Adjuvant and Neoadvuvant Treatment of Resectable, Locally Advanced, Rectal Carcinoma with Radiation Therapy and Chemotherapy

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Patients who undergo apparently curative low anterior or abdominal-perineal resection of locally advanced carcinoma of the rectum have a significant rate of local pelvic recurrence and death from cancer in the years following surgery. Pre- and postoperative irradiation and chemotherapy in various combinations and schedules have been recommended to improve the outcome for these patients. Several randomized trials have evaluated the effectiveness of adjuvant and neoadjuvant treatments in improving survival and reducing the rate of pelvic recurrence with a combination of radiation and chemotherapy. There is some evidence that preoperative treatment with radiation is more effective than postoperative treatment. The treatment program preferred at Ochsner is described.

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En bloc surgical resection of the involved length of large bowel to remove all evident cancer is the primary curative treatment for locally advanced adenocarcinoma of the colon or rectum. Based on this, colon and rectal carcinoma has been classified in several surgical staging systems (Table 1). The Tumor Node Metastasis (TNM) system is the one currently in use. Locally advanced cancers are taken here to be those that invade through the muscularis propria (stage T3 or T4) or have metastasized to regional lymph nodes (N1 or N2).

Recurrence after apparently curative surgery may develop either in structures adjacent to the margin of resection (local recurrence), in regional lymph nodes, or as metastasis to the peritoneal surface or distant organs. Cancers of the more proximal colon usually recur as disseminated metastatic disease with local or regional recurrence less likely. In contrast, local and regional nodal recurrence in the pelvis is an important component of the failure to cure rectal cancer (1-3). The rate of pelvic recurrence after apparent curative resection of locally advanced rectal tumors is reported in the range of 20% to 50% in the absence of adjunctive treatment with radiation or chemotherapy (3-5).

Pelvic recurrence often cannot be salvaged. Further, it can act as the source of distant metastatic disease and often causes significant debilitation on its own. Reduction in the rate of pelvic recurrence is expected to improve survival and prevent some of the suffering of those who will die from rectal cancer. The addition of radiation treatment and chemotherapy to surgical resection to prevent pelvic recurrence and improve survival of patients with locally advanced rectal cancer has been evaluated in clinical studies over the past 25 years. They can be divided into those using only postoperative adjuvant treatment and those that use some preoperative (neoadjuvant) treatment. The optimal treatment program is a matter of clinical judgment, and opinions are still evolving.

Postoperative Adjuvant Treatment

The principle advantage of postoperative adjuvant treatment (in contrast to preoperative treatment) is in the selection of appropriate patients. The stage of a rectal cancer is most reliably determined by findings at surgery and by examination of the resected organ. This allows identification of patients with true

Table 1. Staging of colon and rectal carcinoma.

Dukes	Modified Astler-Coller	Tumor Node Metastasis (AJCC and UICC)	Description
A	A	T1N0	Primary limited to submucosa, nodes negative.
	B1	T2N0	Primary into but not through muscularis propria, nodes negative.
B	B2	T3N0	Primary through muscularis propria, nodes negative.
C	C1	T2N1 or N2	Primary into but not through muscularis propria. 1 to 3 nodes (N1), 4 or more nodes (N2) positive.
	C2	T3N1 or N2	Primary through muscularis propria. Nodes as above.
		T4N1 or N2	Primary invades adjacent organs. Nodes as above.

Table 2. Randomized trials of surgery (S) alone versus surgery followed by irradiation (S + xrt) for rectal carcinoma.

Name (ref) Year Published	No. Patients in Each Arm	Therapy Arm	5-Year Local Recurrence % (p)	5-Year survival % (p)	Comments
GTSG (6,7,8) 1985	58 50	S S + xrt	24 (n.s.) 20	46 (n.s.) 52	40 to 48 Gy in fractions of 1.8 to 2.0 Gy. AP and PA directed fields to pelvis. T3, T4 or node positive patients having curative resection.
Danish (9) 1986	250 244	S S + xrt	18 (n.s.) 16		50 Gy in fraction of 2.0 Gy each through AP/PA and lateral fields.
NSABP R-01 (10) 1988	184 184	S S + xrt	25 (p=0.06) 16	43 (n.s.) 41	46 to 47 Gy in 1.8 Gy fractions. Mostly through AP and PA fields with small lateral or perineal boost. T3, T4 or node positive patients having curative resection.
Dutch (11) 1991	84 88	S S + xrt	33 (n.s.) 24	57 (n.s.) 45	50 Gy in fractions of 2.0 Gy each through AP/PA and lateral fields.
MRC II (12) 1996	235 234	S S + xrt	34 (p=0.001) 20	38 (n.s.) 41	40 Gy in fractions of 2.0 Gy each through AP/PA directed fields to the pelvis. T3 or node positive patients with tumors not fixed on preop examination.

