Int. J. Radiation Oncology Biol. Phys., Vol. 27, pp. 885–889
Printed in the U.S.A.

0360-3016/93 $6.00 + .00

● *Phase I/II Clinical Trials*

ADJUVANT POSTOPERATIVE ACCELERATED HYPERFRACTIONATED RADIOTHERAPY IN RECTAL CANCER: A FEASABILITY STUDY

PHILIPPE A. COUCKE, M.D.,* JEAN-FRANCOIS CUTTAT, M.D.† AND RENÉ O. MIRIMANOFF, M.D.*

Centre Hospitalier Universitaire Vaudois, CHUV, 1011 Lausanne, Switzerland

Purpose: To assess the acute toxicity and hence feasability of postoperative hyperfractionated accelerated radiotherapy in rectal cancer.
Methods and Materials: Twenty patients were submitted to accelerated hyperfractionated radiotherapy after resection of rectal cancer. A total dose of 48 Gy was given in 3 weeks. Two fractions of 1.6 Gy were used with a mean interfraction interval of at least 6 hours. The pelvic volume was treated by a four-field box technique using a linear accelerator (6–18 MV). Acute toxicity was assessed once per week. Small bowel and skin toxicity were scored according to the criteria of the World Health Organization. Bladder toxicity was scored according to the criteria of the Radiation Therapy Oncology Group.
Results: All the patients underwent the treatment as planned except one. No patient presented grade 3 or 4 bladder toxicity. There was only one patient who complained from grade 3 skin toxicity at the end of the treatment. Fourteen patients had some degree of intestinal toxicity. This was the most frequently occurring acute side-effect. Only two out of the fourteen patients had intestinal toxicity exceeding grade 2.
Conclusion: Hyperfractionated accelerated radiotherapy on a pelvic volume is feasable as far as acute toxicity is concerned.

Hyperfractionation, Acceleration, Postoperative radiotherapy, Rectal cancer.

INTRODUCTION

It is stated that preoperative radiotherapy for rectal cancer should be tested on a large scale in randomized trials (3). However, there will always remain a population of patients, primarily treated with surgery which will need postoperative adjuvant radiotherapy.

The reduction of local recurrences after postoperative radiotherapy was marginally significant in two recently published randomized trials and negative in two others (1, 8, 25, 26). Therefore, one should question if moderate to high dose conventional fractionation (50 Gy in 5 weeks)—aimed at increasing local control—is the best approach (19).

To increase local control and hence survival, new treatment schedules should enhance the overall cytotoxic effect of the radiotherapeutic treatment. This can be obtained by combining chemotherapy and radiotherapy as has been published by the Gastro-Intestinal Tumor Study Group (12, 25) and by Krook *et al.* (15). In both trials local control and survival were significantly better for the combination arm compared to postoperative radiotherapy alone. Nevertheless, as stated by Cox *et al.* "fractionation in radiotherapy continues to be an important modality to be pursued in clinical studies because it is the background for the investigation of adjuncts such as chemical modifiers, hyperthermia, as well as integrated treatment with cytotoxic chemotherapy and/or surgical resection" (4).

Recently published values of potential doubling time allows estimation of treatment duration (21, 32). Based on radiobiological data, hyperfractionated accelerated radiotherapy has been started at our institution to test the feasability of accelerating treatment in rectal cancer. In this article, we report the acute toxicity of this treatment approach.

METHODS AND MATERIALS

From December 1989 to May 1991, 20 patients were introduced in this phase I trial. All presented with histo-

Presented at the ECCO-6, (European Conference on Clinical Oncology and Cancer Nursing) Firenze, Italy, 1991; SFRO (Société Française de Radiothérapie Oncologique), Paris, France, 1991; CERRO-7 (Clinical and Experimental Research in Radiation Oncology), St-Martin de Belleville, France, 1992.

* Department of Radiation-Oncology.
† Department of Surgery.
Reprint requests to: Philippe A. Coucke.

Acknowledgement—The authors would like to acknowledge Dr. Rodney H. Withers, M.D., D.Sc., for his critical review of the manuscript.

Accepted for publication 25 March 1993.

logically confirmed rectal adenocarcinoma. They were referred to our institution for postoperative adjuvant radiotherapy because of extention through the bowel wall and/or nodal invasion (Tumor Node Metastases classification Stage II and III).

