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General Review

Chemotherapy in the Management of Invasive Bladder Cancer

A Review

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Summary. *In this review of the management of invasive carcinoma of the bladder the results of primary and systemic therapies are evaluated in the light of the natural history of the disease.*

The clinical and pathological causes of treatment failure are assessed in an attempt to identify new approaches that may be used in the future management of patients with bladder cancer.

To improve survival in this disease requires different approaches to both the control of local disease and the early control of metastatic disease.

Introduction

In this review the use of chemotherapy as a modality of treatment in invasive bladder cancer is set against a background of the natural history, pathogenesis and established primary treatment of this disease. An evaluation of the major local treatment methods used (surgery and radiotherapy) is made to allow definition of a possible role for the use of systemic treatment which includes cytotoxic drug therapy.

In England and Wales carcinoma of the bladder ranks as the sixth commonest cause of death from malignant disease in men and the tenth commonest cause of death from malignant disease in women (Table 1). Its occurrence in an elderly population (commonly seventh decade) raises important questions about the overall management. In particular, the use of chemotherapy in elderly patients, who are less well able to tolerate chemotherapy than younger people, requires careful evaluation in the light of such responses as may be obtained and the overall quality of life.

A retrospective analysis of 111 consecutive patients with Manchester stage III (Table 2) carcinoma of the bladder reveals the age distribution shown in Fig. 1. Although the major incidence occurs in the seventh de-

Table 1. Causes of death from malignant disease[a]

Frequency order	Males		Females	
1.	Lung	1,088	Breast	452
2.	Stomach	297	Lung	243
3.	Colon	177	Colon	241
4.	Prostate	177	Stomach	201
5.	Rectosigmoid	133	Ovary	137
6.	*Bladder*	117	Rectosigmoid	110
7.	Pancreas	116	Pancreas	101
8.	–	–	Cervix	89
9.	–	–	Corpus	49
10.	–	–	*Bladder*	47

[a] No. of deaths per million populations. Figures taken from statistics issued by the Registrar General for England and Wales over 1963–1973 (HM Stationery Office publication)

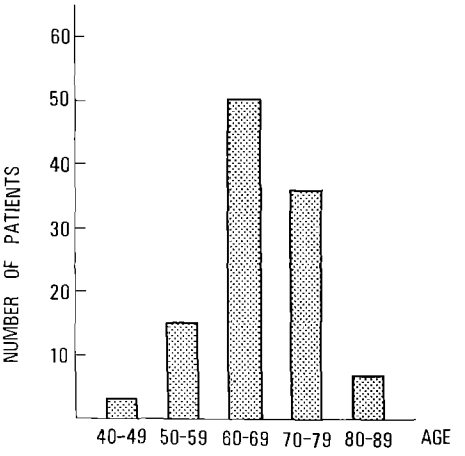

Fig. 1. Age distribution of III patients with stage III bladder cancer

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Table 2. Cause of death in 111 patients with stage III bladder cancer (Christie Hospital, Manchester, 1971)

			Metastasis also present		Primary recurred	
	No.	(%)	No.	(%)	No.	(%)
Death due to primary disease	50[a]/74[b]	(68)	22/50	(44)	–	–
Death due to metastasis	34[a]/74	(46)	–	–	22/34	(65)

[a] Overlap indicates inability to distinguish between primary and secondary disease as the major cause of death

[b] Total number in group dead of bladder cancer 74/111

Table 3. Intercurrent death rate in elderly patients with bladder cancer (Manchester, 1971)

	Number	%
Alive (no evidence of disease)	19	17.1
Alive with disease	1	0.9
Dead intercurrent disease	17	15.3
Dead bladder cancer	74	66.7
Total	111	100.0

cade, analysis of the crude 5-year survival and cancer death rates showed that only 15% of patients in the whole group died of intercurrent disease (Table 3). Attempts to improve the survival rates of patients with invasive bladder cancer are justifiable on the grounds of the poor overall prognosis (20%–50% at 5 years) and on the grounds of the low death rate from intercurrent disease in this elderly population.

