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POST RADIATION CYSTITIS :

A Prospective Study to Evaluate the Use of W.F. 10 in the Treatment of Complicated Post Radiation cystitis

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Abstract

From January 1, 1988 to July 30, 1990. 12 cases of uncontrollable bleeding cystitis under usual standard management were put under WF10 clinical trial. Indicators for the effect evaluation are clinical, haematuria, cystoscopic, and histopathology gradings. The results were very favourable; 10 out of 12 symptom free and no macroscopic haematuria within 4 weeks after administration. Some 1 to 2 weeks delay of corresponding improvement of endoscopic and histopathology grading after clinical and haematuria improvement was noted. Further adjustment of the dosage and duration of administration regime may further improve this present results.

KEY WORDS : *Srinagarind Hospital, carcinoma of the cervix, radiation cystitis, heamaturia, WF10.*

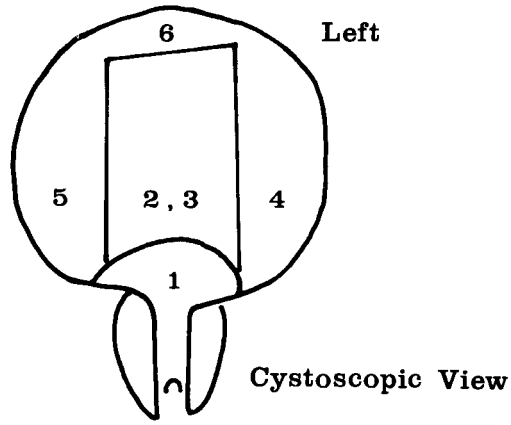
Introduction :

Post radiation cystitis remains a challenging problem in the management of cancer of the cervix in most of the medical centres in the world. At Srinagarind Hospital this is no exception. This is the referring centre in the North Eastern part of Thailand where radiotherapy service is available. Carcinoma of the cervix ranks second in the incidence of all types of cancer in this region after the liver[1]. It is the standard of gynaecology practice here to treat carcinoma of the cervix of stage IB onwards with radiation[2]. Approximately 200 new cases a year are referred for radiation at this Hospital. Of these 15 to 20% of the patients have undesirable effects from radiation treatment, namely cystitis, proctocolitis or both.

Some of these unfortunate cases will develop repeating episodes of bleeding from radiation cystitis. Apart from dysuria and frequency, repeating or uncontrollable haematuria is the main challenge of the clinician. The management of this problem on the whole is still mainly empirical and supportive, i.e. antibiotics, steroid instillation and blood transfusion. The results of these treatments are far from satisfactory. It is then considered

that there is a real need to search for a more adequate agent for dealing with this troublesome clinical problem.

Tetrachlorodecaoxygen (WF 10) is known as a comitogenic oxidant which can enchance fibroblast proliferation in vitro provided that macrophages and lymphocytes are present. Firm evidence that WF10 promotes healing process in several inflammatory conditions including damage from radiation is recently known[3]. This study is to investigate its effect on radiation cystitis presenting with repeating episodes of bleeding and failure to respond to the usual standard of empirical and supportive treatment.



1	Vesical trigone	1.
2	Posterior wall	2.
3	Anterior wall	3.
4	Left wall	4.
5	Right wall	5.
6	Fundus wall	6.

Patients and Methods :

Patient selection :

There are 12 patients included in this study from January 1, 1988 to July 30, 1990. Criteria for selection : Patients with post radiation cystitis are referred from the Gynaecological Department of Srinagarind or other provincial hospitals. These patients all have recurring symptoms which are not successfully treated by the usual conservative management. They are experiencing excessive or uncontrollable bleeding which necessitates intravesicular clot evacuation or blood transfusion.

Criteria for Exclusion :

Patients with recurrent tumour, with post radiation fistula to genito-urinary tract and patients with moribund state. All patients must have provided written consent before WF10 therapy is initiated.

Patients who have fulfilled the above criteria would have undergone clinical assessment and routine laboratory investigations including CBC, urinalysis, urine culture and sensitivity, coagulogram, IVP and pan-endoscopic examination. All findings of panendoscopic examination were recorded and biopsies taken from areas 4, 2 and 5 of bladder wall as illustrated below for histopathology study. WF10 was given on the day of panendoscopic examination according to a set regime :

Dosage : 1.0 ml of WF10 per kg body weight per 24 hours.

Duration of treatment : the above dosage is given on each of two consecutive days.

The route of administration is intravenous. The prescribed dose of WF10 is mixed with 1000 ml 5% D/W as infusion fluid. This solution must be freshly prepared, protected from intense sun-light and given in 24 hours at regular drip.

Follow up for clinical assessment :

Pan-endoscopy, bladder biopsy and histopathology study were again made on week 2, week 4 and week 12.

In case of recurrent apisode of attack of haematuria a second course of WF10 was repeated in the same regime. Therapy will be terminated of the patient develops an allergic response, signs of hepatic toxicity or if the patient demands discontinuation. Adjuvant therapy allowed were : Urinary tract infection if present should be controlled by appropriated systemic antibiotics. Topical anti-biotics and antiseptics delivered by intravesicular instillation

or continuous irrigation was not performed. Intravesicular instillation of steriods or other drugs were prohibited. Only bladder irrigation with normal saline was allowed. Blood transfusion would be given if indicated. Coagulopathy was corrected before the therapy is commenced.

Evaluation of the effectiveness of WF10 in this treatment will consist of 4 parts; namely, symptom of suprapubic pain, sign of Haematuria, Pan-endoscopic picture and Histopathology of bladder wall biopsy.

Suprapubic pain was graded according to the following criteria.

Grade 0 : No pain

Grade 1 : Occasional pain, no interference to normal activity. No analgesic is required.

Grade 2 : Pain required occasional oral analgesics.

Grade 3 : Pain required regular oral analgesics.

Grade 4 : Pain not controllable with oral analgesic treatment.

Haematuria was graded according to the following criteria.

Grade 0 : No red cell is seen microscopically.

Grade 1 : Microscopic Haematuria.

