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● *Original Contribution*

PRE-OPERATIVE IRRADIATION OF *T*3-CARCINOMA IN BILHARZIAL BLADDER:

A COMPARISON BETWEEN HYPERFRACTIONATION AND CONVENTIONAL FRACTIONATION†

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The present report deals with a prospective randomized study investigating the value of pre-operative telecobalt irradiation in the management of *T*3-carcinoma in Bilharzial bladder. A total pre-operative dose of 4000 rad was split into 2 equal courses with a gap of 1 week. Two dose-time regimens were compared: split-course conventional fractionation, 200 rad/day (SC) and hyperfractionation (HF). In the latter, the daily dose amounted to 1000 rad and was divided into 17 hourly acute fractions, 60 rad each.

The SC and HF regimens produced equivalent local tissue reactions. Hyperfractionation, however, was associated with a somewhat higher incidence of radiation sickness. Both regimens resulted in an increase of the 2-year disease-free survival rate from 19 ± 10% (3/16) to 53 ± 9% (17/32) without added surgical hazard; both HF and SC appeared to be equally effective.

An appreciable post-irradiation tumor shrinkage was noted in the majority of patients; this is consistent with a rapid tumor cell turnover rate. Moreover the likelihood of long term local tumor control seemed to be greater in the more rapidly shrinking tumors. This is proposed to be linked to a more extensive reoxygenation process. No correlation was obtained between the quantitative scoring of the cytohistological radiation effect and the outcome of treatment.

Carcinoma, Bladder, Pre-operative irradiation, Hyperfractionation.

INTRODUCTION

Radical cystectomy is the standard treatment adopted in the management of carcinoma arising in Bilharzial bladder in Egypt since most patients are seen when their disease is in clinical Stages *T*3 or *T*4. Radiation therapy in such patients is handicapped by a compromised local tissue tolerance as well as by a poor radiation response principally because of a large tumor volume.[3]

In resectable cases, radical cystectomy offers a 25% 5-year disease free survival rate, and local pelvic recurrence accounts for about 90% of failures.[10,13] Therefore, an adjuvant therapeutic measure is needed to improve the clinical end results.

The present prospective study aims at investigating the value of moderate doses of pre-operative telecobalt irradiation. Two dose-time regimens were compared: conventional fractionation and hyperfractionation. In either case a split-course technique was used since this was demonstrated to increase the local tolerance to fractionated therapy[3] as well as to continuous low dose rate irradiation.[21] Hyperfractionation is an attempt at simulation of continuous low dose rate. Kal and Sissingh[15] have proposed that continuous low dose rate irradiation can enhance the differential between effects on tumor and on normal tissues. This effect can be an advantage in the radiotherapy of carcinoma in Bilharzial bladder. Pierquin

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et al.[21] suggested that the differential effect of external beam therapy can be enhanced when it is delivered at a low dose rate over a period of days.

METHODS AND MATERIALS

Forty eight previously untreated patients with histologically verified carcinoma arising in Bilharzial bladder were included in this study. They all belonged to the *T*3 category according to the clinical staging system of the International Union Against Cancer.[22] This was verified by bimanual examination under anesthesia and by determination of the microscopic depth of infiltration by transurethral endoscopic biopsy. There were 40 men and 8 women ranging in age from 26 to 56 years (median age, 45 years). The association of bladder cancer with Bilharzial cystitis was confirmed by clinical, radiological and histological criteria.[9]

The World Health Organization classification of bladder tumors[19] was adopted for histological typing and grading. The group included 31 cases of squamous cell carcinoma (Grade 1: 13, G2: 13 and G3: 5), 12 cases of transitional cell carcinoma (G2: 6 and G3: 6) and 5 cases of G2 adenocarcinoma.

All patients were considered eligible for radical cystectomy on the basis of the clinical stage (*T*3), general medical status and a good kidney function (blood urea nitrogen level less than 30 mg/100 ml, serum creatine less than 1.8 mg/100 ml and at least 1 normally functioning kidney on excretory urography). Patients above the age of 60 years and patients coming from distant areas and whose regular follow-up could not be assured, were excluded. In May 1976, 48 patients were included in the trial and followed at least 2 years.

