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Cancer Chemotherapy and Pharmacology

Cooperative studies of systemic chemotherapy

A review of the work of the EORTC Urological Group and of the Yorkshire Urological Cancer Research Group (YUCRG)

P. H. Smith[1], J. A. Child[2], J. H. Mulder[3], A. T. Van Oosterom[4], J. A. Martinez-Pineiro[5], B. Richards[6], G. Stoter[7], O. Dalesio[8], M. De Pauw[8], and R. Sylvester[8]

[1] St James's University Hospital, Leeds, England
[2] The General Infirmary at Leeds, Leeds, England
[3] Rotterdam Radiotherapy Institute, Rotterdam, The Netherlands
[4] Akademisch Ziekenhuis, Leiden, The Netherlands
[5] Facultad Antonoma de Medicina, Madrid, Spain
[6] York District Hospital, York, England
[7] Free University Hospital, Amsterdam, The Netherlands
[8] EORTC Data Centre, Brussels, Belgium

Introduction

Until recent years invasive bladder cancer has been treated as though it were a local disease in which the tumour and its extensions were confined to the true pelvis. From this philosophy has stemmed the use of partial, simple, and radical cystectomy, irradiation through small fields confined to the true pelvis, large fields extending to the fifth lumbar vertebra, and combinations of these two forms of therapy. The development of this approach has been of interest and its results can now be assessed. Extensive reviews are available [2, 6, 8, 12, 18, 20, 23, 29, 36, 41–44, 46, 50], and the results are summarized in Table 1.

The figures are approximations but clearly make the point that whilst local treatment controls the pelvic disease in about half the patients treated, it is associated with poor long-term survival. This is largely because of the high early mortality, 40% in the first year (Fig. 1), which persists despite the high rate of control of the local lesions. Since approximately one-third to one-half of the patients die of metastases [25, 27], 78% of which present in the first year after diagnosis [25], one is drawn to the inescapable conclusion that invasive bladder cancer is a systemic disease which requires systemic therapy. It is this conclusion that has determined the activities of the EORTC Urological Group and of the YUCRG in the last 8 years.

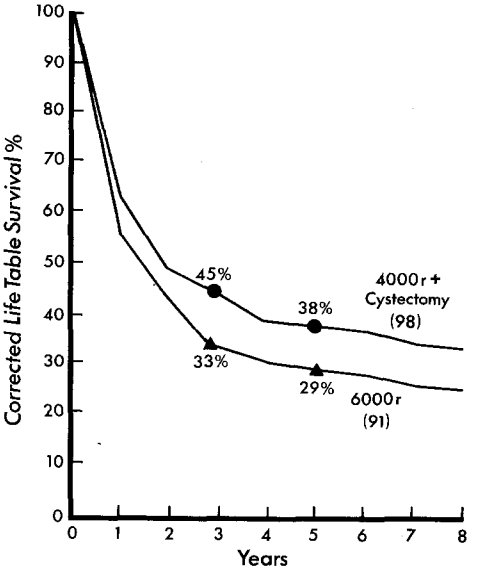


Fig. 1. Survival following radical radiotherapy and pre-operative radiotherapy and cystectomy. Note the high death rate in the first year after start of treatment (reproduced from Bloom et al., 1982, by kind permission of the authors and of the British Journal of Urology) [3]

Table 1. Morbidity and mortality of different therapeutic modalities, and 5-year survival following treatment of invasive bladder cancer (pooled statistics) [2, 6, 8, 12, 18, 20, 23, 29, 36, 41–44, 46, 50]

Treatment	Morbidity (%)	Mortality (%)	Pelvic recurrence rate (%)	5-Year survival (%)	
				T3	T4
Partial cystectomy (± radiotherapy)	5–10	0– 9	Up to 75	20–40	0–25
Total cystectomy	10–25	0–10	28–41	10–25	0– 5
Radical cystectomy	10–43	5–19			
Pre-op. radiotherapy and cystectomy	10–43	2–13	8–20	30–45	0
Radical radiotherapy	8–17	?	39–70	17–31	0–10
Radium implantation	25	4	29–40	9–45	–
Implantation of gold or tantalum	35	1.4	?	21	–
Radiotherapy and salvage cystectomy	26–63	0–23	?	16–42	0– 9