Prognostic Factors.
Invasiveness and Lymphatic Permeation

It has been recognised for many years that one of the most important prognostic indices in bladder cancer is the degree of tumour invasion of the bladder wall muscle [31]. Similarly, evidence has long been available of a close correlation between the depth of bladder wall invasion and the incidence of distant metastases [42]. In cases in which invasion has reached halfway or more through the bladder wall muscle (stage T3 or B2C, Fig. 2), Jewett et al. [43] have amply demonstrated an extremely low 5-year survival; namely 22 of 150 patients, or 15%. In their study patients underwent either segmental or total cystectomy. Since 1964 many studies of varying degree of quality and selection have indicated that the results in invasive bladder cancer, whether surgery or radiotherapy is used alone as the primary treatment, show a survival rate of approximately 20% at 5 years. In Tables 3, 4, and 5 a simplified analysis has been made of the survival rates obtained in invasive bladder cancer with a variety of local treatments. It can be seen that the range of survival rates at 5 years is large, indicating the difficulty of making accurate comparisons of the results of different groups of workers. This may also reflect difficulties in staging and problems of selection. In a recent review of staging methods, Skinner concluded [79] that a simplification of clinical staging was required, with the elimination of stages that cannot be accurately determined by existing methods. In Fig. 2 the Manchester clinical staging method is compared with the American and TNM classifications.

The clinical problem that this review examines in human invasive bladder cancer is simply that seven out of ten patients who develop the disease will die of it in 5 years irrespective of the kinds of treatment(s) used for primary control.

In an autopsy series relating depth of bladder wall infiltration and development of metastases, Jewett et al. [43] further demonstrated that whereas 10% of patients with T1 or T2 tumours developed metastases, 66% of patients with T3 tumours did so. From these results it might be concluded on theoretical grounds that the use of systemic treatment early in the course of the disease might exert a favourable influence on prognosis in relation of death from metastatic disease.

Another important index of prognosis is the presence of lymphatic involvement at the time of diagnosis. Histological and recent radiological evidence suggests a strong correlation between tumour involvement of local bladder wall lymphatics, nodal lymphatics, and increased metastatic spread with a decreased survival rate. Jewett's study [43] provided histological evidence for the conclusion that involvement of bladder wall lymphatics is associated with a poor prognosis.

The role of lymphography in bladder cancer, however, has been controversial. Lang [48] suggested that lymphography in this disease was of little or no value in assessing early metastatic involvement of the regional

Table 4. Primary treatment results in invasive bladder cancer

Treatment	5-year survival by stage			References
	T_2 (B_1)	T_{3a} (B_2)	T_{3b} (C)	
Surgery				
Excision/fulguration	47–57	< 23	< 7	[3, 11, 27, 37, 55, 61]
Segmental resection			8–22	[5, 27, 40, 70, 89, 91]
Simple/total cystectomy			9	[8, 15, 40, 41, 49, 71, 72, 73, 76, 84, 96, 97, 98]
Radical cystectomy		17	13	
Radiotherapy				
External beam	11–46		0–28	[4, 7, 12, 16, 17, 21, 24, 30, 38, 47, 58, 75, 89, 95]
Interstitial	24–40		7–10	[5, 59, 67, 88, 90]
Preoperative irradiation/cystectomy			22–46	[49, 53, 54, 71, 76, 93, 96, 98]

Table 5. Salvage surgery after radical radiotherapy

No. of patients	3-year survival %	5-year survival %	Operative mortality %	References
18	59	52	11	[93]
90	33	31	16	[67]

lymph nodes of the bladder. He referred particularly to obturator and internal iliac nodes. In contrast with this, several recent studies have been reported to show close correlation between positive lymphography and histologically involved lymph nodes in more than 90% of cases [44, 92]. More recently Turner [87] conducted a large prospective study in which emphasis was placed on the relation of lymphographic abnormalities to the histological findings in the regional lymph nodes (Fig. 3). This group confirmed the accuracy of lymphography in the identification of patients who had histologically involved lymph nodes. They first showed that a positive lymphogram was associated with extremely poor prognosis in patients with invasive bladder cancer. Of 131 cases that were radiologically node-negative, 9% developed clinical metastases and 21% were found to have metastases at autopsy; in the node-positive group (91 cases) 33% developed clinical metastases and 56% were found to have metastases at autopsy.

