-up of patients with pancreatic cancer. *Cancer* 1987;60:2428–2431.
 18. Glenn J, Steinberg, WM, Kurtzman SH, *et al.* Evaluation of the utility of a radioimmunoassay for serum CA 19-9 levels in patients before and after treatment of carcinoma of the pancreas. *J Clin Oncol* 1988;6:462–468.
 19. Fuzhou T, Appert HE, Myles J, Howard JM. Prognostic value of serum CA-19-9 levels in pancreatic adenocarcinoma. *Ann Surg* 1992;215:350–355.
 20. Sperti C, Pasquali C, Catalini S, *et al.* CA 19-9, as a prognostic index after resection for pancreatic cancer. *J Surg Oncol* 1993;52:137–141.
 21. Montgomery RC, Hoffman JP, Riley LB, *et al.* Prediction of recurrence and survival by post-resection CA 19-9 values in patients with adenocarcinoma of the pancreas. *Ann Surg Oncol* 1997;4:551–556.