All patients were treated with a linear accelerator adjusted to deliver 6 or 18 MV photons. The target volume was irradiated by a four-field box technique. The upper limit was defined as the L5-S1 interspace. The whole sacrum was systematically included in the four fields. The inferior limit was defined as a function of the type of surgery and the location of the primary tumor versus the anal margin. In case of abdominoperineal resection the whole perineum was systematically covered. In case of low anterior resection, the inferior border of the field was located distally from the anal margin for lesions located at less than 5 cm from the anal verge. The anterior limit of the lateral fields was located just behind the symphysis. The posterior limit was located behind the sacrum with a 1 cm margin. Systematic in vivo dosimetry on the perineum or the anal margin was done with solid state detectors, to confirm that the inferior limit of the field was correct.

Patients were treated in prone position with full bladder (13). Contrast enhancement of small bowel was done during simulation, to optimize small bowel protection by block design whenever possible (14). Closing the peritoneum in order to avoid sliding of intestines into the small pelvis was performed in only nine patients.

A total dose of 48 Gy was applied at the isocenter of the four fields. Two fractions of 1.6 Gy per day were used 5 days per week, separated by at least a 6-hr interval. Only one patient received chemotherapy. For this single patient a combination of 5-FU and levamizole has been used after the completion of the radiotherapeutic treatment.

The acute toxicity was assessed once per week and 2 weeks after completion of the treatment. The highest toxicity score was registered from the start of the radiotherapy on, until 6 months after treatment. The WHO (World Health Organisation) scoring system has been applied for skin and small bowel toxicity (Table 1). For acute bladder toxicity the RTOG (Radiation Therapy oncology Group) guidelines were used. After completion of the treatment, patients were routinely followed every 3 months to assess late complications. Those were defined as occurring after a minimum follow-up of 6 months.

The amount of small bowel within treatment portals was estimated and we tried to correlate this value with acute toxicity (11).

The total surface of small bowel in the treated field surface was assessed by superimposing a 1 cm spread grid (taking into account the magnification factor) on the simulation film. The ratio of the surface containing contrast enhanced small bowel, corrected for blocking in the four fields, to the corrected portal surface yielded the percent of surface of irradiated small bowel (SBS %). The mean value of the sum of the small bowel surface (in percent of the total surface) in the anteroposterior and lateral fields yielded the index of irradiated small bowel. This index (volume index 1) is proportional to the volume of irradiated small bowel. This index can also be approached by taking the square root of the product of the corrected surface of small bowel in anteroposterior (SBS AP%) and lateral fields (SBS Lat %). This "volume index 2" is again proportional to the real volume.

Table 1. Grading of acute and subacute toxic effects according to WHO. For bladder the RTOG scoring system has been used

Toxicity grade	
	Skin
0	No change
1	Erythema
2	Dry desquamation, vesiculation, pruritus
3	Moist desquamation, ulceration
4	Exfoliative dermatitis; necrosis requiring surgical intervention
	Bladder
0	No dysuria
1	Minor dysuria not requiring treatment
2	Dysuria responding to simple outpatient management
3	Frequency, urgency and nycturia hourly or more frequently; dysuria, pelvic pain or bladder spasm requiring narcotics; gross hematuria
4	Hematuria requiring transfusion; acute bladder obstruction not due to clot passage, ulceration or necrosis
	Small bowel
0	No diarrhoea
1	Transient < 2 days
2	Tolerable > 2 days
3	Intolerable requiring therapy
4	Haemorrhagic dehydration

RESULTS

Twenty patients were included in this protocol. The mean age was 64 with a median age of 66 (range 42–76). There were 14 males and 6 females. The majority of patients had Stage II (N = 9) and III disease (N = 8). Patient characteristics are summarized in Table 2.

One patient presented with a local recurrence and a single hepatic metastasis. He underwent local and hepatic surgery with curative intent followed by pelvic radiotherapy and systemic chemotherapy. This case was included in the analysis for estimation of toxicity of accelerated hyperfractionated pelvic irradiation.

All patients had histologically confirmed adenocarcinoma of the rectum. Three patients had well-differentiated tumors. The other ones presented with a moderately to poorly differentiated adenocarcinoma.