Reprint requests should be addressed to P. H. Smith

Phase II studies

Although our desire has been to institute adjuvant chemotherapy, we recognized that effective drug regimens must first be found. Our interest developed at the time that Carter and Wasserman published results on Adriamycin (ADM), 5-fluorouracil (5FU), and mitomycin C (MMC) which, used as single agents, gave response rates of 25%–35% [5]. Our phase II studies have been as follows:

1. ADM + 5FU

This study was undertaken to determine whether the remission rate of the combination of the then two most active agents was greater than that of either of the agents used singly.

The regimen used was ADM 50 mg/m^2 + 5FU 500 mg/m^2 IV every 3 weeks for a minimum of four cycles.

This produced (i) a 40% remission rate in 52 evaluable patients (CR 4; PR 17), the responses varying in duration; and (ii) marked symptomatic relief of bone pain and haematuria (Table 2).

This study has previously been reported in detail elsewhere [9].

2. EORTC protocol 30764
(Coordinator J. H. Mulder, Rotterdam)

This comparative phase II study was designed to evaluate ADM and 5FU as given above against ADM 75 mg/m^2 given alone and cyclophosphamide (CTX) 1 g/m^2 given alone. It failed to attract support and was withdrawn, to be replaced by two further studies, protocols 30771 and 30797.

3. EORTC protocol 30771
(Coordinator J. H. Mulder, Rotterdam)

This study was instituted soon after publication of the report of Sternberg et al. [32], which showed partial remissions in nine of 10 patients given CTX, ADM, and cisplatinum (DDP). In our study the drugs were given IV every 3 weeks in the following doses: CTX 400 mg/m^2; ADM 40 mg/m^2; and DDP 40 mg/m^2.

Of 52 patients entered, 42 were evaluable – all with measurable metastases. Of the 10 patients rejected, five were ineligible and five non-evaluable. The results are shown in Tables 3 and 4 and the survival by response is shown in Fig. 2 [19].

In one patient, a 2-year remission of extensive lesions in the bladder and upper urinary tract was seen after five cycles of therapy (Figs. 3–5). The combination did not prove to be superior to the expected remission rate of 40% with DDP used singly.

4. EORTC protocol 30797 (Coordinator B. Richards, York)

This study was initiated at the same time as protocol 30771, as a second-priority study for patients for whom more intensive therapy was not considered appropriate. In this study vincristine (VCR) 1 mg/m^2 weekly was given to patients with measurable primary or metastatic bladder cancer for at least 8 weeks. In 22 evaluable patients with measurable metastatic lesions and in 14 patients evaluable for changes in the primary tumour, only three partial remissions were seen; in one case, a pulmonary lesion regressed completely after further treatment to 16 weeks. Treatment was then stopped because of abdominal cramps and the remission lasted for 7 months.

Table 2. Effect of chemotherapy with ADM and 5FU upon symptoms

Symptoms	Patients	Improvement
Haematuria	35	25
Frequency and urgency	23	11
Bone pain	9	4
Anorexia	26	11
Weight loss	33	20

Table 3. EORTC protocol 30771: patient characteristics

Registered: 52	Ineligible: 5	Non-evaluable: 5		Evaluable: 42
Remission category	CR	PR	NC	Progression
Remission rate (%)	12	28	48	12
Age (years)	64 (50–76)	65 (39–76)	65 (43–74)	61 (49–63)
Males (%)	60	75	75	80
Karnofsky	90–100	60–100	60–100	70–100
Prior radiation (%)	80	67	50	40
Prior chemotherapy (%)	0	25	20	20

