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Adjuvant postoperative radiotherapy in rectal cancer: 148 cases treated at Florence University with 8 years median follow-up

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Abstract

Background and purpose. To analyse the outcome, the treatment related side effects, the prognostic significance of clinical parameters in a group of patients with rectal cancer receiving postoperative radiotherapy after radical resection. *Materials and methods.* From 1980 to 1990 148 consecutive patients with rectal carcinoma stage B2-B3 or C1-C2-C3 were treated with postoperative radiotherapy after radical surgery. All patients received 50 Gy in 25 sessions in 5 weeks. In 42 a 'flash' dose of 5 Gy was also given within 24 h before surgery. Median follow up was 8.1 years. *Results.* At 5 years the overall survival was 54%, the determined (cancer specific) survival 61%, the local recurrence-free survival 88%. The influence of stage, histotype, distance from anal margin, type of surgery, number of involved nodes and flash dose were analysed. Overall and determined survival and distant metastasis rate were significantly influenced ($P < 0.005$) by the pathological stage. Patients with more than 3 involved nodes presented a significantly lower determined survival ($P < 0.001$) and a higher distant relapse rate ($P < 0.005$) than those with 3 or less involved nodes. A higher determined survival ($P < 0.01$) was also found in patients receiving the preoperative 'flash'; this group was however unbalanced in respect to the relative number of cases with 3 or less involved nodes. The incidence of major side effects requiring surgery or hospitalization for medical treatment was 35% before 1985 and 12% thereafter. The systematic use of small bowel visualization during simulation and the discontinuation of the flash dose were the main modifications introduced in the second period. As a consequence of the small bowel visualization the size of lateral fields was slightly reduced and some patients were excluded from the treatment. *Conclusions.* Value of postoperative radiotherapy to decrease the incidence of local recurrence was confirmed in this retrospective study; the incidence of side effects was however considerable and did not support the addition of chemotherapy as advised by the NIH consensus meeting. Our policy was therefore moved to preoperative irradiation whose combination with chemotherapy was recently reported to be better tolerated and highly effective.

Keywords: Rectal cancer; Radiation therapy; Adjuvant treatment to surgery

1. Introduction

Radiotherapy either pre or postoperative is widely accepted as the standard adjuvant treatment in rectal carcinoma invading the perirectal tissues. A large range of doses was tested preoperatively ranging from a single fraction of 5 Gy within 24 h from surgery, to 45–50 Gy in 25 sessions [1,7,15,17,21,23,28,31,32,35,39,42,43,46,47,49,50,52–54]. A more uniform dose around 50 Gy in 25 sessions was given when radiotherapy was used postoperatively [4,9,30,51,58–61,64]. The main effect of radiotherapy was to decrease the incidence of local recurrence from 25–30% to 10–15%; in some studies the time to relapse was also increased [4]. To achieve this result preoperative radiotherapy must be given at a dose higher than 35 Gy if a conventional fractionation schedule of 1.8–2.0 Gy five times per week is used [6]. A shorter schedule of 20–25 Gy in 4–5 fractions in 5 days

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has been proved to be equally effective [54]. The results of two randomized trials [34,57] also suggest that 5-fluorouracil concomitant to postoperative radiotherapy may produce a significant increase in the overall survival although at the expense of a higher morbidity and a lower compliance.

Whether radiotherapy is better to be given pre- or postoperatively is still controversial. The two options have been compared in a large randomized multicentric study in Sweden [45]: 471 consecutive patients with a respectable rectal carcinoma were randomized either to preoperative irradiation with a dose of 25.5 Gy in 5–7 days (all patients were treated), or to postoperative irradiation with a dose of 60 Gy in 8 weeks (only patients in pathological stage B2,C1,C2 were treated); although survival was similar, the local recurrence rate was significantly lower in the preoperative group (12% vs. 21%); a better compliance and a lower toxicity were also observed in this group. The result of the trial was therefore in favour of the preoperative option; in this group however irradiation was useless in 84 patients, 17 because distant metastasis were detected at surgery and 67 because the tumor was intraparietal (A,B1).