In this study there was good correlation between positive lymphography and a poor survival. Of 131 patients who were radiologically node-negative, 35% survived for 5 years. In the node-positive group (91 cases) no patient with either para-aortic or bilateral lymph node involvement survived for 3 years, (61 patients) and only 6.4% survived for 5 years, i.e., those with lymphographic evidence of unilateral nodal disease.

Malignant invasion and lymphatic involvement have been discussed in some detail here to stress the importance of defining the nature and extent of disease in individual patients before planning local and systemic therapies, and indeed before defining the questions to be answered by clinical trials of systemic agents.

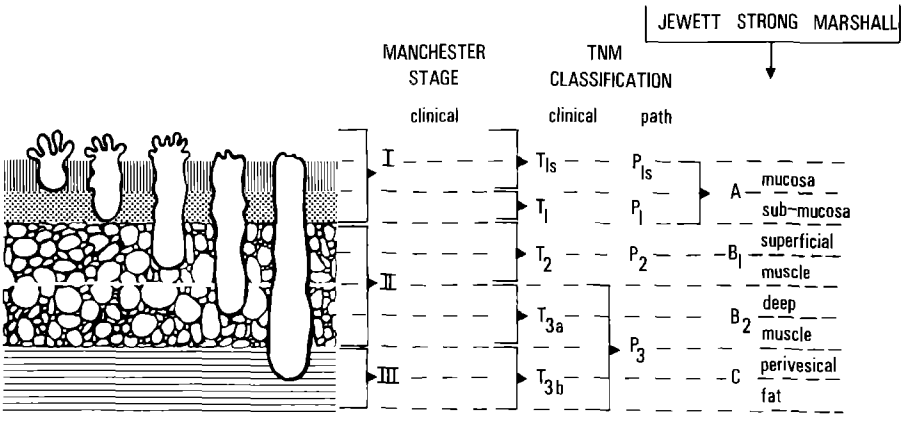

Fig. 2. Comparison of three staging methods in bladder cancer

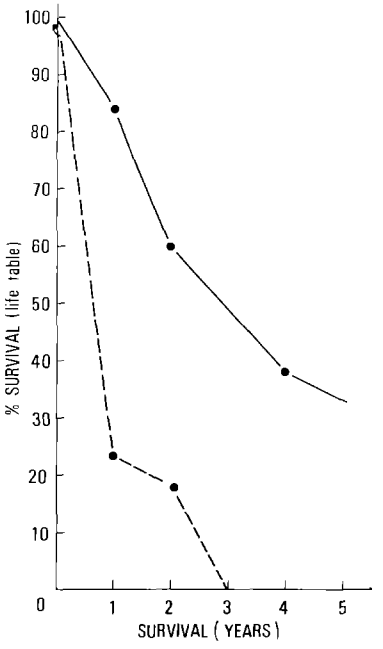

Fig. 3. Survival versus positive/negative lymphography in patients with invasive (T_3) bladder cancer. ●——●, node-negative patients (75); ●– –●, node-positive patients (42). Adapted from Turner et al. (1976)

Results of Local Treatment

A synopsis of some of the commoner treatment modalities for locally invasive bladder cancer is outlined in Table 4. Reference is made to many of the published studies that deal with the primary treatment of invasive carcinoma of the bladder. From these collected series it can be appreciated that with either surgery or radiotherapy alone the 5-year survival rates obtained were approximately 20% or less, with a range of 0–46%. (Table 4). Many studies over the past two decades have suggested that preoperative irradiation followed by cystectomy may improve the 5-year survival rate [96]. It is important to distinguish here between preoperative radiotherapy, and radiotherapy given with radical intent followed by salvage surgery in those patients who relapse early. The concept that combined treatment with surgery and radiotherapy is an improvement over either radiotherapy or surgery alone still has not been completely evaluated. There have been few randomised prospective trials that include large numbers of patients with invasive bladder cancer.