Table 3. Randomized trials of surgery (S) alone versus surgery followed by chemotherpy (S + chemo) for rectal carcinoma.

Name (ref) Year Published	No. Patients in Each Arm	Therapy Arm	5-Year Local Recurrence % (p)	5-Year survival % (p)	Comments
GTSG (6,7,8) 1985	58 48	S S + chemo	24 (n.s.) 27	46 (n.s.) 56	Semustine and 5-fluorouricyl for a total of 18 months after curative surgery. T3, T4 or node positive patients.
NSABP R-01 (10) 1988	184 187	S S + chemo	24.5 21.4	43 (p = 0.05) 53	Semustine, vincristine and 5-fluorouricyl. 10 week cycles for 8 cycles. T3, T4 or node positive patients having curative resection. Survival advantage only seen in males.

Table 4. Randomized trials of surgery alone (S) versus surgery followed by chemotherpy and radiation (S + ch + xrt) and for rectal carcinoma.

Name (ref) Year Published	No. Patients in Each Arm	Therapy Arm	5-Year Local Recurrence % (p)	5-Year survival % (p)	Comments
GTSG (6,7,8) 1985	58 46	S S + ch + xrt	24 (p = 0.009) 11	46 (p = 0.07) 59	Semustine and 5-fluorouricyl in10-week cycles for 18 months after curative surgery. 4o to 44 Gy irradiation in fractions of 1.8 to 2.0 Gy each to the pelvis through AP and PA ports starting within 60 days of surgery.
Norwegian (13,14) 1995	72 72	S S + ch + xrt	30 (p = 0.01) 12	50 (p = 0.05) 64	46 Gy in fractions of 2.0 Gy each starting within 8 weeks of curative surgery. Bolus 5-fluorouricyl on 6 days of radiation treatment. Radiation directed to posterior pelvis with PA and lateral fields.

Table 5. Randomized trials of surgery followed by radiation (S + xrt) versus surgery followed by chemotherpy and radiation (S + ch + xrt) for rectal carcinoma.

Name (ref) Year Published	No. Patients in Each Arm	Therapy Arm	5-Year Local Recurrence % (p)	5-Year survival % (p)	Comments
NCCTG (15) 1991	100 104	S +xrt S + ch + xrt	25 (p = 0.036) 13	47 (p = 0.02) 57	45 to 50.4 Gy in 1.8 Gy fractions to pelvis. Use of AP, PA and lateral fields preferred. Semustine and 5-fluorouricyl given during 64 days prior to starting radiation, during radiation and for 2 months after radiation in chemotherapy arm. Patients with curative resection of T3, T4 or node positive disease.
GTSG (6,7,8) 1985	50 46	S + xrt S + ch + xrt	20 (n.s.) 11	52(n.s.) 59	See GTSG comments in Tables 2 and 3.

T3, T4 or node-positive cancers who have no distant metastatic disease. Such patients have significant chances of local or regional recurrence and the most to gain if recurrence is prevented. They are also candidates for adjuvant treatment and for enrollment in postoperative adjuvant studies. The selection of patients for preoperative adjuvant treatment is without benefit of surgical staging, which is estimated by physical examination, transrectal ultrasound, CT or MRI, and other radiographic findings such as positron emission tomography.

The principal disadvantage of postoperative adjuvant treatment is due to the fact that more small and large bowel reside in the pelvis after rectal excision and are exposed to the radiation treatment. In particular, after low anterior resection both proximal and distal sides of the rectal anastomosis are irradiated. After preoperative irradiation, the proximal side is usually unirradiated bowel, which adapts better to the reservoir function of rectum. The possibility of implantation of cancer cells in the perineal incision during surgery makes it appropriate to include the perineal crease in the postoperative irradiated volume after abdominal-perineal resection. This may result in significant reaction in the sensitive skin of this area during the course of treatment. It is usually unnecessary to include this area in the preoperative radiation treatment volume.