At the University Unit of Radiotherapy in Florence postoperative radiotherapy was routinely used from 1980 to 1990 in 148 consecutive cases of rectal carcinomas submitted to radical surgery and presenting a pathological stage B2-B3 or C1-C2-C3 according to the Astler and Coller classification as modified by Gunderson and Sosin. An update of the results obtained in this series after a minimum follow-up of 4 years is reported in this paper. These results represented the basis for changing our protocol to preoperative radiotherapy with concomitant 5-fluorouracil and folinic acid.

2. Materials and methods

The main clinical characteristics of the patients are reported in Table 1. All patients were defined as 'radically resected'; this definition meant that there was no evidence of macroscopic residual tumor and that the proximal and distal surgical margins were microscopically free of tumor; the circonferential margins however were not systematically assessed. Surgery was an abdomino-perineal resection (APR) in 97, an anterior resection (AR) in 45; less typical surgical techniques were used in the remaining 6 cases.

Table 2 reports the distribution of the histotype, of the type of surgery and of the distance from the anal margin according to the stage group (B2-B3 or C1-C2-C3). Out of the 28 cases presenting a G3 or a colloid tumor, a larger proportion (18 or 68%) were in C1-C2-C3 stage group, while the distance from the anal margin and the type of surgery were evenly distributed in the two stage groups.

Before radiotherapy all patients were restaged with chest X-ray, abdominal ultrasound and CT. All patients were treated with a megavoltage linear accelerator (15 or 25 MV) in prone position; a 4 fields box technique was used in the large majority of cases. The upper border of

Table 1
Patients characteristics

Total cases	148
Stage	
B2, B3	73
C1,C2,C3	75
Sex	
males	88
females	60
Age (years)	
≤40	6
41–50	33
51–60	44
61–70	52
>70	13
Distance from anal margin (cm)	
≤4	33
5–10	72
>10	29
not specified	14
Histotype	
G1	4
G2	105
G3	3
colloid	21
not specified	11
Surgery	
APR	97
AR	45
other	6

APR, abdomino-perineal resection; AR, anterior resection; other, radical surgery other than APR or AR.

Table 2
Distribution of the histotype, of the distance from anal margin and of the type of surgery according to the stage

	Stage group	
	B2,B3	C1,C2,C3
Histotype		
G1	2	2
G2	57	48
G3	2	5
colloid	8	13
not specified	5	6
Surgery		
APR	47	50
AR	24	21
other	2	4
Distance from anal margin (cm)		
<5	16	17
5–10	36	36
>10	15	14
not specified	6	8

APR, abdomino-perineal resection; AR, anterior resection; other, radical surgery other than APR or AR.

the radiation field was at the sacral promontory (S1) in 122 and at the L4/L5 junction in 26; the inferior border was at the inferior edge of the ischiatic bone in patients operated with an AR while the perineum was included in patients receiving an APR; the anterior border included in all cases the posterior bladder wall; it was extended to the posterior edge of the pubic symphysis when the vagina (6 cases, all of whom had a resection of the posterior vaginal wall) or the prostatic capsula (2 cases) were found to be involved by the tumor. The posterior border always included the sacral canal. Since 1985 patients were simulated with opacification of the small bowel and patients in whom a large part of the presacral space on the lateral film was found to contain small bowel loops were not given irradiation. This resulted in the exclusion from the protocol of 7 cases (the number of patients included in the protocol was 60 in the period 1985–90) because the risk of small bowel complications was considered to exceed the possible benefit on the local recurrence risk. The appreciation of amount of small bowel in the presacral space also resulted in a general reduction of the AP size of the lateral field. The dose was calculated at the intersection of the fields axis with a uniform weight from each portal; at least two fields were treated at each session; the total dose was 50 Gy in 25 sessions in 5 weeks. In 42 cases, treated before June 1984 when the negative results of the MRC trial [17] were published, a flash dose of 5.0 Gy was also given within 24 h before surgery using 2 AP/PA fields; there was no selection criteria for this patients group except for the fact that they were all referred from surgical Departments located in our Hospital; the postoperative dose was in these cases 50 Gy in 25 sessions as in those not receiving the preoperative flash. None of the patients received chemotherapy as a part of their adjuvant treatment.