Grade 2 : Gross Haematuria without blood clot in urine.

Grade 3 : Gross Haematuria with small blood clot in urine.

Grade 4 : Gross Haematuria with blood clot causing acute urinary retention.

Grade 5 : Frank blood in urine.

Endoscopic grading of acute radiation cystitis :

Grade 1 : injection of submucosal blood vessel.

Grade 2 : grade 1 plus extravasation of blood stain.

Grade 3 : all grade 1 and 2 plus evidence of ulceration in chronic radiation cystitis,

There is evidence of fibrinous plague.

Bleeding can occur as in any of the above grading.

Histopathology daignosis and grading were made on the following criteria.

Grade 1 : Atrophic mucosa, submucosal fibrosis with telangectasia.

Grade 2 : Granulation tissue formation.

Grade 3 : Exudate and stromal hemorrhage.

Grade 4 : Submucosal ulceration and hemorrhage.

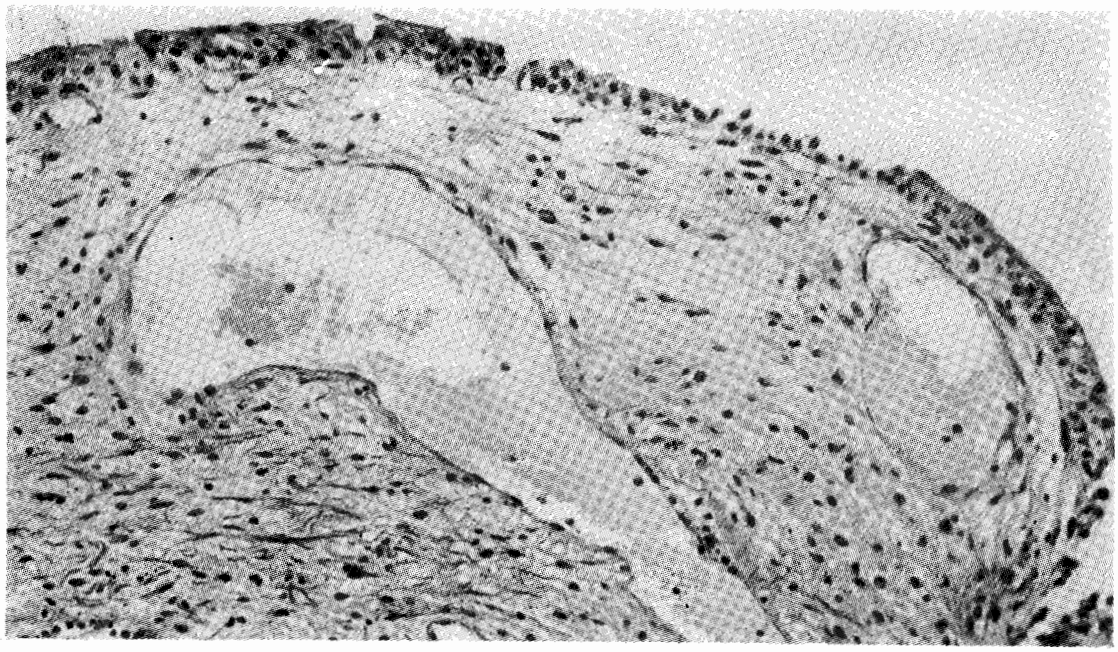
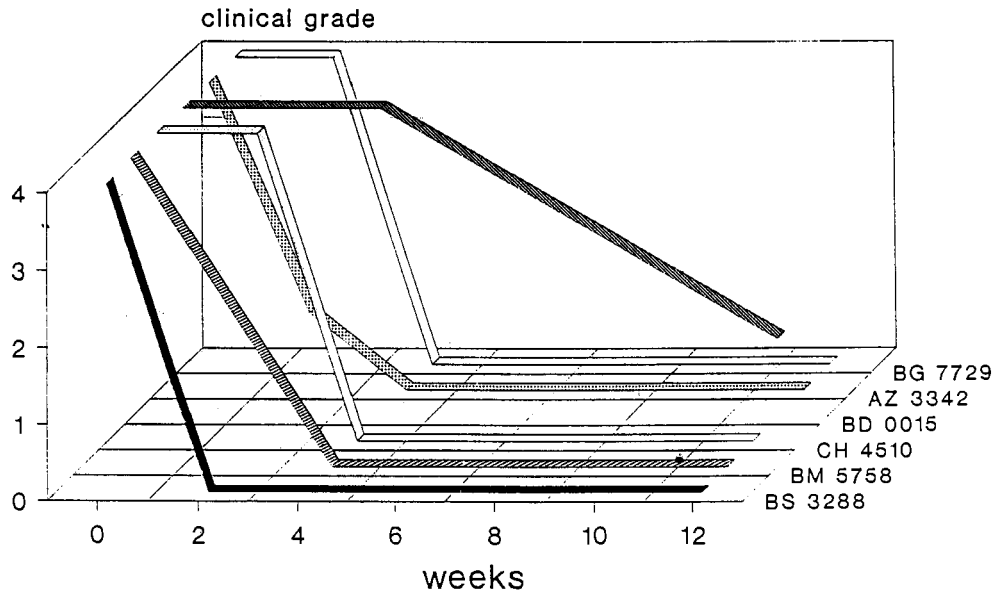


Fig. 1 Grade I Histopathology (Atrophic mucosa, submucosal fibrosis with telangectasia)

All the data and results recorded were then tabulated and analysed in term of WF10 effect on clinical picture, haematuria, endoscopic picture and pathological grading. Graphic computerization were used to illustrate the progress of response.

Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (1) clinical response during 12 weeks



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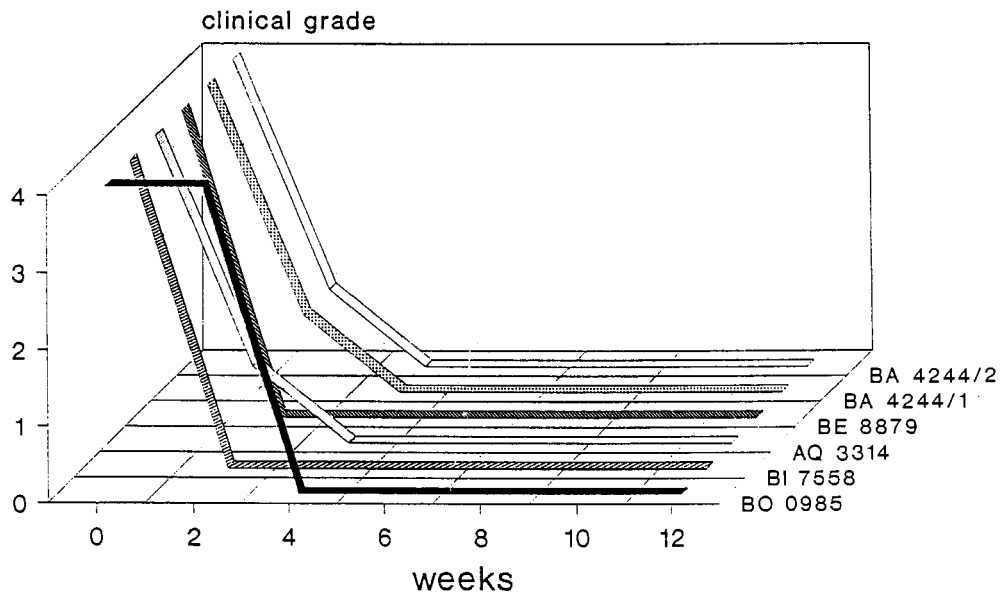
Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (2) clinical response during 12 weeks



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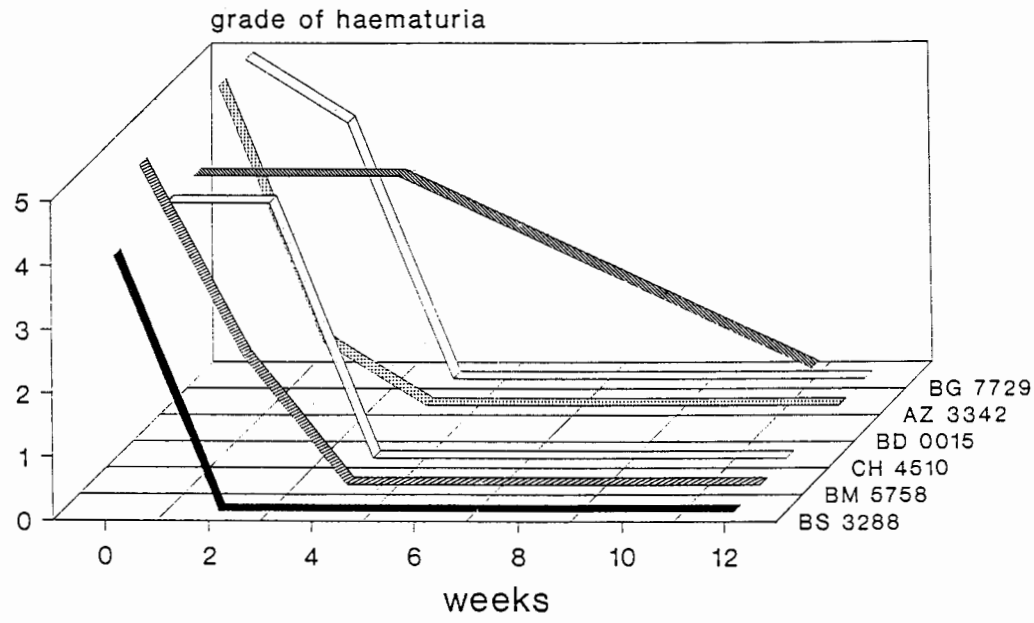
Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (3) haematuria response during 12 weeks



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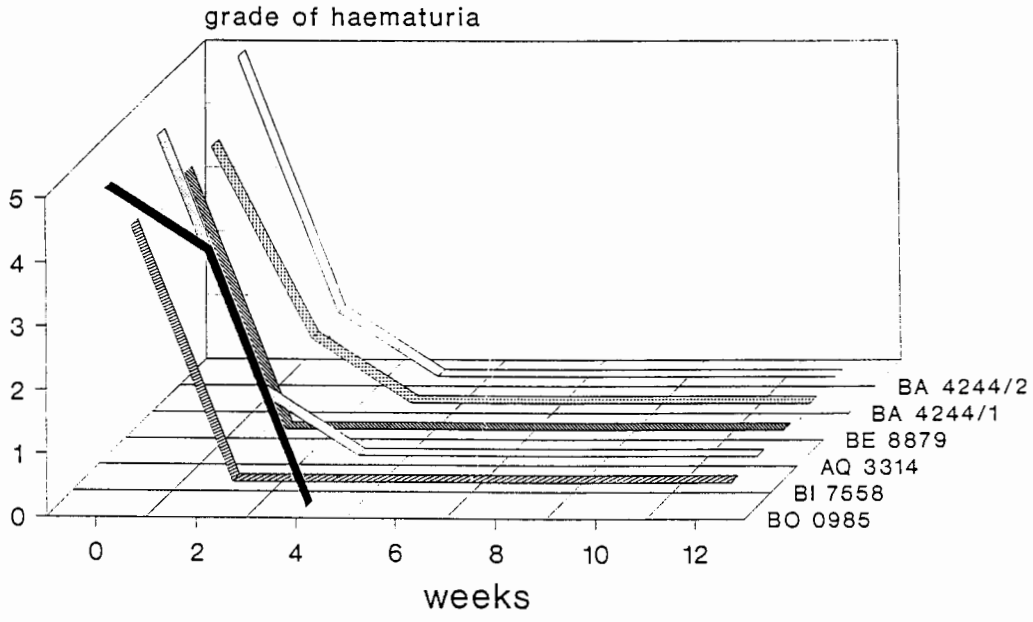
Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (4) haematuria response during 12 weeks