In this context, two recently published randomised prospective trials may be of importance. Wallace and Bloom [93] report an improved 5-year survival rate of 33% in their group of patients randomised for preoperative irradiation followed by cystectomy, compared with a 5-year survival rate of 21% in the group of patients who received irradiation alone. This difference was significant. This randomised prospective study involved 98 patients in the combined-modality treatment group and 91 patients in the group receiving irradiation therapy alone. In a smaller selective randomised prospective study, Miller reports 5-year survival rates of 46% in the combined-treatment groups and 16% in the irradiation only group [53, 54]. In this series, however, the differences observed may be misleading because of the small number of patients studied. These results may be compared with results in a large unselected series of patients in whom radiotherapy alone was used, in which the 5-year survival rate in Manchester stage II disease was 29% and that in stage III disease, 25% [66].

In many of these series a subpopulation of patients can be identified, comprising those patients who fail radical radiotherapy and subsequently undergo salvage cystectomy. In the series of Wallace and Bloom, patients underwent surgery within 18 months of completing radiotherapy. The survival rate for this group was high (52% at 5 years), but this small group was highly selected for radical cystectomy. It is also recognised that the operative mortality in the combined radical radiotherapy/radical surgery group may be as high as 15%–20%. Wallace and Bloom suggest that this figure may be reduced if radiotherapy failures are recognised earlier, and surgery is performed before advanced fibrosis has become established. In their hands the operative mortality was only 11%.

This small selected series of patients may not provide a true reflection of the survival of patients who undergo radical surgery following radical radiotherapy. In a large series of 90 unselected patients who underwent radical surgery following radical radiotherapy, survival rates of 33% at 3 years and 31% at 5 years were achieved [67]. In this group of patients radiotherapy was given with curative intent and not a as preoperative measure. The operative mortality was 16% and the indications for surgery have already been described. These results are very similar to those reported by Wallace and Bloom in their group of patients treated with preoperative radiotherapy followed by cystectomy. Although this approach will salvage a small percentage of the patients who develop local recurrence early after radical radiotherapy, major improvements in overall survival have not been seen.

Definition of Treatment Failure

In all these studies the cause of failure is important in defining the relative roles of local and systemic treatment. Little improvement has been demonstrated in 5-year survival rates of patients with invasive bladder cancer, and the addition of systemic therapy may be of

advantage in attempts to improve the survival. As an approximation, in any population of patients with invasive bladder cancer, a 5-year survival rate of 30% may be expected. Of the 70% of patients who die within the first 5 years, almost half die because of progression of local disease and the other half die as a result of distant metastases [54]. In a study of 111 patients at the Christie Hospital with stage III carcinoma of the bladder, an analysis was made of the cause of death (Table 2). Of the 111 patients who presented in 1971, 74 were dead of bladder cancer at the time of this analysis (1977). Of these 74 patients, 50 died of recurrent primary disease, but half of the deaths due to local recurrence were associated with the presence of metastases. In 34 patients death was associated with advanced metastatic disease. The overlap between these two groups results from an inability to distinguish between the primary cause of death in the situation in which there is both locally advanced disease and advanced metastatic disease. These data were obtained from existing clinical records and death certification. Whether primary disease or metastatic disease was the principle cause of death, the two co-existed in approximately half of the patients.

The design of future studies therefore requires improved approaches to the control of both local and metastatic disease.

Chemotherapy

The chemotherapeutic approaches that will be reviewed here are summarised as follows:

1. Systemic chemotherapy: Single-agent Combination chemotherapy;
2. Local and regional chemotherapy: Arterial perfusion Intravesical chemotherapy;
3. Adjunctive chemotherapy: Concomitant with surgery/radiotherapy;
4. Adjuvant chemotherapy.