Tables 2-6 summarize the results from randomized trials of postoperative adjuvant treatment with radiation and chemotherapy conducted over the past 20 years. Patients had generally undergone an apparently curative low anterior or abdominal-perineal resection, i.e. with the finding of negative resection margins. They had histologically verified stage T3 or T4 primary tumors or lymph node metastases.

The effectiveness of postoperative radiation in reducing the rate of pelvic recurrence after apparently curative resection is amply demonstrated in Tables 2, 4 and 6. This alone, to some, justifies its use. The Norwegian trial (14) used a minimal chemotherapy regimen consisting of only six treatments with a 5-fluorouracil bolus given as a radiation sensitizer and found a statistically significant improvement in survival (Table 4). This can be viewed as a demonstration that postoperative radiation does improve survival. However, survival benefit of postoperative radiation treatment, without any chemotherapy, has yet to be demonstrated in a randomized trial.

Since pelvic recurrence is such an important component of the failure to cure rectal cancer, it is puzzling that several trials show significant reduction in local recurrence but have failed to show survival benefit of postoperative irradiation. This may be due to

Table 6. Randomized trials of surgery followed by chemotherapy (S + ch) versus surgery followed by chemotherapy and radiation (S + ch + xrt) for rectal carcinoma.

Name (ref) Year Published	No. Patients in Each Arm	Therapy Arm	5-Year Local Recurrence % (p)	5-Year survival % (p)	Comments
GTSG (6,7,8) 1985	48 46	S +ch S + ch + xrt	27 11	56 59	See Tables 2 and 3 GTSG comments.
NSABP R-02 (16) 2000	348 346	S + ch S + ch + xrt	14 (p = 0.02) 8	58 (n.s.) 58	5-fluorouricyl, semustine and vincristine in 10-week cycles for 5 cycles (males only), or 5-fluorouricyl and leukovorin in 8-week cycles for 6 cycles (females and some males). 45 to 50.4 Gy in fraction of 1.8 Gy each using AP, PA and lateral fields to the pelvis. Radiation starting 3 to 5 weeks after the first cycle of chemotherapy (14 to 21 weeks after curative resection).

Table 7. Randomized trials of surgery (S) alone versus irradiation followed by surgery for rectal carcinoma.

Name (ref) Year Published	No. Patients in Each Arm	Therapy Arm	5-Year Local Recurrence % (p)	5-Year survival % (p)	Comments
EORTC (19) 1988	175 166	S 34.5 Gy+ S	30 (p < 0.03) 15	59 (n.s.) 52	15 fractions of 2.3 Gy each. surgery a mean of 11 days after end of xrt. AP/PA fields to pelvis and cephalad to L2.
Norwegian (20, 21) 1990	145 155	S 31.5 Gy + S	21 (n.s.) 14	58 (n.s.) 57	18 fractions of 1.75 Gy each. Surgery 2-3 weeks after xrt. AP/PA fields to pelvis and cephalad to L2.
ICRF (22) 1994	234 234	S 15 Gy + S	24 (p < 0.05) 17	------	Surgery within 48 hours after end of xrt. AP/PA fields to pelvis.
Manchester (23) 1994	141 143	S 20 Gy + S	36 (p < 0.0001) 13	28 (p = 0.21*) 41	4 fractions of 5.0 Gy each, surgery within 1 week of xrt. * 5-year survival of those having curative resection: 62% with radiation and 43 % with surgery only (p = 0.03). Rotational fields to pelvis.
Stockholm I (24) 1995	425 424	S 25 Gy + S	28 (p < 0.01) 14	36 (n.s.) 36	5 fractions of 5.0 Gy each. Surgery within 1 week of xrt. AP/PA fields to pelvis and cephalad to L2.
MRC II (25) 1996	140 149	S 40 Gy + S	48 (p = 0.04) 32	19 (p = 0.09*) 26	20 fractions of 2.0 Gy each, Surgery 4+ weeks after xrt. AP/PA fields to pelvis. Fixed or partially fixed tumors. *Disease free survival at 5 years: surgery alone is 23% and with radiation is 31 % (p=0.05).
Swedish (26) 1997	585 583	S 25 Gy + S	27 (p < 0.001) 11	48 (p < 0.001) 58	5 fractions of 5.0 Gy each. Surgery within 1 week of xrt. AP/PA and lateral fields to pelvis.
Stockholm II (17) 2001	285 282	S 25 Gy + S	25 (p < 0.001) 12	36 (p = 0.2*) 39	5 fractions of 5.0 Gy each, surgery within 1 week week of xrt. AP/PA and lateral fields to pelvis. *5-year survival of those having curative resection: 46% for those having preop xrt and 39 % for those having surgery only (p=0.03).
Dutch TME (27) 2001	908 897	S 25 Gy + S	8.2 (p < 0.002*) 2.4	81.8 (n.s.*) 82.0	*2-year local recurrence and survival values. 5 fractions of 5.0 Gy each. AP/PA and lateral fields to pelvis. Total mesorectal excision.