Therapeutic groups

Patients were allocated at random to 1 of 3 groups:

A. Radical cystectomy alone.

B. Split-course (SC) pre-operative radiotherapy group. Two courses were given with a gap of 1 week. Each course comprised 10 fractions of 200 rad apiece, delivered over 14 days. Cystectomy was performed 15–20 days after the end of the second course.

C. Hyperfractionation (HF) pre-operative radiotherapy group.

Two courses also were given with a gap of 1 week. Each course consisted of 2 days of treatment; on each day 17 fractions of 60 rad apiece were delivered at a rate of 1 fraction every hr, i.e., a total daily dose of 1000 rad. Cystectomy was performed 15–20 days after the end of the last course.

The total dose employed in both pre-operative radiotherapy regimens amounted to about two thirds of that used in radical radiotherapy of bladder cancer.

Radiotherapy technique

Telecobalt therapy was used at a source-axis distance (SAD) of 80 cm. The target volume included the entire pelvis and extended upwards to the level of the middle of the body of the fifth lumbar vertebra and laterally for 1.5 cm beyond the inlet of the true pelvis to cover the external iliac nodes. The proximal 1.5 cm of the prostatic urethra was also included.

One direct anterior portal and 2 lateral 60° wedge fields were used. Since a rectal bladder with a terminal colostomy[12] was the urinary diversion procedure performed most frequently, the rectum was spared as much as possible.

Scoring of reactions

The system proposed by Berry *et al.*[4] was used for scoring of acute skin reactions. The scoring system proposed by Arcangel *et al.*[1] was adopted for chronic skin and subcutaneous tissue reactions.

Acute bladder and rectal reactions also were scored using an arbitrary scale 0, 1, 2, 3 for no, mild, moderate and severe reactions, respectively. Blood loss during surgery, the period of hospitalization, time of wound healing, and any post-operative complications were also recorded.

Scoring of post-radiation tumor regression

The degree of change in tumor size was scored on the day preceding surgery as follows:

0 = No change
1 = Less than 50% reduction
2 = More than 50% reduction
3 = No detectable tumor.

Quantitative histopathological analysis

All tumors were of the solid protuberent type and approximately spheroidal. Therefore, the approximate tumor volume was calculated from the equation (0.5 a.b.c.) where a, b and c are the 3 mutually perpendicular dimensions of the tumor.

Quantitative analysis of the histopathological data was based on examination of multiple large histological sections including the entire surgical specimen and mounted on 9 × 12 cm glass slides. These sections passed through the center of the major axis of the tumor and included its thickest part. A 1 × 1 cm grid was drawn on each slide and then projected and printed on a 30 × 40 cm photographic paper (Fig. 1). Each square was microscopically scanned for identification of foci belonging to one of following categories:

1. Stroma: including connective tissue and blood vessels.

2. Foci of tumor cells were classified into 3 categories:

Category I: Morphologically intact tumor cells.

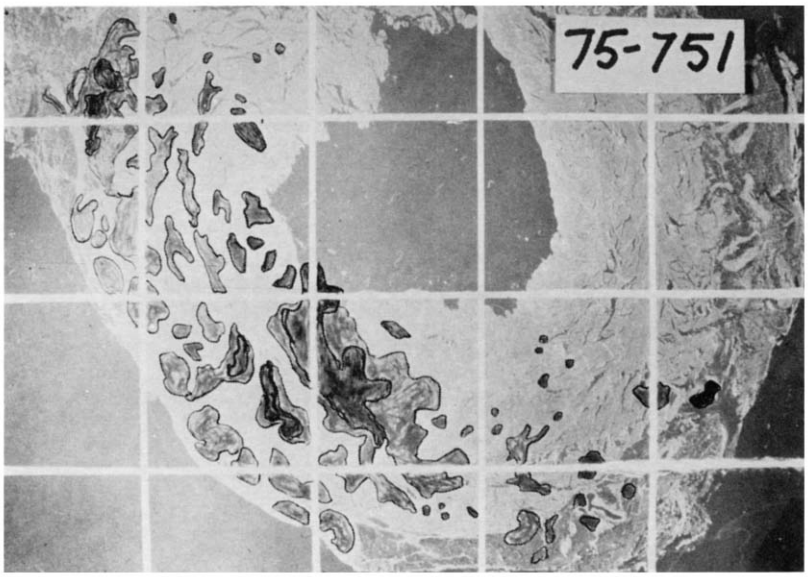

Fig. 1. Large bladder section with 1 × 1 cm grid. The outline of different tumor foci is shown with extension into the perivesical tissue (P3b). Area of each focus is measured planimetrically, and measurements are checked microscopically with the help of an eye-piece graticule.

