

Low Dose Preoperative Radiation in the Treatment of Carcinoma of the Rectum



Ann. Ital. Chir., LXXII, 5, 2001

M. MOHIUDDIN

Professor and Chairman, Department of Radiation Medicine
University of Kentucky, Lexington, Kentucky

Recent advances in the treatment of cancer of the rectum continue to show a steady improvement in survival. Newer surgical techniques and expanding options for adjunctive therapy appear to have had a significant impact on improving both local control and distant disease. Five-year survival of patients now ranges from 85-90% for stage I cancers and 50-55% for stage III cancers. Local recurrence of disease following curative surgical resections is dependent on the stage of the tumor and for some high-risk patients, stages T3/T4 and N+ disease, has been reported as high as 40-60%. In an attempt to lower the rate of local recurrence and improve survival, several approaches to adjuvant therapy have been utilized. Preoperative radiation was one approach that has been used extensively in the last several decades. The clinical and biological basis for the use of preoperative radiation lies in the fact that significant tumor shrinkage can be obtained with relatively modest doses of radiation. In addition sterilization of the periphery of the tumor can allow not only more complete surgical resection of the disease but also prevent lymphatic and venous dissemination of tumor cells during surgery. One of the fundamental arguments against the use of preoperative radiation has been that tumor shrinkage can alter the tumor architecture and hence mask the true stage of disease making it difficult to assess the need for additional therapy or to compare results of treatment.

Initial studies with preoperative radiation, especially prior to 1980, used moderate dose treatment 2000-4000 cGy. The results of the Veteran's Administrative Group ran-

Abstract

Recent advances in the treatment of cancer of the rectum show a steady improvement in survival. Newer surgical techniques and expanding options for adjunctive therapy appear to have had a significant impact on improving both local control and distant disease. Five-year survival of patients now ranges from 85-90% for stage I cancers and 50-55% for stage III cancers. Local recurrence of disease following curative surgical resections is dependent on the stage of the tumor and for some high-risk patients, stages T3/T4 and N+ disease, has been reported as high as 40-60%. In an attempt to lower the rate of local recurrence and improve survival, several approaches to adjuvant therapy have been utilized. Preoperative radiation was one approach that has been used extensively in the last decades. Recently, the large Swedish randomized studies using a short course (5 Gy x 5) of preoperative radiation have reported a clear improvement in local control and survival of patients. These results were achieved with no downstaging of disease since surgery was performed put immediately after irradiation. Therefore it should be presumed that preoperative radiation therapy resulted in the sterilization of tumor cells, which prevented both local and distant dissemination leading to the improved outcome. The question remains, therefore, as to what is the least and/or the most appropriate dose of preoperative irradiation that can achieve the beneficial effect of minimizing tumor cell dissemination at surgery. Low dose preoperative irradiation as a single fraction of 500 cGy appears to have a sound biological basis and in single institutional studies it was shown to be effective but in randomized studies it did not improve results. This is likely to be due to a poor design of trials and/or inappropriate patient selection for these studies. A well-designed study still remains to be done.

Key words: Rectal neoplasms, radiotherapy, dose-response relationship, adjuvant, treatment outcome.

Riassunto

RADIOTERAPIA PREOPERATORIA A BASSE DOSI NEL TRATTAMENTO DEL CARCINOMA RETTALE

I recenti sviluppi nel trattamento del carcinoma rettale continuano a mostrare un progressivo miglioramento in termini di sopravvivenza. Le nuove tecniche chirurgiche e le varie opzioni di terapia adiuvante hanno dimostrato un impatto significativo sia sul controllo locale che sulla incidenza