After the end of radiotherapy patients were regularly followed every 3 months for the first 2 years, every 6 months up to the 5th year and yearly thereafter. The follow-up included clinical examination, CEA and liver US every 3 months for 3 years; every 6 months for the 4th and the 5th year and every year thereafter. CT scan was performed every 6 months for the first 2 years; coloscopy yearly. After 5 years in a few cases living at a large distance from our area the patient status was updated through the house doctor by phone interview. Overall 123 patients had a follow-up larger than 5 years (range 3–14 years; median 8 years).

Relapses were classified as 'local recurrence' (LR) when they occurred inside the treated volume in the pelvic area or in the perineum, as 'distant metastases' (DM) when they occurred in the abdomen outside the pelvis or in extrabdominal sites. The diagnosis of relapse was usually based on clinical or radiological evidence; in a few cases a pathological confirmation was felt necessary. All relapses were reported as a single event.

Late side effects were scored as major when a surgical treatment was necessary or the medical treatment required a prolonged hospitalization of the patient or when the complication resulted in the death of the patient.

2.1. Statistics

The life-table method was used to calculate probability of survival; the overall survival (OS), the determined (or cancer specific) survival (DS) and the local recurrence-free survival (LRFS) were calculated. Comparison of survival curves was done using the log rank test.

3. Results

The pattern of relapse is reported in Table 3 for the overall series and for the two stage groups. An LR was observed in 16 patients or 11% of the all series and a DM in 48 or 33%; 4 cases presented both an LR and a DM. The rate of LR was similar in the two stage groups; the DM rate was significantly higher in the group with involved nodes than in the group with negative nodes with a $P < 0.005$.

The time to LR ranged from 3.6 to 113.4 months (mean 23.9 months). The OS, DS and LRFS at 5 and 10 years were calculated for the all series and for the two stage groups and are reported in Table 4. In the all series the 5 years values were 54% for the OS, 61% for the DS and 88% for the LRFS. Both the OS and the DS were significantly higher in the group in stage B2-B3 than in that in stage C1-C2-C3. The survival curves for the all series and the DS curves for the two stage groups are reported in Figs. 1 and 2.

The pattern of relapse was not significantly affected by the type of surgery, by the histotype and by the distance of the tumor from the anal margin (Table 5). The influence of the type of surgery on the probability of LR

Table 3
Pattern of relapse by stage group

	Total patients	LR (%)	DM (%)
Total series	148	6* (11%)	48* (33%)
Stage			
B2,B3	73	6 (8%)	17 (23%)
		n.s.	$P < 0.005$
C1,C2,C3	75	10 (13%)	31 (41%)

LR, local recurrence; DM, distant metastasis.
*4 cases presented both LR and DM.
n.s., statistically non-significant.

Table 4
5 and 10 years actuarial survival values in the all series and by stage

	Survival values		
	5 years	10 years	
All series			
OS	54%	45%	
DS	61%	55%	
LRFS	88%	81%	
OS by stage			
B2,B3	71%	57%	$P < 0.005$
C1,C2,C3	37%	34%	
DS by stage			
B2,B3	77%	68%	$P < 0.005$
C1,C2,C3	45%	41%	
LRFS by stage			
B2,B3	92%	81%	n.s.
C1,C2,C3	84%	84%	

OS, actuarial overall survival; DS, actuarial determined (cancer specific) survival; LRFS, actuarial local recurrence free survival; n.s., statistically non-significant.

was examined in detail for the group of cases with tumor located below 10 cm; the use of AR did not appear in our series to be followed by a higher probability of LR; the LR probability was in fact 14% after an AR and 13% after an APR. In the group in stage C1-C2-C3 the number of involved nodes (3 or less vs. more than 3) was found to significantly affect the probability of DM and the OS and DS values (Table 6); the LRFS was also higher in the group with less involved nodes but not at a significant level.