Category II: Degenerative nuclear and/or cytoplasmic changes but with preservation of the structural pattern (Fig. 2).

Category III: Nuclear and cytoplasmic degenerative changes with loss of structural pattern or total necrosis (Fig. 3).

The outline of each focus was sketched within the corresponding square on the photographic print. The surface area of each focus was measured planimetrically. This was checked by microscopic measurement with the help of an eyepiece graticule having an area of 1500 μm^2 at the magnification used. The total area of each histological category was then calculated. The sum of stromal and tumor cell areas will be referred to as the "total tumor area".

RESULTS

Tolerance and normal tissue reactions

All patients could tolerate the entire prescribed pre-operative regimens. No significant differences were noted among the 2 pre-operative radiotherapy groups regarding the incidence and severity of maxi-

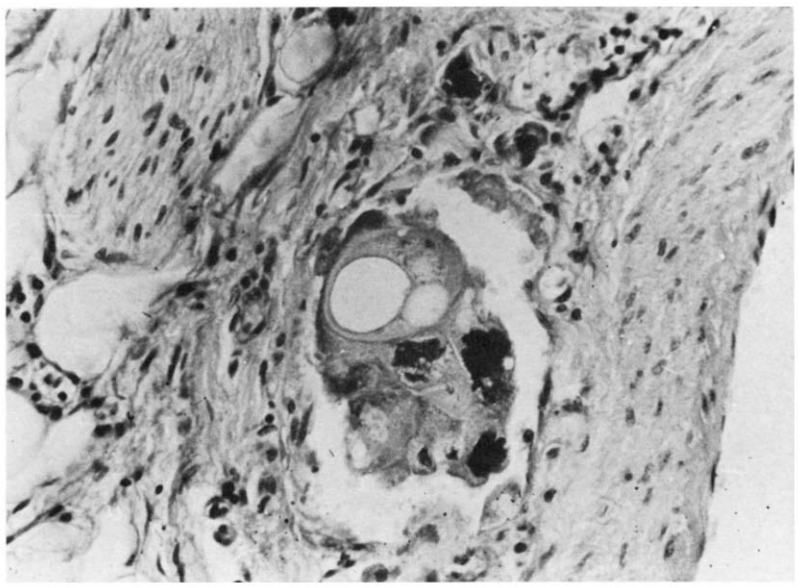

Fig. 2. Category II tumor cells. Aggregate in a lymph vessel with marked cytoplasmic vacuolation and nuclear condensation.

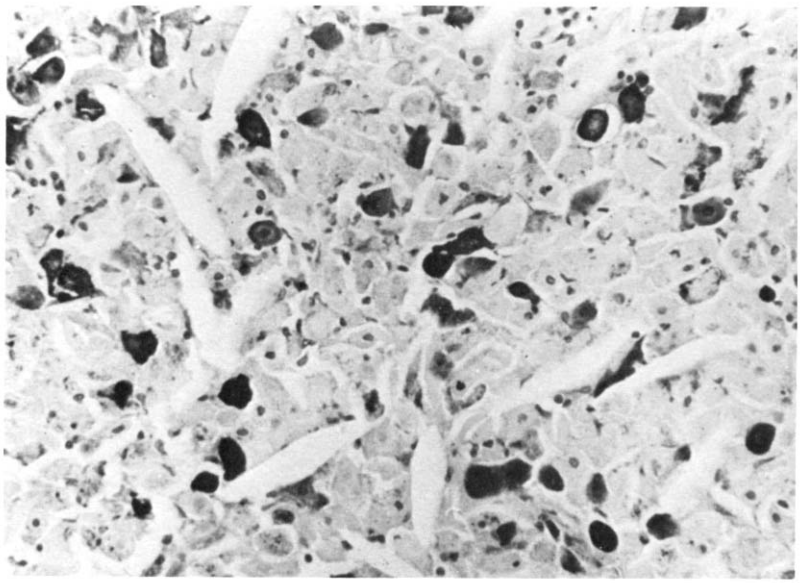

Fig. 3. Category III tumor cells with complete disintegration. Note nuclear debris and clear spaces occupied by needle-shape cholesterol crystals.