di metastasi a distanza. Attualmente, la sopravvivenza a 5 anni dei pazienti con malattia al I stadio è del 85-90%, e nei pazienti con al III stadio è del 50-55%. L'incidenza di recidive locali dopo chirurgia radicale è correlata allo stadio tumorale e, in alcuni sottogruppi di pazienti (T3/4 e N+) raggiunge percentuali del 40-60%. Vari approcci terapeutici sono stati testati nel tentativo di ridurre il tasso di recidive e di migliorare la sopravvivenza. Negli ultimi decenni, in particolare, la radioterapia preoperatoria è stata estesamente testata. Recentemente, i risultati del trial svedese in cui è stato utilizzato un trattamento breve (5 Gy x 5 frazioni) di radioterapia, hanno dimostrato un chiaro vantaggio sia in termini di controllo locale che di sopravvivenza. Questi risultati sono stati ottenuti senza che fosse dimostrabile il "downstaging" della malattia, dal momento che la resezione chirurgica veniva eseguita subito dopo la radioterapia. Si può pertanto presumere che la radioterapia preoperatoria abbia determinato una sterilizzazione delle cellule tumorali, in grado di prevenire sia la disseminazione locale, sia la diffusione a distanza, favorendo in questo modo un migliore "outcome" clinico. Resta pertanto aperto il quesito di quale sia il dosaggio ottimale di radiazioni in grado di minimizzare la disseminazione di cellule durante l'atto chirurgico. L'uso di basse dosi di radioterapia preoperatoria (5 Gy in singola frazione) sembra, in questo senso, possedere un teorico vantaggio biologico; esperienze monoistituzionali hanno suggerito una relativa efficacia di questo regime, anche se successivi studi randomizzati non hanno confermato questo dato. Tuttavia, dal momento che questi ultimi presentavano dei difetti sia nel disegno dello studio, sia nelle modalità di selezione dei pazienti, è auspicabile che in futuro sia eseguito uno studio ben disegnato su questo argomento.

Parole chiave: Neoplasie del retto, radioterapia, correlazione dose-risposta, adiuvante, risultato delle terapie.

Biological Basis for Low Dose Preoperative Radiation for Cancer of the Rectum

In 1964, Powers and Tolmach (4) treated a Gardner lymphosarcoma, a tumor that is considered to be moderately radiation resistant in mice, and found that survival in these animals was significantly improved if the tumors were given 500 cGy of radiation immediately prior to surgical removal (43% with surgery alone to 85% when animals preoperative radiation). This improvement was only seen if surgery was carried out within eight hours of the preoperative radiation.

In a similar study, Agostino and Nixon (5) reported the results of treating an implanted Walker tumor into the cecal appendix of 200 female Wistar rats, simulating a colon carcinoma. They demonstrated that a dose of 500 cGy given preoperatively immediately prior to surgery reduced the local recurrence rate from 73% with surgery alone to 53% with radiation followed by surgery. Several other authors (6, 7, 8) have published similar results. Hoyer (9) hypothesized that this approach if it could be translated to human tumors has many attractive features not the least of which was the absence of delay between radiation and surgery. Both treatments could be done on the same day and since the dose of preoperative radiation was relatively small, the tumor architecture at the time of surgery would not be perturbed and the pathological stages of disease would be preserved to allow for accurate tumor staging. Traditionally, histopathological staging has been utilized for patient selection and further adjuvant therapy based on high risk factors of extra rectal tumor spread or the presence of lymph nodes to prevent local and distant failure. The significant advantage of this approach using a single fraction of low dose preoperative radiation is that tumor cells that reside at the periphery of the tumor or in vascular/lymphatic spaces could be sterilized and prevent potential dissemination during surgery. Since these cells are generally in the low-density areas they are well oxygenated and are therefore sensitive to low and moderate doses of radiation. Nias (10) has shown that in cell culture studies a dose of 500cGy can eradicate 90% of well-oxygenated cells. Powers and Palmer (11) reported that in solid tumors, a single dose of 500 cGy would reduce the tumor cell numbers by 1-2 logs of cells. While this reduction in tumor burden would not change the tumor architecture substantially it can have a significant impact on tumor growth delay. One of the fundamental problems with the management of rectal cancer especially low rectal cancers, is the surgical manipulation of the tissue planes that is required to mobilize the cancer. This surgical manipulation has the potential for significant venous and peritoneal dissemination of tumor cells. Several studies have consistently shown the presence of a large number of tumor cells in peritoneal washing (12) and in venous drainage (13, 14, 15) during surgical resection of colon and rectal cancer.

domized trial (1) and the Memorial Sloan Kettering Cancer Center studies (2) indicated significant improvement in survival for stage III cancers with radiation doses of 2000-2500 cGy. However, subsequent confirmatory studies failed to substantiate these results. More recently however the large Swedish randomized studies using a short course (5 Gy x 5) of preoperative radiation have reported a clear improvement in local control and survival of patients (3). These results were obtained without observing any downstaging of disease since surgery was carried out immediately after the radiation. It therefore has to be presumed that the preoperative radiation resulted in sterilization of tumor cells, which prevented both local and distant dissemination leading to the improved outcome. The question remains, therefore, as to what is the least and/or the most appropriate dose of preoperative radiation that can achieve this beneficial effect of minimizing tumor cell dissemination at surgery.