distant metastases being a more important cause of death than was supposed, or to secondary effects of radiation causing an increase in the death rate from nonrectal cancer causes. It is possible that the irradiation of bowel after surgery increases the risk of subsequent nonrectal cancer death, as has been observed for some preoperative studies (17). If so, irradiation with multiple fields sparing more bowel may be important. Such technique, used in the Norwegian trial, has become standard in the past 10 years.

On the other hand, the addition of chemotherapy to a postoperative adjuvant treatment regimen (Tables 3 and 5) has produced statistically significant improvement in survival in two of the four trials: NSABP R-01 (10) and NCCTG (15), which also demonstrated a significant effect on local recurrence. The inclusion of both chemotherapy and radiation in postoperative adjuvant treatment (Table 3) resulted in significant improvement in both local recurrence and survival. The results from the R-01 trial and the Gastrointestinal Tumor Study Group (GITSG) trial (8) were influential in the National Institutes of Health (NIH) consensus recommendation of postoperative radiation and chemotherapy as adjuvant treatment for locally advanced, curatively resected rectal cancer (18). The absence of survival benefit with the addition of radiation to postoperative chemotherapy in the recent NSABP R0-2 trial (16) suggests, to some, that radiation treatment need not be included routinely in postoperative adjuvant treatments. The failure of radiation to increase survival in this trial may be due to either a surprisingly low local recurrence rate in the arm with no radiation and the long delay (up to 21 weeks after surgery) before starting radiation.

Preoperative Adjuvant (Neoadjuvant) Treatment

Several further advantages have been claimed of preoperative treatment that could lead to a decrease in local recurrence and improved survival. The cell kill from radiation treatment prior to surgery may reduce the chance of implantation of viable cells in the surgical wound and the chance of perioperative spread of viable cells to the peritoneal cavity or distant sites. Tumor shrinkage and down-staging may facilitate curative resection and, for the more distal tumors, sphincter-preserving surgery. There is concern, however, that preoperative pelvic irradiation may impair postsurgical healing.

Randomized trials comparing preoperative (neoadjuvant) radiation treatment with surgery alone are summarized in Table 7. None has included chemotherapy. All showed a decrease in local recurrence in the treatment arm. With the exception of the Norwegian study, this reached statistical significance.

The Swedish trial (26) alone showed a statistically significant improvement in survival at 5 years in favor of preoperative radiation treatment, considering all randomized patients. However, if only patients who actually had a curative resection are considered, the Stockholm II trial (17) and the Manchester trial (22) showed statistically significant improvement in 5-year survival. The Medical Research Council Rectal Cancer Working Party (MRC II) trial (25) nearly showed statistically significant improvement in overall survival ($p=.09$). The benefit in disease-free survival was statistically significant. The estimated rate of cause-specific death in the MRC II trial indicates a statistically significant 29% reduction in the chance of death from rectal cancer ($p = 0.03$).