Table 1. Frequency of radiation sickness, skin, bladder and rectal reactions

	Radiation sickness		Acute skin reactions		Chronic skin reactions		Cystitis		Proctitis	
Score	HF†	SC‡	HF	SC	HF	SC	HF	SC	HF	SC
0	7/16	12/16	2/16	3/16	2/16	0/16	5/16	2/16	12/16	14/16
1	7/16	2/16	12/16	9/16	5/16	5/16	5/16	6/16	3/16	2/16
2	2/16	2/16	2/16	4/16	6/16	10/16	6/16	8/16	1/16	0/16
P§ =	0.059		0.53		0.12		0.16		0.33	

†Hyperfractionation (HF).
‡Split Course (SC).
§"Ridit" analysis.[11]

mum skin, rectal and bladder reactions. Hyperfractionation was associated with a somewhat greater incidence of radiation sickness, although the difference was not highly significant ($P = 0.059$ according to the ridit analysis[11]) (Table 1).

Table 2. Pathological staging

	Control	HF	SC
*P*0	0/16	1/16	1/16
*P*2	2/16	2/16	4/16
*P*3a	5/16	5/16	5/16
*P*3b	4/16	5/16	3/16
*P*4	5/16	3/16	3/16
Downstaging	2/16	8/32	
Upstaging	5/16	6/32	

Clinical end results

Clinical and radiological examination performed 1–2 days before cystectomy showed that some degree of tumor shrinkage was achieved in 26 of the 32 patients of the 2 pre-operative radiotherapy groups. In 6 patients no tumor could be detected. In 2 patients complete tumor disappearance was confirmed in the cystectomy specimens (Table 2).

Radical cystectomy including pelvic lymphadenectomy could be performed in all except 7 patients (control group: 2, SC: 1 and HF: 4 patients). In 4 the common iliac nodes could not be removed completely because they were fixed to iliac vessels; in 1, the lower aortic nodes also were involved. Peritoneal malignant nodules were found in 2 patients and only palliative cystectomy was performed. In the seventh patient, the rectum and part of the anterior abdominal wall had to be excised since they were infiltrated by tumor.

Table 3. Clinical end results

	Control	HF	SC
No. of patients	16	16	16
Operative mortality	1	3	1
Cause	Peritonitis	-Peritonitis -C. hemorrhage -liver failure	Peritonitis
Alive and NED†			
1 Year	4	8	11
2 Year	3	8	9
Died of disease within 2 year	12	5	4
Died of other causes	0	0	2‡

†No evidence of disease.
‡Hematemesis (portal hypertension; coronary heart disease).

Pre-operative radiotherapy did not seem to increase the operative mortality or the incidence of the common post-operative complications. The overall operative mortality of the entire series was 10%; peritonitis as a result of leakage through anastomotic lines was the most common cause (Table 3).

The 1-year and 2-year disease free survival rates in patients receiving pre-operative radiotherapy were $59 \pm 9\%$ (19/32) and $53 \pm 9\%$ (17/32) respectively (Table 3). In the surgery alone group the corresponding rates were significantly lower, $25 \pm 11\%$ and $19 \pm 10\%$ respectively ($P < 0.05$). The survival rates did not differ significantly in the SC and HF groups, however.

Local pelvic recurrence accounted for all treatment failures in patients that died of the malignant disease. In one patient inguinal nodal metastases also developed. Two patients of the SC group died during the second post-cystectomy year of causes other than the malignant tumor (Table 3).