However, the significance of this tumor cell dissemination in patients with cancers of the rectum and colon has not been clearly established (16, 17). Studies have shown that cells obtained from peritoneal washings during rectal cancer surgery are viable and can be grown in culture and can form tumors in mice if transplanted. Other studies have also shown that when the rectum is perforated, during surgical resection patients have a worse outcome because of tumor cell dissemination than patients in whom the rectum remains intact during surgery (18). In earlier studies, Turnbull (19), from the Cleveland Clinic, had demonstrated that using a "no touch" technique in colon cancer surgery can reduce the presence of tumor cells in the peripheral venous blood of patients and can significantly improve survival of patients. He had recommended that early ligation of the inferior mesenteric vein can also reduce the number of tumor cells in circulation and therefore is an essential part of colon cancer resection. While the "no touch technique" no longer remains the central focus of rectal surgery, early ligation of the inferior mesenteric vein and minimal manipulation of the tumor continue to remain the hallmarks of good surgery. Thus the prevention of tumor cell dissemination from the low density areas of tumor periphery or vascular/lymphatic spaces around the tumor, with the use of low dose preoperative radiation, can yield a similar beneficial effect and improve survival in this disease.

Clinical studies

Based on the biological rationale, the first clinical study utilizing low dose preoperative radiation was undertaken by Ryder et al (20) at the Princess Margaret Hospital in Toronto. Patients with adenocarcinoma of the rectum, considered to be surgically resectable, were randomized to either receive a single dose of 500cGy or were given sham radiation just prior to surgical resection of the tumor. A total of 125 patients were entered into the study with 65 patients in the control group and 60 patients receiving preoperative radiation. The overall survival at 5 years in the two groups was similar (55% in controls and 56% for the treatment group) with no statistical difference. Analysis by the Duke stage showed no difference in survival for Duke Stage A & B tumors, however in stage C cancers the 5-year survival in the irradiated group was approximately twice that of the control group. (37% vs 19% $p = 0.014$).

Based on the results of this study, the Medical Research Council, England, (21) undertook a three-arm randomized study to evaluate the effectiveness of low dose preoperative radiation in the management of resectable cancer of the rectum. 824 patients were randomized to either surgery alone, 2000 cGy in 10 daily fractions of 200 cGy followed by surgery or 500 cGy given as a single fraction. The results of this study indicated that a

Tab. I – SURVIVAL - MRC EXPERIENCE

	<i>Surgery only</i>	<i>5Gy preop + Surgery</i>	<i>20 Gy preop RT + Surgery</i>
Overall Survival	38%	42%	40%
Disease Free Survival	47%	50%	46%

statistically significant reduction in the size of the primary cancer and proportion of the Duke's C tumors was seen in the group given 2000 cGy in multiple fractions. However, there appeared to be no effect of the single fraction of 500 cGy on the distribution of pathological stages when compared to controls. Overall survival at 5 years in the control arm was 38% and 42% for the 500 cGy single dose and 40% in the 2000 cGy arms. Cancer free survival was 47% in the control arm, 50% in the 500 cGy arm and 46% in the multiple fraction arm (Tab. I). These differences while not significant do show a small benefit for the low dose preoperative radiation (5 Gy) arm. There was no significant difference in survival in patients with Duke C cancer as was seen in the study from Princess Margaret Hospital. However, there appeared to be no increase in tumor morbidity or mortality in the treatment arms as compared to controls. An unfortunate aspect of this study, was the inclusion of the high numbers of patients with fixed cancers. Only 49% of the tumors were mobile and 44% (364) had tethered cancers. The remaining patients had totally fixed rectal cancers. 20% of the mobile cancers were unable to undergo surgical resection and 44% of the patients with tethered tumors also did not undergo resection of disease. With such a large ineligibility rate of patients due to non-resectability, the effects of low dose preoperative radiation would have been hard to demonstrate. 30% of patients with mobile cancers developed local recurrence of disease and 63% of the patients with tethered/fixed cancers developed local recurrence. This appears excessive as measured by today's standards for surgical resection and therefore in this study, this overwhelming incidence of local recurrence could mask the full potential benefit from low dose preoperative radiation and would be impossible to demonstrate except in a study with very large patient numbers.