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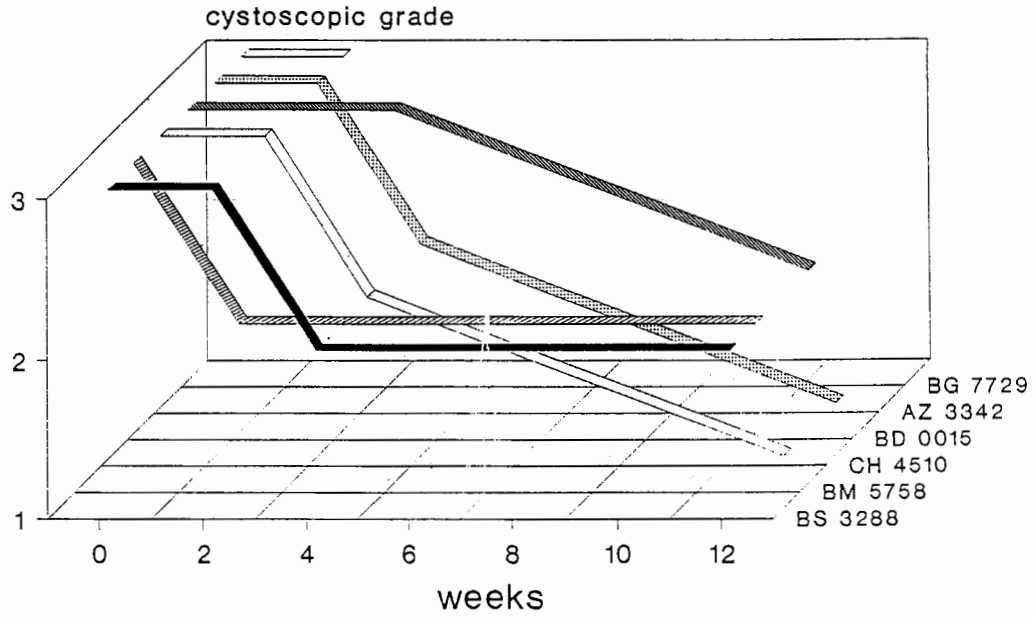
Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (5) cystoscopic response during 12 weeks



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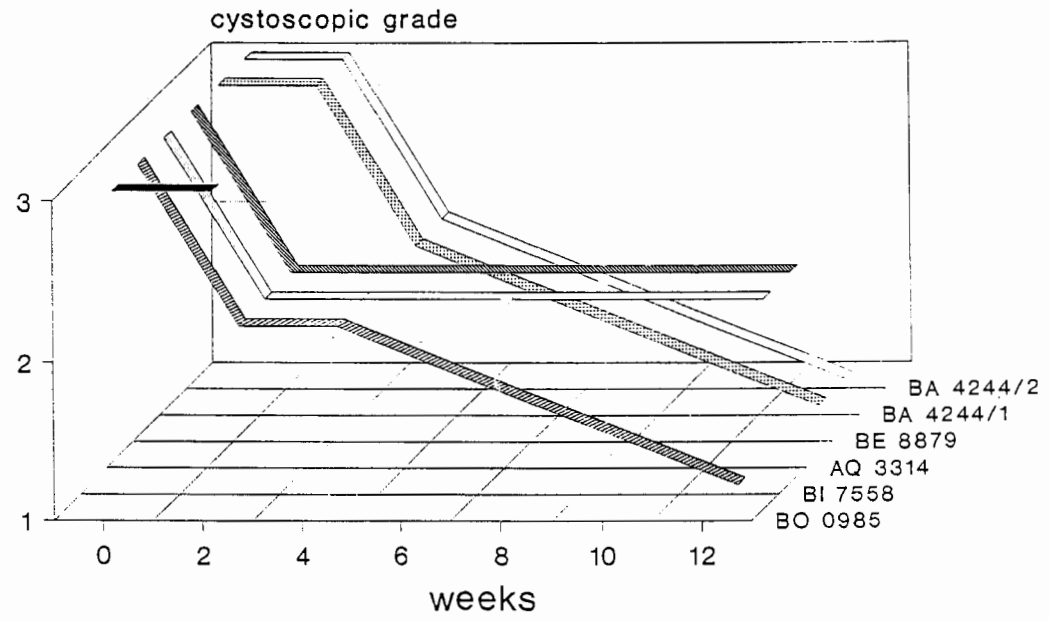
Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (6) cystoscopic response during 12 weeks



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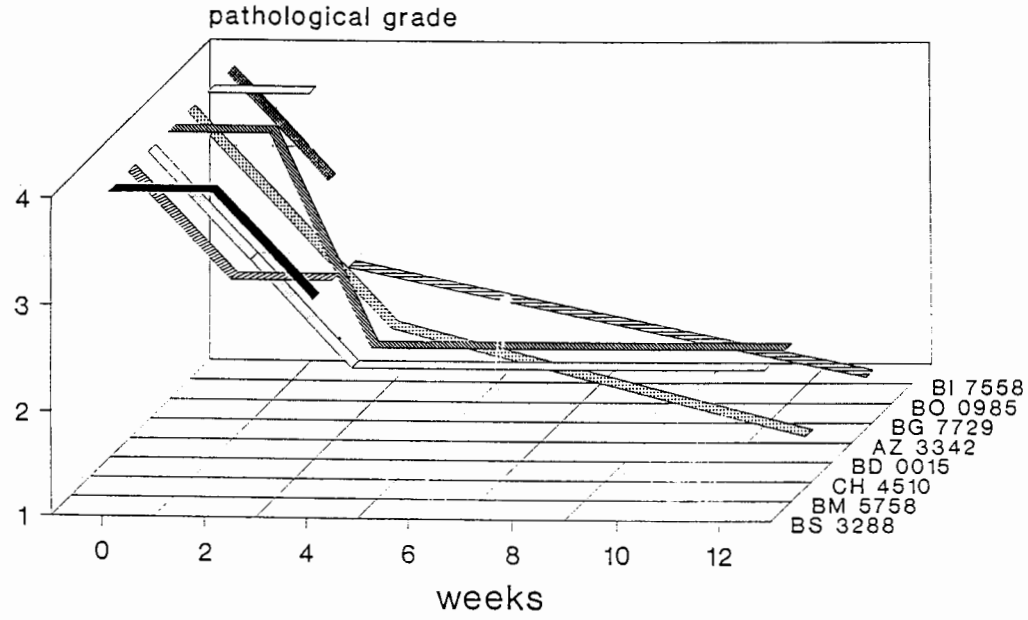
Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (7)pathological response during 12 weeks