Table 4. Correlation between post-radiation tumor regression and local tumor control at 1 year†

	Regression index‡				
	0	1	2	3	Total
Controlled	2 (0)	5	9 (8)	3	19 (16)
Uncontrolled	4	3	1	1	9
Total	6 (4)	8	10 (9)	4	28 (25)

†"Ridit" analysis[11] for all histological types: $z = 2.37$; $P = 0.018$. For transitional and squamous cell carcinoma: $z = 2.94$; $P = 0.0032$.
‡Figures in parenthesis exclude adenocarcinomas

Correlation between clinical end results and initial post-treatment tumor regression

Nineteen of the 28 patients that were subjected to pre-operative irradiation and survived surgery were alive without evidence of disease 1 year after treatment. Table 4 gives the distribution of locally controlled and uncontrolled patients at 1-year over the various degrees of tumor shrinkage as scored 1–2 days prior to surgery. Rapid tumor skrinkage seemed to be associated with a greater probability of long-term control. A "ridit" analysis[11] was used to determine the statistical significance of this relationship. This test maintains and takes advantage of the crucial information on the natural ordering of the scores.

For the 3 histological types, the relationship between the probability of local control and the degree of post-radiation tumor shrinkage was statistically significant ($P = 0.018$). The level of significance improved when the analysis was restricted to squamous and transitional cell carcinoma by exclusion of adenocarcinomas ($P = 0.0032$).

Histopathological data and their correlation with clinical end results

Two irradiated bladders did not show evidence of tumor. Apart from this, the frequency of upstaging and downstaging did not differ significantly among the 3 therapeutic groups (Table 2).

The quantitative histopathological data are given in Tables 5, 6 and 7. Because of the marked skewed distribution of most measurements, the Wilcoxon rank test[20] was employed when comparing the 3 therapeutic groups. It can be seen that:

1. The mean tumor volume, total tumor area, stromal and tumor cell areas were significantly smaller in irradiated tumors compared with tumors of the surgery alone group ($P < 0.005$) (Table 5).

Table 5. Tumor volume, total tumor area and the relative abundance of stroma and tumor cells

	Control 15 patients	HF 16 patients	SC 15 patients	SC + HF 31 patients
Tumor volume (cm^3)				
Mean	70	42	35	39
Median	75	42	30	24
Range	18–168	0–252	0–88	0–252
Total tumor area (mm^2)				
Mean	727	391	289	341
Median	670	290	223	223
Range	56–2530	0–2189	0–1032	0–2189
Stroma (mm^2)				
Mean	244	165	80	124
Median	185	91	45	62
Range	3–1265	0–880	0–288	0–880
Tumor cells (mm^2)				
Mean	483	241	208	218
Median	479	166	184	166
Range	40–1265	0–1310	0–744	01310

2. There was no significant difference between HF and SC groups regarding the mean tumor volume, total tumor area or the representation of tumor cells and stroma (Table 5).

3. Irradiated tumors contained significantly greater proportions of cells exhibiting degenerative changes (cell categories II & III). The representation of 3 cell categories did not, however, differ significantly among the HF and SC groups (Table 6).

4. The correlation between the probability of long-term local control and the histopathological measurements made on the residual tumor in the cystectomy specimen was tested in the group of 28 patients who were subjected to pre-operative irradiation and survived surgery. Compared with patients with recurrent disease, those with no clinical evidence of disease at 1 year had significantly smaller mean tumor volume ($P < 0.025$) and total tumor area ($P < 0.01$). Both the stromal and tumor cell areas were also significantly smaller in controlled patients ($P < 0.01$ and $P < 0.025$, respectively, Table 7). These relationships were maintained at the same statistically significant levels when the analysis was made on the results of 2-year follow-up. The ratio of stroma to tumor cells, the absolute and relative representation of the different tumor cell categories did not differ

Table 6. Distribution of cellular categories†

	Control		HF		SC	
	mm^2	%	mm^2	%	mm^2	%
Category I						
Mean	466	94	104	49	148	63
Median	418	99	190	49	165	63
Range	39–1210	77–100	0–470	3–89	0–437	54–91
Category II						
Mean	39	2.5	39	29	29	13
Median	39	25	24	19	14	8
Range	22–56	2.4–2.6	0–131	4–56	0–148	2–37
Category III						
Mean	17	7	97	31	42	23
Median	95	2	32	39	13	33
Range	3–53	0.1–2.2	0–710	5–70	0–273	19–69

†Excluding the 2 irradiated patients where no tumor was found in cystectomy specimens.