In 1976, a slightly different approach was undertaken at Thomas Jefferson University Hospital (22). Keeping in mind that local recurrence after curative surgery can range from 20-50%, depending on the pathological stage of disease, an approach of combining low dose preoperative radiation followed by immediate surgery and high dose postoperative radiation for high risk patients (pathological stage B2, C1 and C2 cancers) was initiated. One hundred and twenty patients were treated in the study with all patients receiving 500 cGy either on the day of or the day before radical curative surgery. The preope-

ratively radiation was administered using AP/PA fields to the whole pelvis. Thirty-five patients underwent an abdominoperineal resection and 85 patients underwent radical sphincter saving surgical resection either low anterior resection (LAR = 65) or an abdominal transsacral resection (CATS = 20). Patients were pathologically staged according to the Astler-Collier modification of Dukes' staging. Thirty-four patients corresponding to stage A or B1 tumors (low risk for local recurrence) were followed with no further treatment. Of 86 patients who were found to have Stage B2, C1 or C2 cancers, 54 patients received the planned postoperative therapy (4500 cGy pelvic postoperative radiation using custom shaped fields with an AP/PA and 2 laterals "box" technique) as per protocol. The remaining 32 patients did not receive postoperative radiation (23). The results of these patients were compared with 53 similarly staged patients treated at Thomas Jefferson University Hospital during the same time period but given postoperative radiotherapy without low dose preoperative radiation (24). Results were assessed after a minimum follow up of 5 years. None of the patients experienced small or large bowel toxicity following the 500 cGy preoperative radiation alone and 3 patients (6%) treated with high dose postoperative radiation, and 2 patients (4%) treated with combined low dose preoperative and post operative radiation experienced small bowel complications.

The thirty-four patients with Stage A and B1 disease receiving 500 cGy preoperatively with no further treatment had an excellent 5 year and 10 year survival of 91%. Only one patient failed locally and distally and one patient failed locally (3%). The pattern of failure in patients with B2, C1 and C2 cancers is shown in Tab. II. Patients receiving low dose preoperative radiation alone had an overall local recurrence rate of 34%, (11 of 32 patients). The local recurrence rate by stage of disease was 21%, 50% and 40% for stages B2, C1, C2 respectively. In the patients receiving high dose postoperative radiation alone local recurrences were seen in 21% of patients. Recurrence by stage of disease was 6%, 13% and 31% for stages B2, C1 and C2 disease respectively. In patients receiving both low dose preoperative and postoperative radiation local recurrence were observed in 4%, 0% and 15% of patients with B2, C1, C2 disease respectively for an overall local recurrence rate of 11%, (5 of 46) indicating that patients benefited most from the combined treatment. The rate of distant metastasis

Tab. II – PATTERN OF FAILURE - JEFFERSON EXPERIENCE (STAGES B2 AND C)

	5 Gy preop RT + Surgery	5 Gy preop + 45 Gy postop RT	Surgery + 45 Gy postop RT
Local Recurrence	19%	6%	8%
Local + Distant	16%	4%	13%
Distant Metastasis	13%	15%	25%

Tab. III – SURVIVAL - JEFFERSON EXPERIENCE (STAGES B2 AND C)

	5 Gy preop RT + Surgery	5 Gy preop + 45 Gy postop RT	Surgery + 45 Gy postop RT
5 yr. survival	54%	72%	41%
10 yr. survival	38%	62%	28%

in the three groups of patients was also different. In the low dose preoperative group, 9 patients developed distant metastases for an overall rate of 28%. In patients receiving high dose postoperative radiation alone, 38% developed distant metastases. For patients receiving both pre and postoperative radiation, the incidence of distant metastasis was 19%. The 5 and 10 year survival in the three groups of patients is shown in Tab. III. Survival was 54% for patients with low dose preoperative radiation, 41% for those receiving high dose postoperative radiation alone and 72% for patients receiving combined pre and postoperative radiation. These differences were statistically significant and reflect a reduction in both local recurrence rates and distant metastasis with combined pre and postoperative radiation.

In a similar study undertaken at Massachusetts General Hospital, Gunderson, et al., (25) reported a five year survival of 79% for patients with stage B2 and C rectal cancer receiving 500 cGy single dose radiation or 1000 cGy (200 cGy x 5) preoperatively followed curative surgery and postoperative radiation of 4500 to 6500 cGy. Shank, et al., (26) at Memorial Sloan Kettering Cancer Center used a slightly higher preoperative dose (300 cGy x 5) followed by immediate radical resection and high dose postoperative radiation for Stage B2 and C cancers. Their results showed an actuarial survival rate of 82% at 3 years for the sandwich group.