Table 2. Summary of patient characteristics

	No.
Topographic localisation of the primary	
Superior border below peritoneal reflection	9
In front of peritoneal reflection	10
Inferior border above peritoneal reflection	0
Unknown	1
Type of surgery	
Abdominoperineal resection	11
Anterior resection	7
Hartman	1
Endoscopic resection	1
Reconstruction of peritoneal floor	9
No reconstruction	7
Unknown	4

All received a total dose of 48 Gy except for one patient who developed major toxicity (grade 4 diarrhea) at 44.8 Gy. The median elapsed treatment time was 21.5 days (range 19–24). This was slightly more than the projected treatment duration of 19 days. This projected treatment duration could only be achieved if the treatment was started on Monday and if there were no interruptions for technical problems or holidays.

The dose-intensity, defined by us as the ratio of total dose in cGy versus total elapsed time in days, ranged from 253 cGy/day to 195 cGy/day with a median value of 223.4 cGy/day (Table 3 for comparison with dose intensity for other treatment regimens). The median interfraction interval was 6.5 hr (mean value 7.3 hr, range 5.9 to 13 hr).

Acute toxicity was acceptable. No patients developed grade 3 and 4 cutaneous or bladder toxicity (Table 4). Fifty percent of patients had no urinary complaints at all at the end of the treatment. Fifteen out of 20 patients had some degree of cutaneous toxicity in the perineum, mainly grade 2 (8/15). Intestinal toxicity was the most frequently occurring side effect (14/20). However, only 2 out of 14 patients who had some degree of small bowel complications needed hospitalisation and only one of these required

Table 3. Comparison of dose intensity (DI) defined as total dose (TD) vs. elapsed treatment time (ET) according to protocol prescription (cGy/day) (for a review see ref. 1)

Trial	R/NR	Year	TD (Gy)	ET* (days)	DI (cGy/day)
EORTC-40811	R		46	31	148
Stockholm	R	1986	50	47	106
MDAH	NR	1987	40–50	33	151
GITSG	R	1988	40	26	154
			48	33	154
NCCTG	R	1988	50.4	40	126
NSABP-R01	R	1988	47	33	142
Dutch Multicenter	R	1991	50	33	151
Lausanne	NR	1992	48	19	253

* For these calculations treatment is assumed to start on Monday.

R = Randomized trial; NR = Not randomized.

Table 4. Incidence of highest toxicity scores for small bowel, bladder and skin*

	WHO - 0	WHO - I	WHO - II	WHO - III	WHO - IV
Intestinal	6	5	7	1	1
Cutaneous	5	6	8	1	0
Bladder	9	10	1	0	0

* The decision to stop the treatment is usually based on the highest level of toxicity in our department.

a break in treatment. The median follow-up is 12.6 months for surviving patients (mean 13.5 months). So far no case of late damage has occurred. One patient with an initial stage T3N2 died from distant metastatic disease 5 months after treatment but locally controlled. Two patients, one with a local recurrence and an hepatic metastases surgically removed prior to the accelerated radiotherapy, and one initially referred with a stage T4N0, died from local recurrence and progression of liver metastases 8 months after treatment.

There were no treatment interruptions for toxicity except for one patient who received a total of 44.8 Gy. She presented with grade 2 diarrhea after surgery and prior to radiotherapy. During the third week of accelerated radiotherapy, she complained of nausea, vomiting and hemorrhagic diarrhea. Treatment was interrupted at 44.8 Gy and she had to be admitted to the hospital for intensive rehydratation and realimentation. After partial recovery, a gastroduodenoscopy showed the presence of a bleeding ulcer in the initial part of the duodenum. This was outside treatment fields.

The sizes of treatment portals were calculated. The mean corrected surface (i.e. small bowel blocks accounted for) of anteroposterior-posteroanterior fields was 294.3 cm^2 with a median value of 281.8 cm^2. The anteroposterior blocks represented a mean value of 16.5% and a median value of 17.9% of the total surface of the anteroposterior portal. The mean corrected surface of the lateral fields was 286.8 cm^2 with a median value of 292.3 cm^2 (range 201 cm^2 to 405 cm^2). In the lateral fields a mean of 11.1% and a median of 9.5% was blocked to protect the small bowel as much as acceptable.

The small bowel surface SBS AP% and SBS Lat% and the calculated volume index (index I and II) have been plotted against the mean toxicity grade per quartile. There seems to be a linear relationship between mean toxicity grade and small bowel surface illustrating the importance of a volume effect in the occurrence of acute toxicity (Fig. 1). The estimation of a small bowel surface on simulation films and calculated index I and II seem to be an adequate estimate of the real small bowel volume and hence of the risk of acute complication. Follow-up is too short (median 16 months, mean 16.2 months) to evaluate the predictive value of this small bowel volume estimate on late complications.