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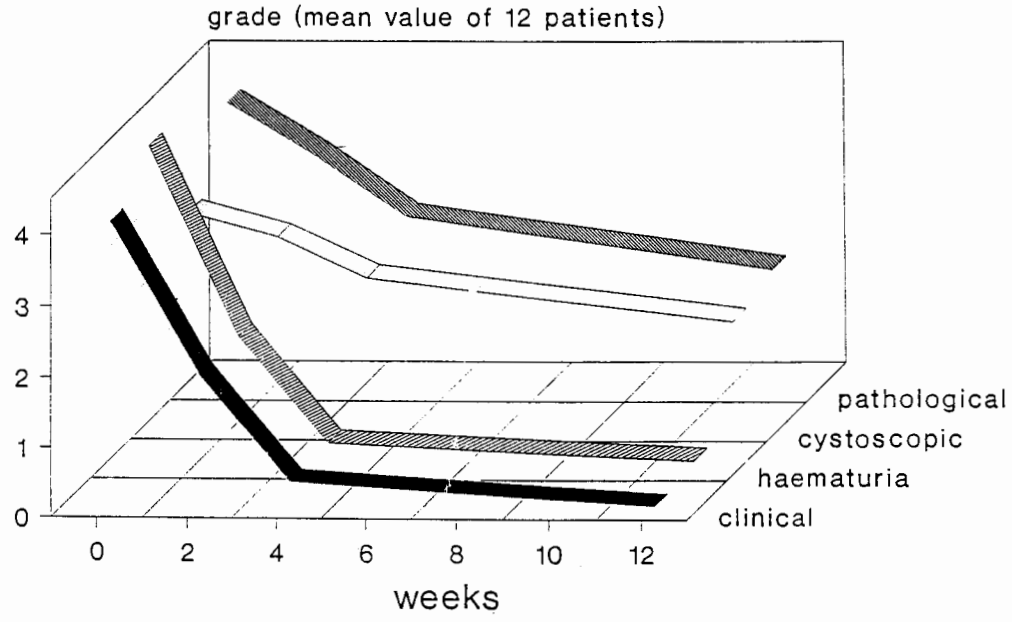
Efficacy of TCDO (WF10 solution) in the treatment of chronic radiation cystitis (8) response during 12 weeks



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Results

All 12 patients had previous history of carcinoma of the cervix, age ranging from 40 to 70 with the mean age of 55. Two were in stage IB when first presented, six stage II B and the remaining four were in stage III B.

All had radiation therapy on the same year of presentation. Two had only external radiation, ten had both external and implantation. The time taken from radiation therapy to macroscopic haematuria ranges from 0 or the same year to 10 years later with the mean of 4 years. The time taken from when macrohaematuria occurred to WF10 therapy ranges from 0 or the same year to 3 years. Seven were on the same year, three were 1 year later, one was 2 and one was 3 years respectively. That is 60% had WF10 on the same year when macroscopic haematuria first detected.

Clinical grading or suprapubic pain grading at the time of commencing the therapy (WO) all were in grade 4 (grade ranging 0 to 4). Haematuria grading, six were in grade 4 and six were in grade 5. (grade ranging 0 to 5). The cystoscopic grading all twelve were in grade 3 (grade ranging 0 to 3). The histopathological grading six were in grade 4 and six histological gradings were missing. (grading ranges 1 to 4). On week 2 (W2) after commencing the therapy three clinical grading were 0 or symptoms free, four were in grade 1, one was in grade 2., none in grade 3, four were in grade 4. Heamaturia grading four were in grade 0, four were in grade 1, one in grade 2, none in grade 3, three were in grade 4, and one was in grade 5. Cystoscopic grading four were in grade 2, eight were in grade 3. Pathological grading : one was in grade 2, four were in grade 3., two were in grade 4, five pathological grading were missing.

On week 4, (W4) clinical grading ten were in grade 0, one were still in grade 4, and one was on trial progress. Haematuria grading ten were in grade 0, one was still in grade 4, and one is being on trial progress. Cystoscopic grading nine were in grade 2, one was in grade 3, one refused cystoscopy and one was being on trial progress. Pathological grading : four were in grade 2, two were in grade 3, five were missing and one is being on trial progress. On week 12 after therapy, clinical grading nine were in grade 0, two in grade 1 and one still in trial progress. Haematuria grading also nine were in grade 0, two in grade 1 and one still on trial progress. Cystoscopic picture five were in grade 1, five in grade 2.

Discussion.

Basically radiation cystitis on its quiescent state is a chronic inflammatory process. However there is an exacerbation phase when patches of the bladder epithelial lining and its subepithelial layer are having acute inflammatory reaction predisposing bleeding from its telangectasia and ulceration. According to Elstner[4] and Youngman[5] WF10 in the tissue in conjunction with heme proteins, forms an activated heme-TCDO Complex. It can complete with cytochrome oxidase in oxidising cytochrome C, where the complex itself is reduced to water, Chloride ($\bar{Cl}$), and molecular oxygen (O_2) and oxidated haemoprotein are produced. In this manner cytochrome oxidase which normally transfers the electrons to molecular oxygen by reducing it to H_2O, is kept out of the mitochondrial flow of electrons. According to this theory therefore there is a greater supply of O_2 in the tissue. This may result in cellular and humoral response promoting tissue repair. In animal experiment Tetrachlorodecaoxygen anion complex has proved to be suitable for the treatment of tissue damage caused by ionizing radiation[6].