The survival values and the pattern of relapse of the patients group receiving the preoperative flash dose in addition to the postoperative irradiation were compared to those of the main group receiving the postoperative irradiation only (Table 7). The DS was significantly higher and the DM probability significantly lower in the

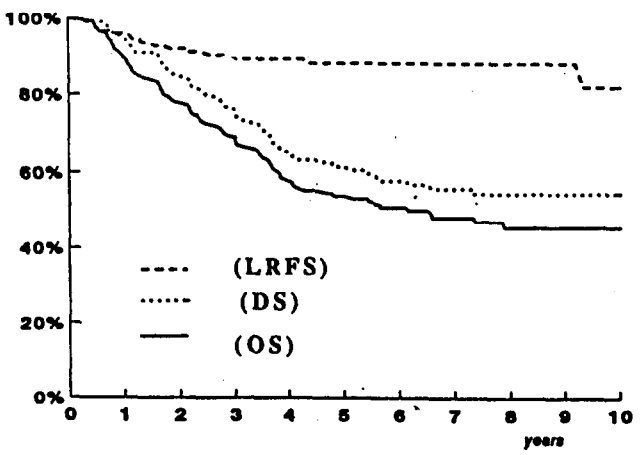

Fig. 1. Survival curves for the whole patients group.

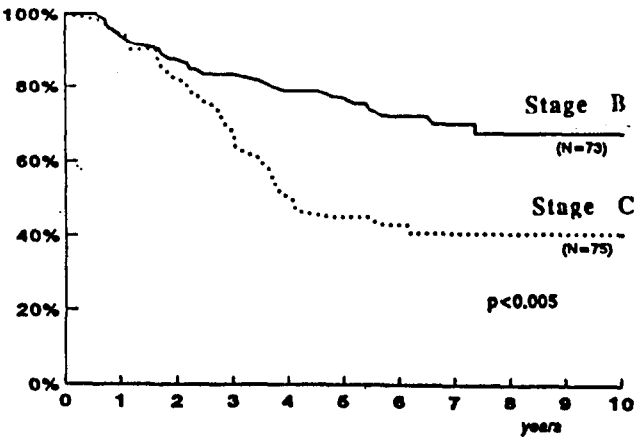

Fig. 2. Determined survival curves for the two stages groups.

former group; the OS value was also higher in this group but the difference was not statistically significant. The curves of DS in the groups with and without preoperative flash are reported in Fig. 3. The analysis of the characteristics of the two groups (Table 8) revealed however that the group receiving the flash dose had a relatively higher number of cases with 3 or less nodes compared to the group treated postoperatively only.

Major late side effects were observed in 38 patients (26%). In 8 presenting chronic diarrhea and malabsorption a hospitalization for medical treatment was required; a surgical treatment was necessary in the remaining.30 patients (20%). Surgery was a lysis of intestinal adhesions in 8, an ileal resection or an ileo colic bypass for a permanent ileal stenosis in 20, a colostomy for a rectal stenosis in 2 and a ureteroplasty for a fibrotic ureteral stricture in 2 (both also had a viscerolisis). Ten patients (6.7%) died because of complications related to

Table 5
Pattern of relapse according to the type of surgery, to the histotype and to the distance from anal margin

	Total patients	LR (%)	DM (%)
Type of surgery			
APR	97	6 (6%)	29 (30%)
AR	45	5 (11%)	14 (31%)
other	6	1 (17%)	1 (17%)
Histotype			
colloid	21	3 (14%)	6 (28%)
non-colloid	127	13 (10%)	62 (33%)
Distance from anal margin (cm)			
<5 cm	33	2 (6%)	—
5–10 cm	72	10 (14%)	—
>10 cm	29	3 (10%)	—
not specified	14	1 (7%)	—

APR, abdomino-perineal resection; AR, anterior resection.