Table 4. Response data of combination chemotherapy with CTX, ADM, and DDP in 42 evaluable patients with advanced bladder carcinoma in EORTC Protocol 30771

Tumor response			Indicator lesion	Method of evaluation
Complete	1	12%	Intra-abdominal	Laparotomy
	1		Nodal	Physical examination
	3		Pulmonary	Radiography
Partial	1	28%	Pelvic	Pyelogram and cystoscopy
	2		Nodal	Physical examination
	7		Pulmonary	Radiography
	1		Hepatic	Computerized transaxial tomography
	1		Skeletal	Radiography

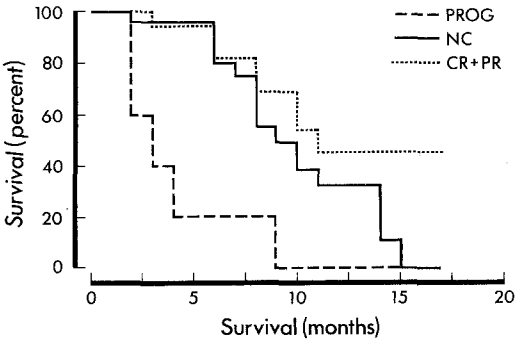
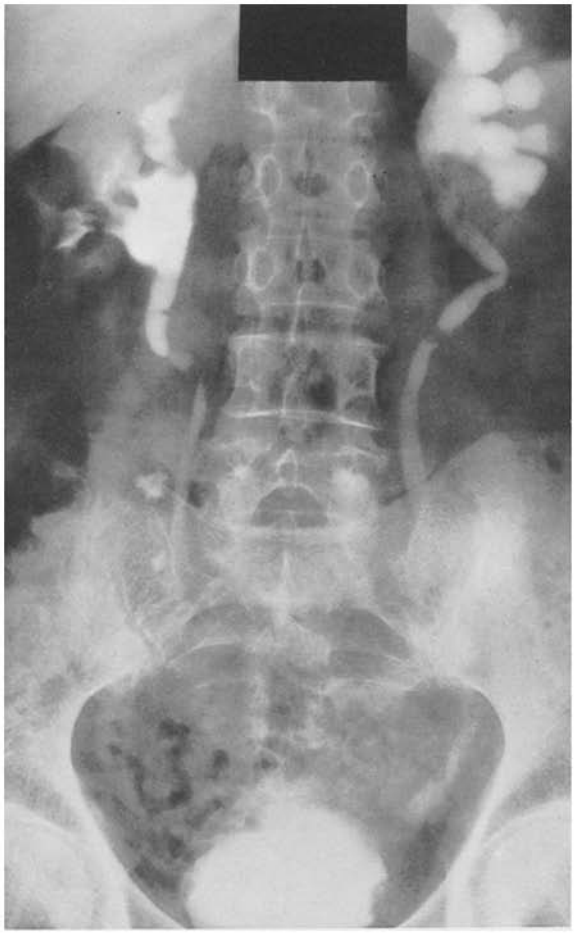


Fig. 2. Survival from start of CTX, ADM, and DDP combination chemotherapy to follow-up, or death as a result of metastatic disease in EORTC Protocol 30771