The mean toxicity scale was calculated for those patients who underwent peritoneal closing and compared to those

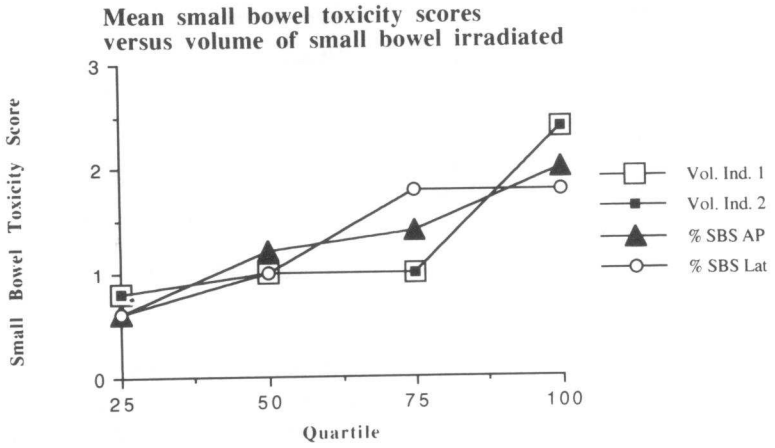

Fig. 1. Relationship between volume-index per quartile, SBS-AP% and SBS-Lat% and calculated mean toxicity score. Volume index has been defined as the mean of calculated corrected surfaces of small bowel in anteroposterior and lateral fields or as the square root of the product of small bowel surface of both fields (anteroposterior and lateral).

patient who did not undergo this surgical reconstruction. The difference (toxicity score surgical reconstruction of peritoneal floor vs. no surgical reconstruction) was not significant due to the small patient number ($p = 0.2$). However, there was a trend toward improvement of tolerance when peritoneal closing was performed during surgery. The mean small bowel toxicity for the patients submitted to a schedule with a dose intensity $\geq$ 223.4 cGy/day was higher. Again this difference did not reach a statistically significant level ($p = 0.1$).

DISCUSSION

Postoperative radiotherapy is considered as a part of the standard adjuvant treatment in stage II and III surgically resected rectal cancer (8). This moderate to high dose radiotherapy (50 Gy in 5 weeks), is aimed at increasing local control compared to surgery alone. In randomized trials, local failure was reduced and survival increased only when radiotherapy was combined with chemotherapy (12, 15, 25). Thus, currently recommended radiotherapy is only moderately effective in rectal cancer. It's effectiveness may be increased by treatment intensification. This can be achieved either by increasing total dose using hyperfractionated treatment (4), or by reducing total elapsed treatment time or both (10). According to Suit and Overgaard, a total dose of 45 to 50 Gy should be sufficient to control microscopic residual disease in most common tumors (20, 23).

Treatment intensification by reducing total treatment duration can be achieved either by increasing dose per fraction or by giving multiple fractions a day. The increase of dose per fraction is associated with an increase of the risk of late toxicity (2, 8). Hyperfractionation and multiple fractions a day offers the double advantage of accelerating treatment (to overcome repopulation and reducing the probability of late complications by the use of a reduced dose per fraction (2, 5, 6, 9, 10, 17, 24, 27–31, 33), keeping healthy tissue volume as low as possible (16, 34).

The Gray Laboratory recently published data concerning cellular kinetics in rectal cancer (21, 32). The median value of potential doubling time for all rectal tumors is about 3.9 days (range 1.7–212.4 days). For diploid rectal tumors the median value was 5.4 days (range 1.7–21.4 days) whereas for aneuploid tumors the median value did not exceed 3.5 days (range 1.9–15.4 days). Therefore, considering rectal tumors as being of intermediate radiosensitivity (0.2–0.6 $Gy^{-1} = \alpha$) (7, 18), and for a range of α/β from 4 to 17 Gy (proportional to α according to Fowler) (9, 10), acceleration may be indicated in a large proportion of tumors.

Based on these preliminary data from this Phase I trial, Hyperfractionated Accelerated Adjuvant Radiotherapy (HART) seems to be feasible. Acute toxicity can be managed easily. One out of the twenty treatments has been interrupted due to grade 4 diarrhea and dehydration. This major acute toxicity for this single case is partly explained by acute radiation toxicity. However the presence of bleeding duodenal ulcers located outside the treatment fields may have worsened the general condition of this patient.