In our series all 12 patients with radiation cystitis, the clinical grading and haematuria grading were all very severe : in grade 4 and grade 5. However after the first 2 day course at week 12 (W12), all grading of both clinical and haematuria became 0., except one BO.0015

whose clinical and haematuria grading were 1. It is quite obvious that there is a closed relationship between the clinical grading improvement and haematuria grading (Fig 2,3). When viewing cystoscopic grading and pathology grading there is a time lag of objective response detected when compared with clinical and haematuria gradings. However after week 4, all four component gradings appear to correspond with one another very well (Fig 4).

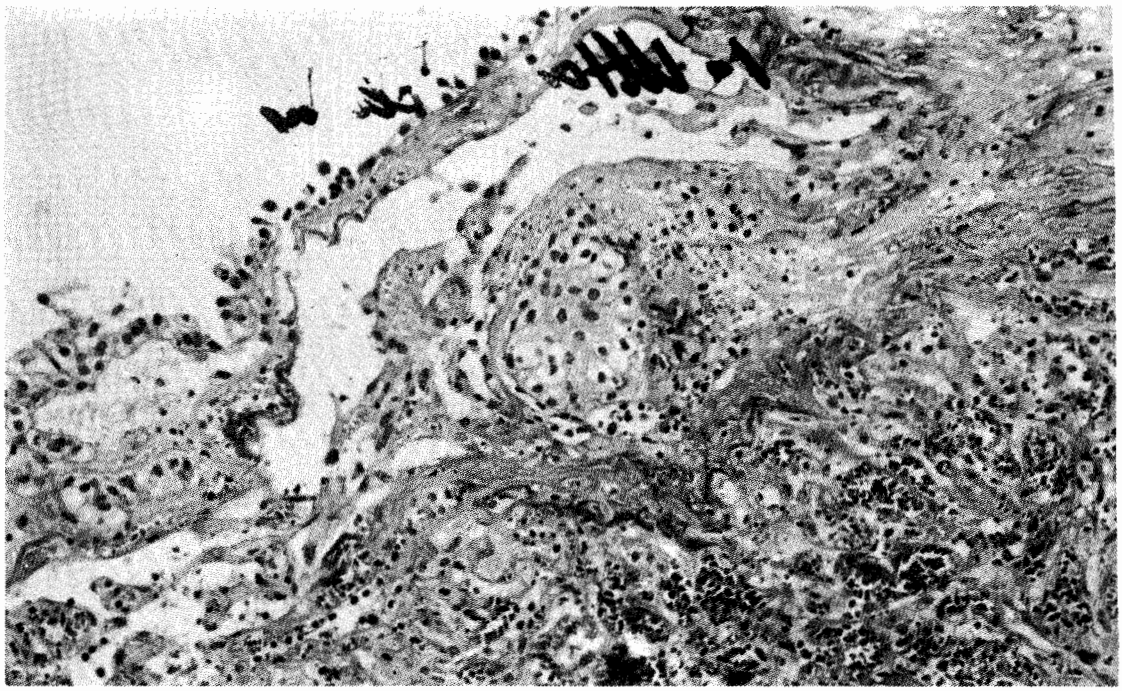

Fig. 2 Grade II Histopathology (Granulation tissue formation)

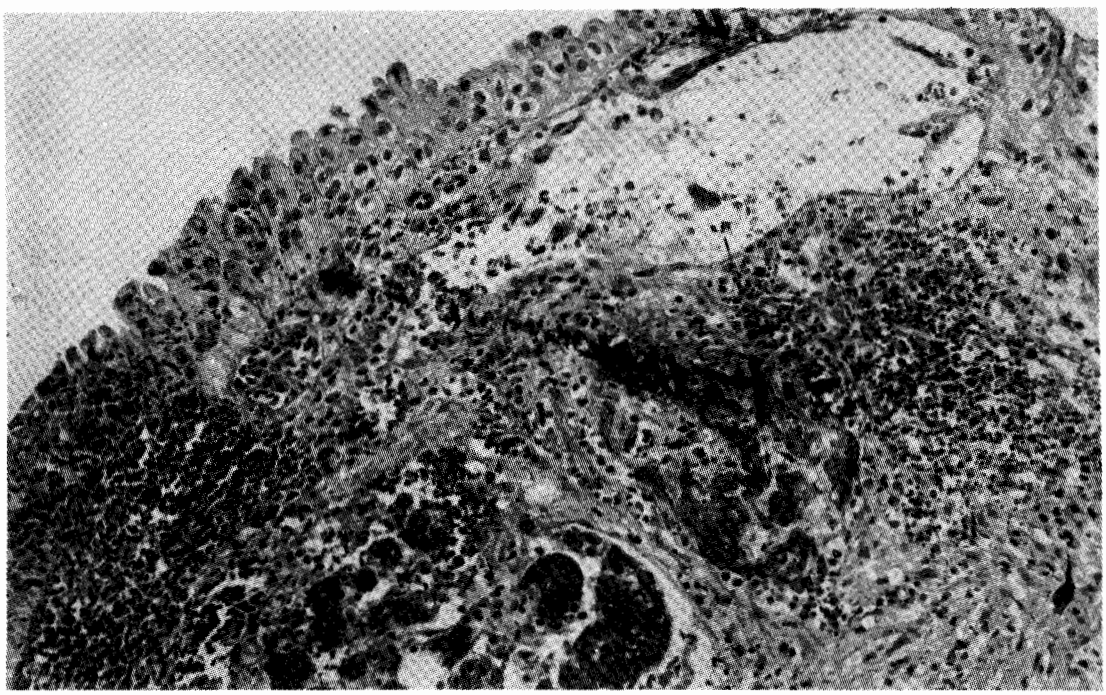

Fig. 3 Grade III Histopathology (Exudate & stromal hemorrhage)