Table 6
Pattern of relapse and 5 years actuarial survival values in stage C by number of involved nodes

	Number of involved nodes		
	≤3 (42)	>3 (26)	
Pattern of relapse			
LR	4 (9%)	6 (23%)	n.s.
DM	12 (29%)	16 (61%)	$P < 0.005$
Survival values			
OS	56%	29%	$P < 0.005$
DS	64%	30%	$P < 0.001$
LRFS	89%	73%	n.s.

OS, actuarial overall survival; DS, actuarial determined (cancer specific) survival; LRFS, actuarial local recurrence-free survival; LR, local recurrence; DM, distant metastasis; n.s., statistically non-significant.

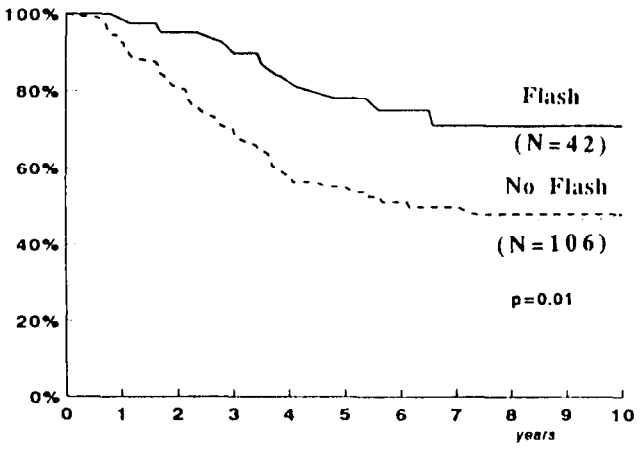

Fig. 3. Determined survival curves for the groups receiving the preoperative flash or treated postoperatively only.

these side effects without evidence of disease. In 6 patients the death occurred because of a perioperative complication (usually perforation and peritonitis) shortly after the operation performed for a small bowel obstruction. In all of these cases surgery was done in an emergency unit of another hospital where surgeons were not aware of the previous treatment of the patient. Three patients died because of malabsorption after extensive ileal resection and 1 because of rectal hemorrhage. All deaths and the majority of major complications occurred during the early period of our experience. The incidence of major side effects was in fact 35% in the period from 1980 to 1985 and 12% after 1985. The main modifications introduced in the second period were the exclusion of the preoperative flash dose, and the introduction of the small bowel visualization for the simulation procedure; this last measure resulted in a more careful selection of the lateral fields size and in the exclusion from irradiation of some cases with a larger amount of small bowel in the presacral space. Table 9 reports the correlation of type of surgery, preoperative flash dose, position of the upper border of the treated area and period of treatment with the incidence of major side effects. The period of treatment before or after 1985 was the only significant factor. A considerable increase of major side effects was also observed in the group of patients receiving the preoperative flash dose.

Table 7
Actuarial 5-years survival values and pattern of relapse in the patient group receiving the pre-operative flash; comparison with the group treated post-operatively only

	Pre-operative flash dose		
	Yes (42 pts.)	No (106 pts.)	
Survival values			
OS	64%	50%	n.s.
DS	78%	55%	$P < 0.01$
LRFS	92%	87%	n.s.
Pattern of relapse			
LR	3 (7%)	13 (12%)	n.s.
DM	8 (19%)	41 (39%)	$P < 0.01$

OS, actuarial overall survival; DS, actuarial determined (cancer specific) survival; LRFS, actuarial local recurrence-free survival; LR, local recurrence; DM, distant metastasis; n.s., statistically non-significant.

4. Discussion

A large number of papers have been published in the last 20 years reporting the results of postoperative radiotherapy in rectal cancer; in four [3,18,57,58] postoperative radiotherapy was compared in a randomized trial with surgery only; in some papers [10,30,38,42, 56,60] there was a historical comparison with a previous series treated with surgery only; in most [9,13,14,16, 24,40,51,62–64] there was no control series and the results were compared with those of the current surgical literature. In all studies patients receiving postoperative

Table 8
Distribution by stage and by number of involved nodes in the group receiving the pre-operative flash dose and in the group treated post-operatively only