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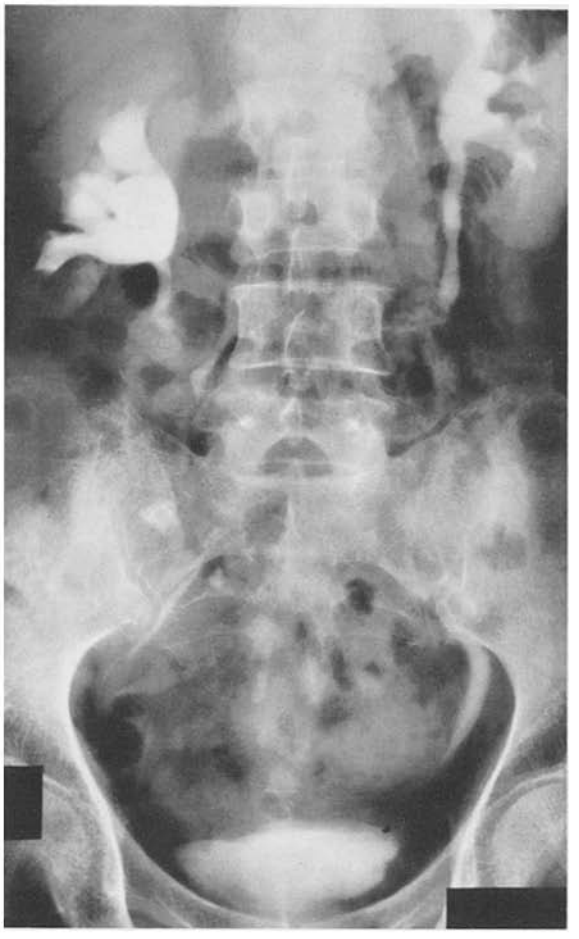
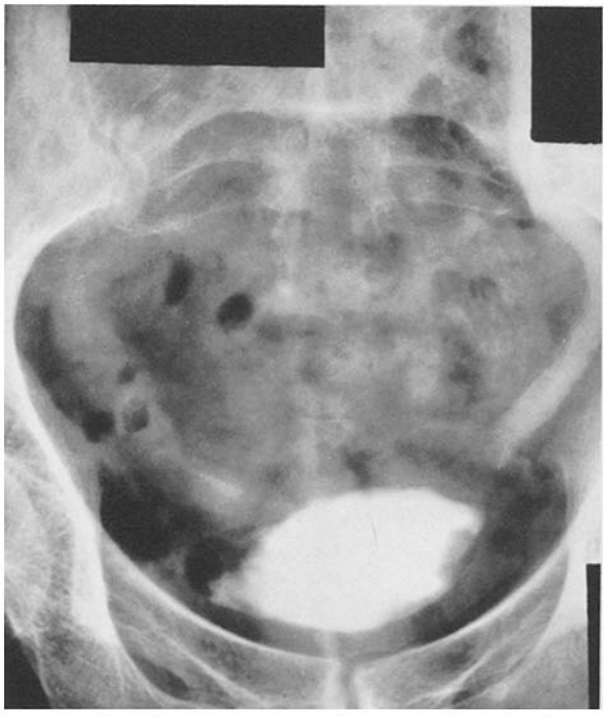


Fig. 4. Appearances 5 months after status in Fig. 3, following four cycles of cyclophosphamide, Adriamycin, and cisplatinum



b

Fig. 3. (a) IVP to show tumours in upper urinary tracts with left hydro-ureter. **(b)** Sam IVP showing fullness of left ureter and filling defect in bladder