Based on these studies, the Radiation Therapy Oncology Group (RTOG 81-15) undertook a study comparing the 500 cGy preoperative regimen followed by immediate surgery and postoperative radiation to 4500 cGy compared to surgery and postoperative (4500 cGy) radiation alone. The results of the study indicated no benefit from the addition of 500 cGy of preoperative radiation (27). The preoperative radiation was allowed to be delivered within 24 hours prior to surgery but in contrast to other studies that have shown a benefit with the single dose of preoperative radiation delivered either on the day of or the day before surgery several patients received their treatment up to several days before surgery. Powers and Tolmach (4) had shown that in animal tumors a delay of greater than 8 hours was detrimental to the outcome. Additionally a number of patients scheduled to receive postoperative radiation for B2 and C cancers in the combined postoperative group failed to receive the postoperative component of treatment in contrast to fewer patients in the postoperative radiation group alone. As

Tab. IV – SURVIVAL - LOW DOSE PREOPERATIVE RADIATION + SURGERY RANDOMIZED STUDIES

	5 Gy preop RT + Surgery	Surgery only	
Rider et al (all stages)	40%	35%	p = 0.014 ns
(stages C)	37%	19%	
MRC (all stages)	42%	38%	
	5 Gy preop + 45 Gy postop RT	Surgery + 45 Gy postop RT	
RTOG (81-15)			
(stages B2, C)	54%	54%	ns

was seen in the Jefferson study, both pre and postoperative radiation were crucial for improved results. When the data was analyzed by treatment actually delivered there still appeared to be no significant differences between the two groups of patients. One of the interesting results of the trial was that the overall survival in both the control arm and the experimental arm of the study was better than the traditional survival results for stages B2 and C seen in other studies (Tab. IV). Unfortunately based on the results of the RTOG and MRC studies, low dose preoperative radiation was felt not to be an effective approach in the treatment of this disease. There has been no further analysis of the RTOG data based on the time interval between low dose preoperative radiation and surgery, which might have shown a difference in outcome. There are at present no further studies investigating the role of low dose preoperative radiation in rectal or other cancers.

In summary low dose preoperative radiation used as a single fraction of 500cGy appears to have sound biological basis and in single institutional studies has been shown to be efficacious but has not been shown in randomized studies to improve results. The later is likely due to poor design of trials and/or inappropriate patient selection for these studies. A well-designed study still remains to be done.