Further increase of treatment intensity such as for example association of chemotherapy and HART (15, 22), will need specific small bowel protection in order to keep therapeutic index constant or even increased.

REFERENCES

1. Balslev, I.; Pedersen, M.; Teglbjaerg, P. S.; Hanberg-Soerensen, F.; Bone, J.; Jacobsen, N. O.; Overgaard, J.; Sell, A.; Bertelsen, K.; Hage, E.; Fenger, C.; Kronborg, O.; Hansen, L.; Hoestrup, H.; Noergaard-Pedersen, B. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectumn and rectosigmoid. Cancer 58:22–28;1986.

2. Barendsen, G. W. Dose fractionation, dose rate and iso-effect relationship for normal tissue responses. Int. J. Radiat. Oncol. Biol. Phys. 8:1981–1997;1982.
3. Bosset, J. F. Radiothérapie externe adjuvante des cancers du rectum. résultats-perspectives. Bull. Cancer/Radiothér 77:157–166;1990.
4. Cox, J. D.; Guse, C.; Asbell, S.; Rubin, P.; Sause, W. T. Tolerance of pelvic normal tissues to hyperfractionated radiation therapy: results of protocol 83-08 of the Radiation Therapy Oncology Group. Int. J. Radiat. Oncol. Biol. Phys. 15:1331–1336;1988.
5. Dale R. G. The potential of radiobiological modelling in radiotherapy treatment design. Radioth. Oncol. 19:245–255;1990.
6. Dische, S.; Saunders, M. I. The rationale for continuous, hyperfractionated accelerated radiotherapy. Int. J. Radiat. Oncol. Biol. Phys. 19:1317–1320;1990.
7. Fertil, B.; Malaise, E. P. Intrinsic radiosensitivity of human cell lines is correlated with radioresponsiveness of human tumors: analysis of 101 published survival curves. Int. J. Radiat. Oncol. Biol. Phys. 11:1699–1707;1985.
8. Fisher, B.; Wolmark, N.; Rockette, H.; Redmond, C.; Deutsch, M.; Wickerman, L. D.; Fisher, E. R.; Caplan, R.; Jones, J.; Lerner, H.; Gordon, P.; Feldman, M.; Cruz, A.; Legault-Poisson, S.; Wexler, M.; Lawrence, W.; Robidoux, A.; other NSABP Investigators. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP Protocol R-01. JNCI 80:21–29;1988.
9. Fowler, J. F. The linear-quadratic formula and progress in fractionated radiotherapy. Br. J. Radiol. 62:679–694;1989.
10. Fowler, J. F. How worthwhile are short schedules in radiotherapy?: A series of exploratory calculations. Radioth. Oncol. 18:165–181;1990.
11. Gallagher, M. J.; Brereton, H. D.; Rostock, R. A.; Zero, J. M.; Zekoski, D. A.; Poyss, L. F.; Richter, M. P.; Kligerman, M. M. A prospective study of treatment techniques to minimize the volume of pelvic small bowel with reduction of acute and late effects associated with pelvic irradiation. Int. J. Radiat. Oncol. Biol. Phys. 12:1565–1573;1986.
12. Gastrointestinal Tumor Study Group. Prolongation of the diseases-free interval in surgically treated rectal carcinoma. N. Engl. J. Med. 312:1465–1472;1985.
13. Gunderson, L. L.; Russell, A. H.; Llewellyn, H. J.; Doppke, K. P.; Tepper, J. E. Treatment planning for colorectal cancer: radiation and surgical techniques and value of small bowel films. Int. J. Radiat. Oncol. Biol. Phys. 11:1379–1393;1985.
14. Herbert, S. H.; Curran, W. J.; Solin, L. J.; Stafford, P. M.; Lanciano, R. M.; Hanks, G. E. decreasing gastrointestinal morbidity with the use of small bowel contrast during treatment planning for pelvic irradiation. Int. J. Radiat. Oncol. Biol. Phys. 20:835–842;1991.
15. Krook, J. E.; Moertel, C. G.; Gunderson, L. L.; Wieand, H. S.; Collins, R. T.; Beart, R. W.; Kubista, T. P.; Poon, M. A.; Meyers, W. C.; Maillard, J. A.; Twito, D. I.; Morton, R. F.; Veeder, M. H.; Witzig, T. E.; Cha, S.; Vidyarthi, S. C. Effective surgical adjuvant therapy for high-risk rectal carcinoma. N. Eng. J. Med. 14:709–715;1991.