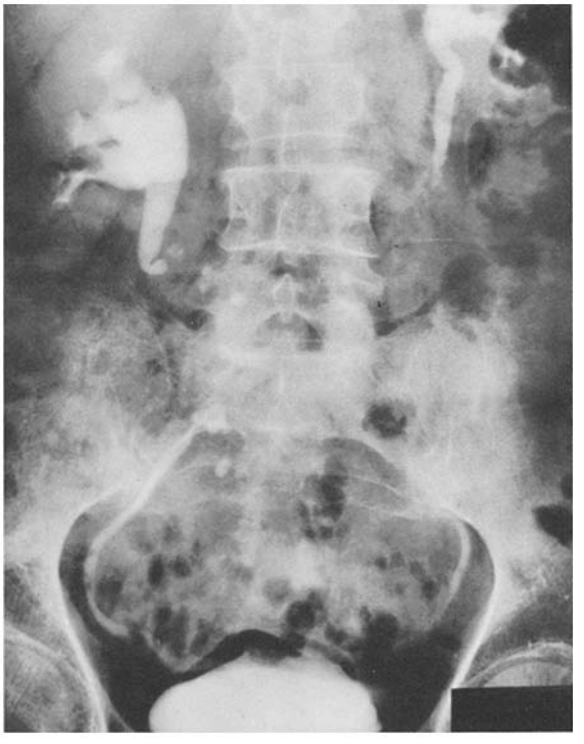


Fig. 5. Same patient as in Fig. 4 1 year later without further chemotherapy

Table 5. Response rate and toxicity following vincristine 1 mg/m^2 weekly in EORTC Protocol 30797

Evaluable patients	Response at 8/52				Early death	Toxicity	
	CR	PR	NC	Progression		Neurological	Alimentary
Metastatic marker lesions 22	(1)	←1	8	10	3	13	2
Evaluable primary lesion 14		2	2	8	2	4	3

Table 6. Some examples of the remission rates after cytotoxic chemotherapy in phase II studies, to emphasize the small number of complete remissions with different regimens [4, 9, 10, 11, 14–17, 19, 21, 22, 24, 26, 30, 32–35, 40, 45, 47, 48]

Single-agent therapy	Evaluable patients	CR	PR	Median response (months)
ADM				
Merrin et al. 1975	10	1	–	10
Weinstein and Schmidt 1976	19	–	1	–
Yagoda 1977	37	1	5	3
O'Bryan et al. 1977	65	2	9	–
CTX				
Fox 1965	8	2	–	1
Merrin et al. 1975	21	8	3	10
DDP				
Yagoda 1977	23	–	8	2
Peters and O'Neill 1980	8	–	4	9.5
Herr 1980	21	3	6	CR > 12, PR 5.7
Soloway et al. 1981	27	–	9	7
MTX				
Turner et al. 1977	61	4	19	10
Natale et al. 1981	42	–	11	6
Combination therapy				
ADM + 5FU				
EORTC 1977	52	4	17	–
Martino et al. 1980	21	2	6	6.5
ADM + CTX				
Merrin et al. 1975	18	5	4	10
Yagoda 1977	18	–	3	5
ADM + VM26				
Rodriguez et al. 1977	27	–	5	17.8 PR vs 6.3 non-responders
CTX + DDP				
Yagoda 1978	32	–	15	7
DDP + VM26				
Stoter 1982	41	4	17	6
ADM + CTX + DDP				
Sternberg et al. 1977	10	1	8	–
Troner and Hemstreet 1981	38	3	10	6
Kedia et al. 1981	23	5	14	9
Campbell et al. 1981	15	–	2	9
Mulder et al. 1982	42	5	11	11
ADM + DDP + 5FU				
Williams et al. 1979	18	–	11	6
ADM + BLEO + CTX				
Levi et al. 1980	23	–	8	7

Because of the low remission rate and the considerable neurological toxicity, VCR is considered to be of no value in the control of invasive bladder cancer (Table 5).

5. EORTC protocol 30802 (Coordinator G. Stoter, Amsterdam)

This study replaced Protocol 30771 [33]. Patients with bidimensionally measurable metastases and without significant impairment of renal function received DDP 70 mg/m^2 on day 1 and VM26 100 mg/m^2 on days 1 + 2, every 3 weeks.

Of 57 patients entered, eight were ineligible and eight inevaluable. Evaluation by WHO criteria after a minimum of two cycles in the 41 evaluable patients showed complete remission in four (10%) and partial remission in 17 (41%). Eleven patients showed no change, in seven the disease progressed, and there were two early deaths from malignant disease. This response rate and its median duration of 6 months is no better than expected from DDP alone in this patient group without prior systemic chemotherapy (Table 6).