The Stockholm and Swedish trials used nearly the same treatment regimen, which illustrates some implications of choices made in designing preoperative radiation treatment. Irradiation was carried out over a period of 5-7 days, and surgery took place within a week of the last radiation treatment. This regimen of radiation was chosen to be biologically equivalent to a longer course of about 45 Gy in fractions of 1.8 to 2.0 Gy over a 4-5 week period, such as is used in most postoperative treatment. The Stockholm I trial (24) specified the radiation field to cover the pelvic and para-aortic nodal areas up to and including L2 and to be given through anteroposterior-directed and posteroanterior-directed fields only. The postoperative mortality within 30 days in Stockholm I was increased significantly in the irradiated patients, particularly in the elderly. The later Stockholm II and Swedish trials reduced the field size to include only the pelvis and up to the lower half of L4 and specified the addition of lateral-directed fields to exclude some bowel from the full dose of radiation. In the Swedish trial, postoperative in-house deaths were 3% (15 patients) among the surgery alone group and 4% (22 patients) among those irradiated—not a statistically significant difference. It was also noted in the Stockholm II trial that 5% of the irradiated patients and only 1% of control patients died of intercurrent disease within 6 months of surgery ($p = 0.02$). Cardiovascular illness was the most frequent cause of intercurrent death, suggesting an unexpected relation to pelvic irradiation. The excess cardiovascular deaths were most frequent among a minority of patients who were treated with anteroposterior and posteroanterior field without any lateral field to spare anterior bowel. Intercurrent death more than 6 months after surgery was similar in each arm. Postoperative complications occurred in 44% of irradiated patients and 34% of surgery-only patients. The excess in complications was attributable to an excess of perineal wound infections in the irradiated patients. The perineum was routinely included in the treated field; this is now felt to be unnecessary for most patients.

In the Stockholm and Swedish trials, any patient was eligible for whom a low anterior or abdominal-perineal resection was expected to be curative. This excluded those with preoperative evidence of metastatic disease, those for whom a local excision was planned, and those who were anticipated to have unresectable disease. The design includes some patients with node-negative disease and T1 or

T2 primary tumors that have relatively good chance of cure without adjuvant treatment. In the Swedish trial, 33% of irradiated and 28% of surgery-only patients were found to have T1N0 or T2N0 disease after resection. Stage T3N0 was found in 35% of irradiated a 31% of surgery-only patients. Node-positive disease was found in 32% of irradiated and 41% of surgery-only patients (28). The imbalance in stages could be by chance or could reflect a slight tendency to down-staging resulting from the radiation treatment, even though the short interval between beginning radiation and surgery is not expected to allow for much disappearance of cancer.

In the Norwegian trial (21), patients in the treated arm were irradiated to a dose of 31.5 Gy in 18 fractions of 1.75 Gy each over a 3.5-week period, and surgery followed 2-3 weeks after (Table 7). This regimen has an estimated biological effectiveness of about two-thirds of that of the Stockholm and Swedish regimens. The longer interval between starting radiation treatment and surgery is expected to allow for more response of the cancer to the radiation before resection. The Norwegian trial found the average tumor size at surgery was significantly reduced in the treatment arm. Six patients (4.4%) had no tumor remaining in the specimen at surgery. The surgery-only arm had 27.5% and the irradiated arm had 18.4% ($p < 0.05$) of patients with carcinoma in the lymph nodes removed at surgery. These results with relatively low-dose preoperative radiation treatment indicate that there is down-staging. In the Norwegian trial, there was no apparent effect of the preoperative treatment on survival.

The MRC II trial and the Manchester trials differ from others shown in Table 7 in that only patients with cancers judged to be tethered (partly fixed) or fixed were randomized. These patients likely had more locally advanced cancers than the Swedish and Stockholm trial patients. The MRC II trial differs from the Norwegian trial in that a longer, higher-dose course of preoperative radiation was employed (i.e. 20 fractions of 2.0 Gy each over 4 weeks), and a longer interval of 4 weeks between radiation and surgery was specified. The MRC II trial confirms the observation of the Norwegian trial that significant down-staging occurs after irradiation.

The Dutch trial (27) was devised to test the proposal that total mesorectal excision (TME) of the rectum by trained rectal surgeons may reduce the chance of residual cancer in enough patients to remove the advantage of adjuvant or neoadjuvant pelvic irradiation. Patients eligible for enrollment in the trial were similar to those of the Stockholm and Swedish trial. Those with fixed tumors were explicitly excluded. Randomization was to either TME alone or TME preceded by a course of radiation the same as in the Swedish and Stockholm II trials. Participating surgeons were trained in the TME operation. The results at 2 years follow-up, as postulated, show an unusually low local recurrence rate in the surgery only arm of 8.2%. As in almost all prior preoperative irradiation trials, there is statistically significant reduction in local recurrence to 2.4% in the irradiated arm. No survival difference is evident; however, this may develop with longer follow-up.