16. Lyman, J. T.; Wolbarst, A. B. Optimization of radiation therapy, III: A method of assessing complication probabilities from dose-volume histograms. Int. J. Radiat. Oncol. Biol. Phys. 13:103–109;1987.
17. Maciejewski, B.; Withers, R. H.; Taylor, J. M. G.; Hliniak, A. Dose fractionation and regeneration in radiotherapy for cancer of the oral cavity and oropharynx: Tumor dose-response and repopulation. Int. J. Radiat. Oncol. Biol. Phys. 16:831–843;1989.
18. Malaise, E. P.; Fertil, B.; Chavaudra, N.; Guichard, M. Distribution of radiation sensitivities for human tumour cells of specific histological types: Comparison of *in vitro* to *in vivo* data. Int. J. Radiat. Oncol. Biol. Phys. 12:617–624;1986.
19. NIH Consensus Conference. Adjuvant therapy for patients with colon and rectal cancer. JAMA 264:1444–1450;1990.
20. Overgaard, M.; Overgaard, J.; Sell, A. Dose-response relationship for radiation therapy of recurrent, residual, and primarily inoperable colorectal cancer. Radioth. Oncol. 1: 217–225;1984.
21. Rew, D. A.; Wilson, G. D.; Taylor, I.; Weaver, P. C. Proliferation characteristics of human colorectal carcinomas measured *in vivo*. Br. J. Surg. 78:60–66;1991.
22. Steele, G. J. Combined-modality therapy for rectal carcinoma—The time has come. NEJM 324:764–766;1991.
23. Suit, H. D. Basic principles of radiotherapy. Radiation biology: A basis for radiotherapy. In: Fletcher, G. H., ed. Textbook of radiotherapy. Philadelphia: Lea & Febiger; 1973;75–120.
24. Thames, H. D.; Withers, R. H.; Peters, L. J.; Fletcher, G. H. Changes in early and late radiation responses with altered dose fractionation: Implications for dose-survival relationships. Int. J. Radiat. Oncol. Biol. Phys. 8:219–226;1982.
25. Thomas, P. R.; Lindblad, A. S. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: A review of the Gastrointestinal Tumor Study Group Experience. Radioth. Oncol. 13:245–252;1988.
26. Treurniet-Donker, A. D.; van Putten, W. L. J.; Wereldsma, J. C. J.; Brugginck, E. D. M.; Hoogenraad, W. J.; Roukema, J. A.; Snijders-Keilholz, A.; Meiier, W. S.; Meerwaldt, J. H.; Wijnmaalen, A. J.; Wiggers, Th. Postoperative radiation therapy for rectal cancer. An interim analysis of a prospective randomized multicenter trial in The Netherlands. Cancer 67:2042–2048;1991.
27. Trott, K. R.; Kummermehr, J. What is known about tumor proliferation rates to choose between accelerated fractionation or hyperfractionation. Radioth. Oncol. 3:1–9;1985.
28. Trott, K. R. Cell repopulation and overall treatment time. Int. J. Radiat. Oncol. Biol. Phys. 19:1071–1075;1990.
29. Tucker, S. L. Expected changes in local tumor control rates resulting from the selective use of accelerated fractionation. Int. J. Radiat. Biol. 56:739–743;1989.
30. Tucker, S. L.; Travis, E. L. Comments on a time dependent version of the linear-quadratic model. Radioth. Oncol. 18: 155–163;1990.
31. Tucker, S. L.; Chan, K. S. The selection of patients for accelerated radiotherapy on the basis of tumor growth kinetics and intrinsic radiosensitivity. Radioth. Oncol. 18:197–211;1990.
32. Wilson, G. D.; McNally, N. J.; Dische, S.; Saunders, M. I.; Des Rochers, C.; Lewis, A. A.; Bennett, M. H. Measurement of cell kinetics in human tumours *in vivo* using bromodeoxyuridine incorporation and flow cytometry. Br. J. Cancer 58:423–431;1988.
33. Withers, R. H.; Taylor, J. M. G.; Maciejewski, B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol. 27:131–146;1988.
34. Withers, R. H.; Taylor, J. M. G.; Maciejewski, B. Treatment volume and tissue tolerance. Int. J. Radiat. Oncol. Biol. Phys. 14:751–759;1988.