The group's current studies are as follows:

6. EORTC protocol 30821 (Coordinators J. A. Child, Leeds, B. Richards, York, and G. Stoter, Amsterdam)

In this study the combination of DDP and methotrexate (MTX) will be assessed. Both are active but potentially nephrotoxic. The risk of nephrotoxicity is appreciably reduced by simple measures, notably hydration of patients. Also, in this study the drugs are given sequentially rather than concurrently to patients whose renal function is not seriously impaired (serum creatinine < 140 µmol/l, creatinine clearance > 60 ml/min) to increase the safety margin further.

Patients receive DDP 70 mg/m^2 IV on day 1 and MTX 40 mg/m^2 IV on days 8 and 15, every 3 weeks.

Recruitment started in May 1982 and no information is yet available.

7. EORTC protocol 30823
(Coordinator A. T. Van Oosterom, Leiden)

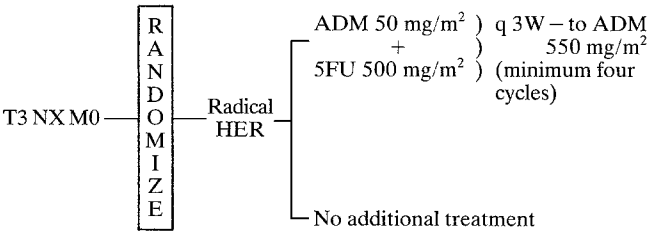
This study replaced the VCR protocol and is a second-priority study for patients failing in, or ineligible for, study 30821. Mitoxantrone is one of many anthraquinone analogues developed since it was recognized that Adriamycin was an active agent. It has shown activity in animal tumour systems and in human cell lines [13, 39, 49]. Phase I and II studies suggest that 12–14 mg/m^2 is a suitable dose range [7, 31, 37].

In this study patients not previously treated with Adriamycin or any other anthracycline analogue will receive mitoxantrone 12 mg/m^2 in 100 ml 5% dextrose solution IV over 30 min every 3 weeks, with dose escalations after every second cycle for patients who have neither responded or progressed. Recruitment started in May 1982 and no information is yet available.

In conclusion, one may say that the EORTC Urological Group has shown increasing activity in the implementation of phase II studies in patients with advanced bladder cancer with metastatic lesions. Its studies and the results to date are shown in Table 7.

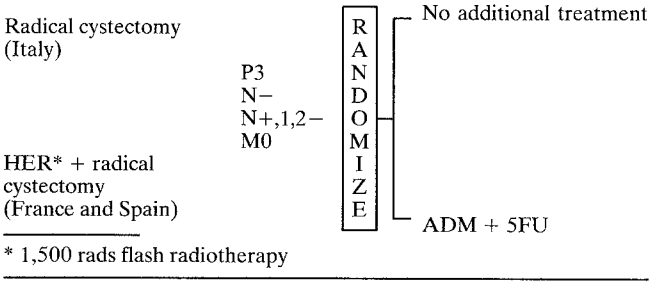
Table 7. Results of phase II trials of chemotherapy in patients with advanced bladder cancer undertaken by the EORTC Urological Group

Study	Evaluable patients	Remissions	
		CR (%)	PR (%)
ADM + 5FU	52	4 (8)	17 (32)
ADM + CTX + DDP	42	5 (12)	11 (28)
VCR	36	1 (3)	2 (5)
DDP + VM26	41	4 (10)	17 (41)



YUCRG Protocol 771. Study Coordinator: B. Richards, York, England

Fig. 6. Schema of YUCRG Protocol 771



EORTC Protocol 30784. Study Coordinator J. A. Martinez-Pineiro, Madrid, Spain

Fig. 7. Schema of EORTC Protocol 30784

Adjuvant therapy

The need for therapy additional to that conventionally given, i.e., radiotherapy and surgery, is clear from the survival figures. The results of the initial study using ADM + 5FU seemed encouraging enough to justify launching two adjuvant therapy studies, one for surgeons favouring cystectomy with or without preoperative irradiation as primary treatment (EORTC Protocol 30784, Coordinator J. A. Martinez-Pineiro, Madrid) and the second for those preferring to rely on radical radiotherapy (YUCRG Protocol 771, Coordinator B. Richards, York). The schemas for these studies are shown in Figs. 6 and 7, respectively.