References

- Higgins G.A., Conn J.H., Jordan P.H. et al.: *Preoperative radiotherapy for colorectal cancer*. Ann Surg, 181:624-630, 1975.
- Quan S.H., Daldish M.R., Stearns M.W.: *The effect of preoperative roentgen therapy upon the 10 and 5 year results of the surgical treatment of cancer of the rectum*. Surg Gynecol Obstet, 111:507-508, 1960.
- Swedish Rectal Cancer Trial: *Local recurrence rate in a randomized multicentre trial of preoperative radiotherapy compared to surgery alone in resectable rectal carcinoma*. Eur J Surg, 162:397-402, 1996.
- Powers W.E., Tolmach L.J.: *Preoperative radiation therapy: Biological basis and experimental investigation*. Nature, 201:172-204, 1964.
- Agostino D., Nickson J.: *Preoperative x-ray therapy in a simulated colon carcinoma in the rat*. Radiology, 74:816-819, 1960.
- Hoye R.C., Smith R.R.: *Effectiveness of small amounts of irradiation in decreasing number of metastases in experimental system*. S Forum, 10:72-76, 1959.
- Olch P.D., Eck R.V., Smith E.E.: *Experimental study of effect of irradiation on dissemination of cancer*. Cancer Res, 19:464-467, 1959.
- Reinhard M.C., Goltz H.L., Warner S.G.: *Effect of radiation on transplantable mouse tumor cells*. Cancer Res, 12:433-437, 1952.
- Hoye R.C., Smith R.R.: *The effectiveness of small amounts of preoperative irradiation in preventing the growth of tumor cells disseminated at surgery: an experimental study*. Cancer, 14:284-294, 1961.
- Nias H.W.: *Radiobiological aspects of pre-operative irradiation*. J Radiol, 40:166-169, 1967.
- Powers W.E., Palmer I.A.: *Biologic basis of preoperative radiation treatment*. 102:176-192, 1968.
- Zirngibl H., Huseman B., Hermanek P.: *Intraoperative spillage of tumor cells in surgery for rectal cancer*. Dis Col Rectum, 33:610-614, 1982.
- Yaw P.B., Sentany M., Link W.J., Wahle W.M., Glover J.L.: *Tumor cells carried through autotransfusion: contraindication to intraoperative blood recovery?* JAMA, 231:490-491, 1975.
- Hansen E., Wolff N., Kneuchel R., Ruschoff J., Ferdinand H., Taeger K.: *Tumor cells in blood shed from the surgical field*. Arch Surg, 130:387-393.
- Hansen E., Frey I., Knuechel R., Ruschoff J., Taeger K.: *Tumor cells in intraoperatively salvaged blood and their elimination by leucocyte filters or γ -irradiation*. Anesthesiology, 79 (suppl. 3A): A122, 1993.
- Salsbury A.J.: *The significance of circulating cancer cell*. Cancer Treat Rev, 2:55-72. Porter G, 1975.
- Ranberger K.R., Johnston W.D., Chang J.C.: *Prognostic significance of surgical perforation of the rectum during abdominoperineal resection for rectal carcinoma*. Am J Surg, 143:186-188, 1982.
- Porter G.A., O'Keefe G., Yakimets W.: *Inadvertent perforation of the rectum during abdominoperineal resection*. Am J Surg, 172:324-327, 1996.
- Turnbull R.B., Jr., Kyle K., Watson F.R. et al.: *Cancer of the colon: The influence of the no-touch isolation technique on survival rates*. Ann Surg, 166:420-427, 1967.
- Rider W.D., Palmer J.A., Mahoney L.J. et al.: *Preoperative irradiation in operable cancer of the rectum: Report of the Toronto trial*. Can J Surg, 20:335-338, 1977.
- Ducan W., Smith A.N., Freedman L.S., Alderson M.R., Arnott S.J., Bleehen N.M., Bond W.H., Crowther D., Deeley T.J., Duthie H.L., Dyken P.W., Fielding L.P., Flatman G.E., Goligher J.C., Hawley P.R., Hughes L.E., Joslin C.A.F., Koriech O.M., Morson B.C., Oates G.D., Peckham M.J., Sandland M.R., Scholfield P.F., Slack W., Slaney G., Smith J.A.R., Scott J.S., Whitehouse J.M.A., P.F.M. Wrigley, Mason A.: *The evaluation of low dose pre-operative x-ray therapy in the management of operable rectal cancer; results of a randomly controlled trial. Second report of an MRC working party*. Br J Surg, 71:21-25, 1984.
- Mohiuddin M., Jerome D., Marks G., Kramer S.: *Results of adjuvant radiation therapy in cancer in the rectum*. Thomas Jefferson

University Hospital Experience. Cancer, 55:350-353, 1985.

23) Mohiuddin M., Lingareddy V., Marks G.: *Long term results of "selective sandwich" adjunctive radiotherapy for cancer of the rectum.* Am J Clin Oncol, (CCT) 17(3):264-268, 1994.

24) Lingareddy V., Mohiuddin M., Marks G.: *The importance of patient selection for adjunctive postoperative radiation therapy for cancer of the rectum.* Cancer, 73:1805-1810, 1994.

25) Gunderson L.L., Dosorety D., Blitzer D.H. et al.: *Low dose preoperative irradiation, surgery and elective postoperative irradiation*

for resectable rectal and rectosigmoid carcinoma. Cancer, 52:446-451, 1983.

26) Shank B., Enker W., Santant J., Morrissey K., Daly J., Quan S., Knapper W.: *Local control with preoperative radiotherapy alone versus "Sandwich" radiotherapy for rectal carcinoma.* Int J Radia Onc Biol Phys, 13:111-115.

27) Sause W.T., Thomas P.F., Noyes R., Dobelbower R., Fischbach J., Doggett S., Mohiuddin M.: *Evaluation of preoperative radiation therapy in operable colorectal cancer.* Ann Surg, 220:668-675, 1994.

Autore corrispondente:

Mohammed MOHIUDDIN M.D.
Professor and Chairman
University of Kentucky
Department of Radiation Medicine
LEXINGTON - KENTUCKY
40506 USA