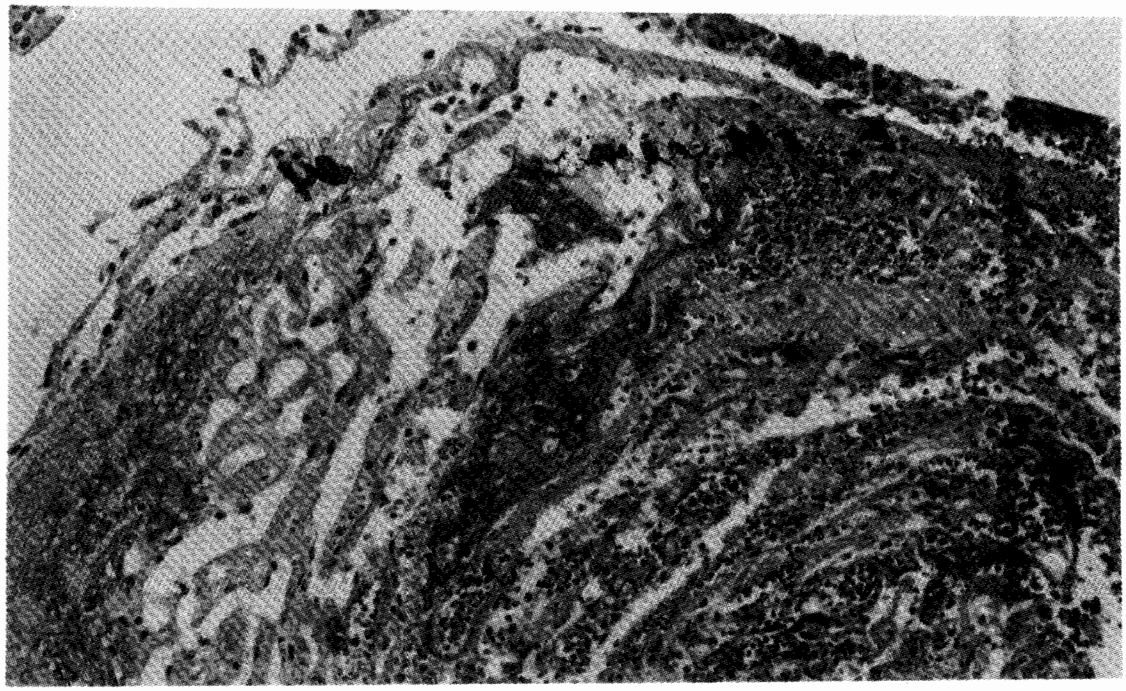

Fig. 4 Grade IV Histopathology (Submucosal ulceration)

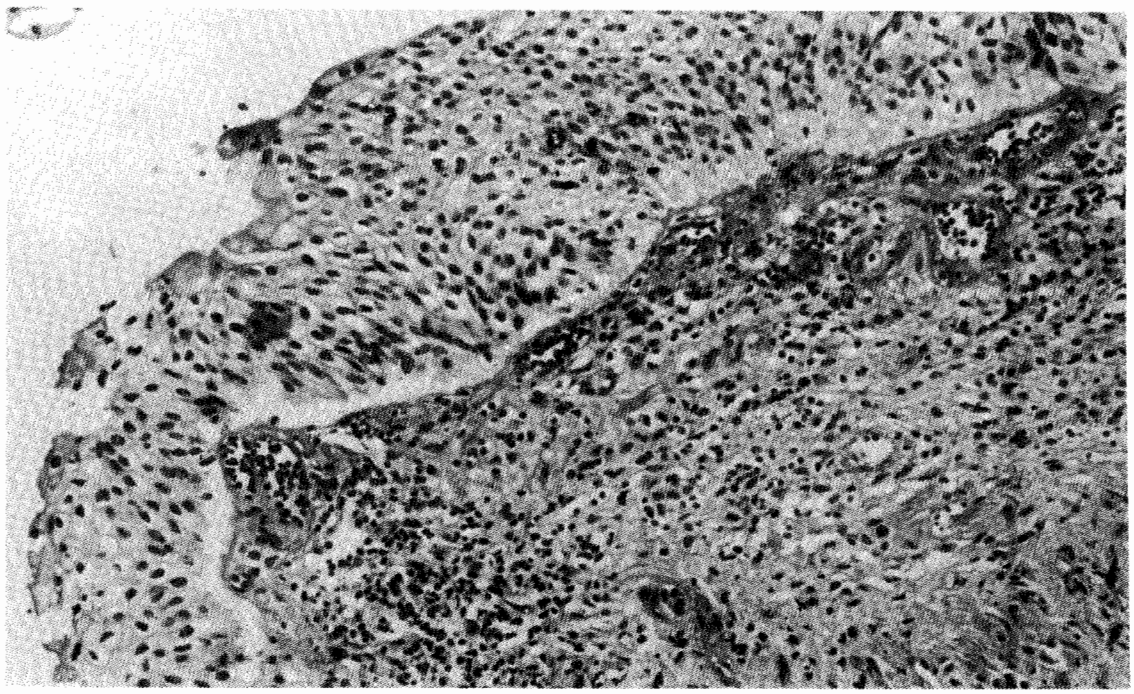

Fig. 7 Healing process involved the superficial area nest to the epithelium

There were 6 cases required more than 1 two day course, (Table I remarks). In view of the delay in response, or recurrence of bleeding the decisions were made to repeat WF10 2 day course during the trial in progress. This may indicate that there is a place for manipulation both the dosage and the period of administration to obtain the optimal result in future trial.

On close examination of pathological histology and its grading, the cellular activity of healing process appeared to be mostly on the superficial area near epithelial lining. This may explain the early improvement of clinical and haematuria gradings prior to cystoscopic and pathological (Fig 7, 8 Histopathology) Using the dosage and duration of administration in this series we note no adverse effect from the agent used. We also noted that patient with liver cirrhosis appeared to have a delay in response to the treatment. (Table I BO-0015)

On the basis of the above findings it may be suggested that WF10 is a very worth-while added armament in the management of this troublesome bleeding radiation cystitis. Morever futher modification of the dosage and the duration of administration may continue to improve this present result.