	Pre-operative flash dose	
	Yes (42 pts.)	No (106 pts.)
Stage		
B2,B3	21 (50%)	52 (49%)
C1,C2,C3	21	54
No. of involved nodes		
≤3	14 (67%)	28 (52%)
>3	5 (24%)	21 (39%)
not specified	3 (14%)	5 (9%)

Table 9
Type of surgery, pre-operative flash dose, level of the upper field border and period of treatment in patients presenting major late side effects

	Total patients	No. with major side effects (%)	
Type of surgery			
APR	97	25 (26%)	n.s.
AR and other	51	13 (25%)	
Pre-op. flash dose			
Yes	42	14 (33%)	n.s.
No	106	24 (23%)	
Upper field border			
L5-S1	122	30 (25%)	n.s.
L4-L5	26	8 (31%)	
Period of treatment			
1980–85	88	31 (35%)	$P < 0.005$
1986–90	60	7 (12%)	

APR, abdomino-perineal resection; AR, anterior resection; other, radical surgery other than APR or AR; n.s., statistically non-significant.

radiotherapy had perirectal infiltration and/or positive nodes. A higher (although not statistically significant) 5 years OS was reported with postoperative radiotherapy (46% vs. 36% with surgery only) in the randomized trial carried out by the Gastrointestinal Tumor Study Group first published in 1985 [22] and updated in 1988 [57] with an 8 years follow-up; no advantage was observed in the other 3 studies. The incidence of LR was lower (although not at a statistically significant level) after postoperative irradiation than after surgery only, in 3 of the 4 randomized trials and in all studies with a historical control; values of LR lower than generally expected after surgery only were also reported in all of the studies without a control arm. Acute side effects of postoperative radiotherapy required the early stop of treatment in a considerable number of cases. According to the review of Bosset and Horiot [6] in the published trials of postoperative radiotherapy 12–27% of patients did not receive the full planned dose. Late side effects after postoperative irradiation were also definitely higher than after surgery only. Up to 20–30% of the irradiated patients experienced complications requiring some modification of their life style (diet, intestinal function, sexual function, bladder function); from 5–15% presented major complications essentially affecting the small bowel (adhesion, stenosis, malabsorption) requiring hospitalization for medical treatment or a surgical treatment; from 2–5% had a treatment related death. In the Swedish trial [20] 41% of patients undergoing postoperative irradiation with 60 Gy in 8 weeks, experienced complications possibly related to radiotherapy compared to 23% of a historical control group treated by surgery only. In the Danish Trial [4] severe complications were reported in 21% of cases receiving postoperative radiotherapy vs. 8.4% for the group treated by surgery only. A frequency of bowel obstruction requiring surgery between 4% and 13% was also reported after postoperative radiotherapy in a number of studies without a control arm [7,29,55,57,60,61]. Letschert [36] in a retrospective review of 111 cases treated with radiation after rectal surgery, found a dose volume correlation for small bowel complications; the incidence of severe small bowel complications was 37% when 2 AP/PA large fields were used and 6% for limited three-field technique. The bowel function was assessed in detail by Kollmorgen et al. [33] in a group of 100 cases with a minimum of 2 years follow-up after anterior resection of the rectum; 41 received postoperative chemoradiation, while 59 were only operated; night time bowel movements were present in 46% in the first group vs. 19% in the second, occasional incontinence in 39% vs. 17%, fecal urgency in 78% vs 19%.

The LR rates reported after postoperative radiotherapy in the studies reviewed are between 6% and 25%. In our series the incidence of LR was evaluated both by dividing the number of LR observed and the total number of patients and by the actuarial curves of LRFS at 5 years. All our values are within the more favourable end of the range reported in the literature and support the opinion that postoperative radiotherapy is able to significantly reduce the incidence of local relapses in the pelvis.

The actuarial 5 years overall survival in the same literature series range between 40% and 55% and our value of 53.8% is within this range. Similar survival figures are however reported in several surgical series for the Duke's stages B and C. The value of postoperative radiotherapy on survival in rectal cancer therefore remains still unproven.