Unfortunately the EORTC study failed to recruit sufficient patients and was stopped. In Yorkshire, however, we were able to enter 121 patients in 3 years, 104 of whom are now evaluable. Although this study has yet to be analysed in detail, it can be seen from Fig. 8 that there is little difference in the survival curves as yet and that there is unlikely to be a difference of > 20% even with further follow-up.

Adjuvant therapy is well reviewed by Bertino [1], with reference to its indications and the importance of dose, timing, and combination treatment.

The failure of the YUCRG adjuvant regimen to influence the outcome of the disease may be related to the choice of

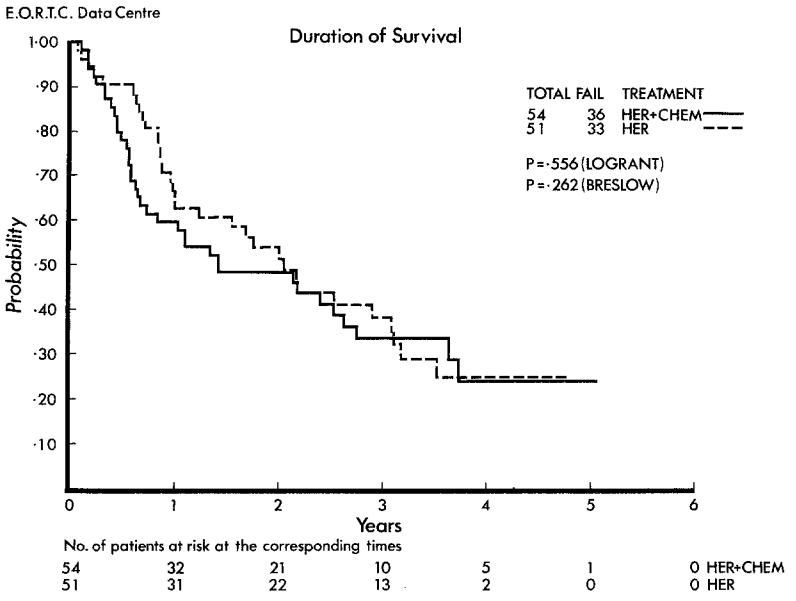


Fig. 8. Kaplan-Meier curve to show survival in patients in YUCRG Protocol 771 (kindly prepared by Dr S. Suciu of the EORTC Data Centre)

drugs, inadequate dosage, or the decision to use chemotherapy only after completion of primary treatment.

Successful adjuvant therapy is usually possible only after phase II studies have shown a high incidence of complete remission (> 20%), usually with combination therapy and preferably with a prolonged response. This situation has not yet been reached in bladder cancer, as can be seen from Table 6, in which the incidence of complete and partial response in some phase II studies of single agents and two- and three-drug combinations is seen.

The urologist is naturally inclined to use chemotherapy after the completion of standard therapy designed to control the disease in the pelvis. Although this approach was adopted by the EORTC Urological Group, it may be illogical to delay the introduction of treatment that might control the disseminated disease. Therefore the approach adopted by the cooperative group in London and Oxford, in which chemotherapy is given before and after treatment of the primary tumour, is of great interest since it will give information both on the benefits of early chemotherapy and on the risks, if any, of radiotherapy and cystectomy after initial systemic chemotherapy.

The fact that patients with invasive bladder cancer die in large numbers and within 1–2 years after diagnosis, i.e., 40%–50% deaths within 1 year [28, 38], despite control of the local lesion in up to 90% of the patients [42] emphasizes the need for additional and systemic treatment, since this is the only way in which any progress is likely to be made in the near future. The EORTC Urological Group and the YUCRG hope to be able to contribute to this progress.

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