The Stockholm II, Swedish, MRC II, and the Manchester trials demonstrate that with well-chosen dosage, dose fractionation, and treatment technique minimizing the volume of irradiated bowel, preoperative radiation treatment not only decreases local recurrence in the pelvis, it likely improves the chance of curing the cancer by surgical resection and improves survival. It accomplishes this by eradicating cancer cells that are not removed in the surgical specimen. These cells are likely found in soft tissue at the radial margin of the dissection (29) and in lymph nodes on the pelvic wall not removed with the rectum. There is also down-staging that may permit sphincter-sparing surgery.

Summary of Current Treatment Issues

The improvement in survival and freedom from pelvic recurrence that is achieved with the addition of adjuvant or neoadjuvant chemotherapy and pelvic irradiation to the treatment of resectable, locally advanced, rectal carcinoma, as demonstrated in several of the randomized trials listed in Tables 2-7, justifies the recommendation of both chemotherapy and radiation in these patients.

The choice between preoperative or postoperative irradiation as part of an adjuvant treatment program is usually determined by the preference of the surgeon. A randomized trial of preoperative irradiation versus postoperative irradiation to help resolve this issue was reported in 1990 (30,31). Patients were eligible if they had a resectable rectal cancer for which an abdominal-perineal or anterior resection was planned. Those randomized to preoperative treatment were treated with five fractions of 5.1 Gy each over a 1-week period and operated within 1 week of the final radiation treatment. Of the 471 patients, those randomized to have postoperative treatment were staged after the surgery. Those found to have T1N0 or T2N0 stages were given no adjuvant treatment. Those with T3 or T4 or node-positive cancers were treated with 40 Gy in 2 Gy fractions over 4 weeks starting 4-8 weeks after surgery and with an additional 20 Gy in 2 Gy fractions after a 2-week break. The field was reduced for the last 10 Gy. Radiation treatments were with a 3-field technique to spare anterior bowel. Overall survival and cancer specific survival were not significantly different in the two arms. The 5-year local recurrence rate was about 14% in the preoperative arm and 28% in the postoperative arm, which is statistically significant. The authors concluded that the preoperative treatment was preferable because of the greater effectiveness in reducing local recurrence with a dose that is biologically less than used in the postoperative arm.

If preoperative treatment is planned, it is desirable to exclude patients with T1N0, T2N0, and metastatic disease by thorough evaluation including transrectal ultrasound. The regimen we

prefer consists of pelvic irradiation, utilizing 3 or 4 fields to exclude anterior lying bowel from the full dose of irradiation and excluding the perineum from the treatment volume in all but the most distal tumors. Irradiation is to a dose of 45 to 50.4 Gy in fractions of 1.8 or 2.0 Gy over a 5-week period. Chemotherapy including 5-fluorouracil is given during the course of radiation as a sensitizer. The patient is then given about 6 weeks of rest to recover before undergoing the planned surgery. If the findings at surgery indicate there was nodal metastasis or penetration through the bowel wall, as expected, additional courses of chemotherapy are given. Retrospective series of patients similarly treated have recently been reported (32,33) that confirm the expectation of low local recurrence, high survival, and low morbidity of treatment. Alternatively, a shorter 1-week course of higher fractional dose radiation treatment with immediate postradiation surgery (like the treatment favored in the Scandinavian trials) may be chosen. Postoperative chemotherapy may be reserved for those found to have locally advanced disease stages. The longer course is particularly suitable for patients with tethered or fixed tumors of doubtful resectability, to take advantage of down-staging. However, a randomized trial comparing the longer and shorter preoperative radiation courses would be helpful.

If postoperative adjuvant treatment is preferred, or if a patient is found at surgery to have more locally advanced disease than was anticipated, a course of treatment with radiation and chemotherapy based on those of the NCCTG, NSABP or GTSG trials can be used.

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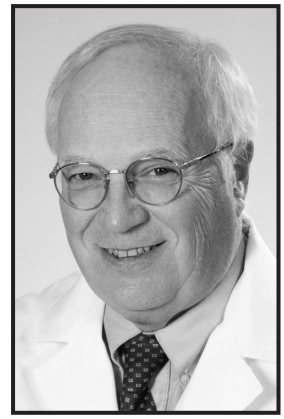

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