The prognostic significance of the main characteristics of the patient, of the disease and of the treatment were also assessed in our series. The pathological stage was confirmed as the first prognostic factor for survival; the worse prognosis of C cases was due to the much higher incidence of DM while the incidence of LR was very similar than in B cases. The number of positive nodes was also found to have a significant prognostic value suggesting the differentiation of two subtypes of stage C, with 3 or less and with more than 3 involved nodes. This factor turned out to affect the risk of DM and not the risk of LR. The prognostic value of the number of involved nodes in rectal cancer was already reported in the literature. In their series submitted to systematic second look after primary curative surgery, Gunderson et al. had more than 3 nodes involved in 22 of the 40 patients presenting a failure and only in 3 of the 20 remaining disease free; the site of failure was however not specified. In the GITSG series [34] the number of involved nodes was mentioned as one of the independent determinants of DM but not

of LR. In the Mayo Clinic series published by Schild et al. [51] a number of involved nodes was associated with a higher incidence of DM and a lower survival, while the incidence of LR was similar than in the group with less than 4 nodes involved. No prognostic relevance was found for the distance from the anal margin, for the histotype and for the type of surgery.

The use of a flash dose of 5 Gy within 24 h before the operation followed by postoperative irradiation was reported in a few series [5,8,10,25,26,37,52,63]; in none of them was there a randomized comparison and the number of cases treated was always quite small. The results of these studies, although very favourable, cannot therefore be validated. Furthermore, negative results have been reported in a large randomized trial carried on by the MRC [17] demonstrating the absence of any effect when the flash dose was used alone. In our series the use of the preoperative flash, although not randomized, was not intentionally selected for any factor and it was stopped after the publication of the negative result of the MRC trial. It was therefore very surprising to discover at the initial analysis of our series that there was a statistically significant advantage for DS in the group receiving the preoperative flash with respect to the group only receiving the postoperative irradiation. This advantage in survival was due to a lower incidence of DM supporting the hypothesis that the flash dose might decrease the viability of cells disseminated during the surgical manipulation. Further analysis of the two groups demonstrated however that the distribution of one of the two prognostic factors, the number of positive nodes, was unbalanced in favour of the group receiving the preoperative flash. Whether this can fully explain the observed difference cannot be stated but it certainly introduces a considerable bias and it does not allow to support the value of the flash dose.

The incidence of serious complications was higher than reported in the recent literature in the early phase of our study. The main reason was that the unfavourable influence of rectal surgery on the tolerance of small bowel to radiation was not sufficiently appreciated at that time. The complications rate decreased in fact from 35.2% to 11.7% when we started to evaluate systematically the amount of small bowel in the irradiated volume and the use of the flash dose was stopped. Our experience also demonstrated that both the patient and the family doctor should be carefully informed of the potential risks of this treatment. It is likely that some deaths occurring after an emergency operation with extensive resection and multiple anastomoses of adherent loops for an intestinal occlusion, were avoidable if the patient was referred to us at the first appearance of symptoms and not sent to a peripheral hospital when he was already in critical condition. These cases are in fact often better managed with medical treatment and less aggressive surgery.

The lower but still considerable incidence of side effects observed with postoperative radiotherapy even after this measure, made us reluctant to start the combination with chemotherapy as advised by the NIH consensus meeting [44]; although justified by the attempt to decrease the number of DM, this approach was in fact reported to be followed by a higher number of complications and a lower compliance.

Based on the better tolerance reported for preoperative radiotherapy [2,6,20,45] and on the favourable results obtained with the combination of radio and chemotherapy in tethered or inoperable tumors [11,12,19,27,41,48] our policy has now been moved to the use of preoperative irradiation with concomitant chemotherapy (5 fluorouracil and folinic acid); this treatment is reserved to patients with tumors arising in the extraperitoneal portion of the rectum and staged as T3 by digital examination (tethered or fixed) or/and by endorectal ultrasound or RM. This seems at present the best approach to be tested in locally advanced rectal cancer to improve the patients survival with less morbidity.

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