Table 7. Quantitative histopathological measurements in the 1 year controlled and recurrent tumors that were subjected to pre-operative irradiation and survived surgery

	Controlled (19 patients)	Recurrent (9 patients)	P† <
Tumor volume (cm^3)			
Mean	26	65	0.025
Median	24	60	
Range	0–75	12–252	
Total area (mm^2)			
Mean	212	630	0.01
Median	198	309	
Range	0–629	59–2189	
Stroma (mm^2)			
Mean	71	254	0.005
Median	33	177	
Range	0–375	15–879	
Tumor cells (mm^2)			
Mean	135	380	0.025
Median	139	378	
Range	0–396	43–1310	

†One-tail Wilcoxon rank test.[20]

significantly in patients with controlled and recurrent disease, however.

DISCUSSION

The present prospective study shows that moderate doses of pre-operative radiotherapy improved the clinical end results in patients with carcinoma in Bilharzial bladder associated with deep infiltration of the bladder wall ($T3$). Similar results were reported in deeply infiltrating bladder tumors of the transitional cell variety prevailing in Europe and North America.[23–25]

In the present series, the majority of irradiated tumors showed some degree of shrinkage that amounted to more than 50% of the pre-treatment volume in more than half of the patients. Such a degree of an immediate tumor response is expected on the basis of prevalence of a relatively high cell birth rate and a large cell loss factor, i.e., a rapid turnover rate.[2]

The correlation between tumor regression during radiotherapy and the probability of local control has been the subject of a number of studies with conflicting results that have been surveyed recently by Denekamp.[7] In the present series, irradiated bladder tumors presented some features that suggest the existence of such a correlation. Patients with controlled disease showed significantly greater post-radiation tumor shrinkage than those with recurrent disease. Moreover, patients with locally controlled disease at 1 year had significantly smaller residual tumors in the cystectomy specimens. In animal tumor systems, Denekamp[7] demonstrated that tumors exhibiting rapid shrinkage during treatment generally had the highest local control rate. Similar correlations were also observed in case of carcinoma of the cervix uteri in humans[8,14,18] and in transitional cell bladder cancer subjected to pre-operative irradiation.[23]

The capacity of a given tumor to shrink during the course of a radiation treatment seems to depend on the efficiency of the host to remove "doomed" cells. In animal tumor systems, this is strongly linked with the cell loss factor. Tumors which normally possess a very high cell loss factor shrink rapidly after irradiation and also are capable of more efficient reoxygenation.[5–7] The observed better prognosis of rapidly shrinking bladder tumors noted in the present study may be related to a more extensive reoxygenation, which renders the tumor more sensitive to successive doses of irradiation.

In the present study, we attempted to grade the cytological radiation effect and to correlate this grading with the outcome of treatment. However, no significant correlation could be demonstrated. It seems therefore that the grading system employed is a poor indicator of the extent of cell killing which is the deciding factor determining the probability of local control.

In the present study, hyperfractionation involved the delivery of a daily dose of 1000 rad divided into 17 hourly fractions of 60 rad each. Since continuous low dose rate irradiation can be considered as an infinite number of small fractions,[16] the adopted hyperfractionation scheme seems to be a reasonable approximation to that modality. A total dose of 4000 rad split into 2 parts with a gap of 1 week was well tolerated. The local reactions did not appear to differ from those of split-course treatment with conventional fractionation. Moreover, the immediate tumor response and the 2 year end results of the 2 regimens were equivalent.

Therefore, hyperfractionation did not offer any therapeutic advantages when it was used as a pre-operative measure in carcinoma in Bilharzial bladder. It should be noted, however, that the dose used did not exploit all of the available local tissue tolerance. It remains to be seen whether hyperfractionation offers advantages in radical radiotherapy of this disease when doses approaching those of full tolerance must be given. It is worth noting that Littbrand *et al.*[17] showed an improved therapeutic ratio when a low dose-fractionation scheme was used in the radical treatment of transitional cell bladder cancer.

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