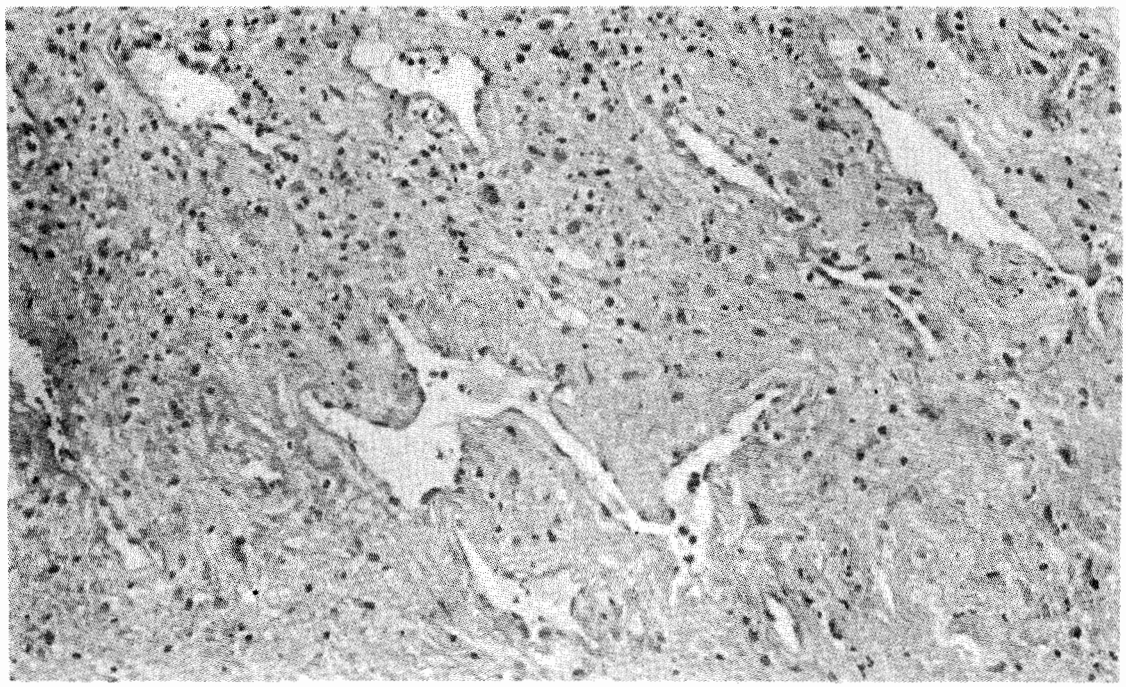

Fig. 8 Higher Magnification of Fibrotic Healing Process.

Table 1. Data summary the effects of WF10 in term of gradings and the remarks W = week, m = missing

No.	HN, Age	Diag.	Rad.	Haem	WF10		WO	W2	W4	W12	Remarks
1.	BS3288 43 yrs	CA Cx St. IB 1987	Ext. Rad. 1987	1988	1989	Cl	4	0	0	0	1989 2 two day courses WO, W1
						Haem	4	0	0	0	
						Cyst	3	3	2	2	
						Path	4	4	3	m	
2.	BM5758 45 yrs	CA Cx St.IB 1987	Ext. Rad. 1988	1988	1989	Cl	4	2	0	0	1989 1 two day course WO
						Haem	5	2	0	0	
						Cyst	3	2	2	2	
						Path	4	3	3	m	
3.	CH4510 62 yrs	CA Cx St. III B 1988	Ext. Implan-tation 1988	1990	1990	Cl	4	4	0	0	1990 2 two day courses W0, W1
						Haem	4	4	0	0	
						Cyst	3	3	2	1	
						Path	4	3	2	2	
4.	BD0015 60 yrs	CA Cx St. II B 1980	Ext. Implan-tation 1980	1985	1988	Cl	4	4	4	1	1988 2 two day courses W0, W1 liver cirrhosis Death : septicemia Loc. Pyocalyx (R)
						Haem	4	4	4	1	
						Cyst	3	3	3	2	
						Path	4	4	2*	2	
5.	AZ3342 51 yrs	CA Cx St. II B 1985	Ext. Implan-tation 1985	1988	1988	Cl	4	1	0	0	1988 3 two day courses W0, W1
						Haem	5	1	0	0	
						Cyst	3	3	2	1	
						Path	4	2	3	1	
6.	BG7729 55 yrs	CA Cx St. III B 1985	Ext. Implan-tation 1985	1989	1989	Cl	4	4	0	0	1989 1 two day course W0 patient-refused cystoscopy on W4, W12
						Haem	5	4	0	0	
						Cyst	3	3	m	m	
						Path	4	4	m	m	
7.	BO0985 64 yrs	CA Cx St. III B 1987	Ext. Implan-tation 1987	1990	1990	Cl	4	4	0	0	1990 2 two day course W0, W4 *Cauterization required W6
						Haem	5	4	0	–	
						Cyst	3	3	–	–	
						Path	4	3	–	–	

No.	HN, Age	Diag.	Rad.	Haem	WF10		WO	W2	W4	W12	Remarks
8.	BI7558 48 yrs	CA Cx St. II B 1986	Ext. Implantation 1986	1989	1989	CI	4	0	0	0	1989 1 two day course W0
						Haem	4	0	0	0	
						Cyst	3	2	2	1	
						Path	m	2	m	1	
9.	AQ3314 40 yrs	CA Cx St. III B During Preg Y 1979	Ext. Implantation 1979	1989	1989	CI	4	1	0	0	1989 1 two day course W0
						Haem	5	1	0	0	
						Cyst	3	2	2	2	
						Path	m	m	m	m	
10.	BE8879 38 yrs	CA Cx St. II B 1985	Ext. Implantation 1985	1988		CI	4	0	0	0	1988 1 two day course W0
						Haem	4	0	0	0	
						Cyst	3	2	2	2	
						Path	m	m	m	m	
11.	BA4244 50 yrs	CA Cx St. II B 1985	Ext. Implantation 1985	1988	1989	CI	4	1	0	0	1989 1 two day course W0 Bleeding recurrec 1 year after 1st course
						Haem	4	1	0	0	
						Cyst	3	3	2	1	
						Path	m	m	m	m	
12.	BA4244 50 yrs	CA Cx St. II B 1986	Ext. Implantation 1986	1989	1990	CI	4	1	0	0	1990 2nd two day course W0, W1
						Haem	5	1	0	0	
						Cyst	3	3	2	1	
						Path	m	m	m	m	

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