Single-Agent Chemotherapy

Chemotherapy has been used for bladder cancer for over 30 years. The use of chemicals in the treatment of bladder neoplasm has a long history. Many investigators approached the problem initially by using intravesical agents [35, 77]. Despite, this Carter and Wasserman [13], in a recent review, concluded that evaluation of the role of systemic chemotherapy in bladder cancer was a neglected area of oncologic study. At present only a few agents have been evaluated in this disease.

The literature is replete with studies conducted in the absence of defined selection, involving small numbers of patients, variable drug scheduling, and undefined assessment of response. Comparison between studies is often not possible, and this is reflected in the variability of published response rates (Table 6).

Single agents active in this disease include cyclophosphamide, 5-fluorouracil, adriamycin, mitomycin C and *cis*-platinum. Recently neocarcinostatin has been shown to have some activity against transitional cell carcinoma of the bladder [37], but this result was recorded in a small series and the drug toxicity was considerable. Previous evaluation of cyclophosphamide [28, 78] suggested that this drug had relevantly low activity. More recently, a re-evaluation has suggested that this agent has a greater activity than was previously reported [52]. In this last study a response rate of over 50% was reported, but in such a small series of patients accurate response rates are not assessable.

With adriamycin alone objective response rates vary from zero to 37% (Table 5), but the uncontrolled and poorly defined nature of these studies often prevents accurate interpretation. A reasonable estimate of the response rate to adriamycin appears to be between 15% and 30%, and a recent evaluation of adriamycin in a large study suggests an overall response of 24% in 175 patients [104, 105]. Evaluation of 5-fluorouracil is equally difficult, but more data are available. Carter reported response rates of 35% from a collected series

Table 6. Response rates to single agents in bladder cancer

Drug	No. of patients	Ave % response (objective)	Range (%)	References
Methotrexate	88	24	17–56	[1, 9, 33, 87]
Adriamycin	235	23	0–37	[6, 13, 29, 80, 94]
5-Fluorouracil	56	39	0–75	[2, 26, 32, 39, 46, 56, 68, 83, 95, 100]
Cyclophosphamide	41	41	0–53	[19, 28, 52, 78, 103]
Mitomycin C	50	20	16–33	[22, 63, 65]
Cis-platinum	24	35	–	[104, 105]
Neocarcinostatin	15	66	–	[37]
Vincristine	20	30	–	[36]
Epidophyllotoxin (VM26)	24	25	–	[25]

[13]. Mitomycin C produced a response in 13 of 51 patients (25%) in one study [22]. The use of *cis*-platinum in the treatment of bladder cancer suggests that it may have more activity than many of the other agents so far mentioned. Merrin et al. [52] reported a response rate of 60% in a small group of patients treated with 6-h infusions of *cis*-platinum. The symptomatic toxicity associated with this drug makes its use limited, and in addition its nephrotoxicity makes its use in elderly patients with potentially impaired renal function inadvisable.

Whichever single agent is used, few complete responses are seen and the partial responses obtained are of short duration only [105].

The assessment of response can be extremely difficult in this disease. Accurate quantitation of resolution of pelvic and abdominal lymph node masses is often required and seldom undertaken.

Combination Chemotherapy

In many malignant diseases the use of combinations of cytotoxic drugs has been demonstrated to produce greater response rates than have the individual agents used singly [20, 34].

Some attempt has been made to develop combination chemotherapy for bladder cancer rationally on the basis of a murine experimental bladder cancer model system [81, 82]. Soloway has evaluated the cytotoxic potential of cyclophosphamide, 5-fluorouracil, adriamycin, and *cis*-platinum as single agents and in combinations. Significantly greater reductions in primary tumour mass were seen with the two combinations of cyclophosphamide/adriamycin and cyclophosphamide/5-fluorouracil than with any of these three agents used singly.

In man there are few reports of the use of drug combinations in invasive bladder cancer (Table 6). Merrin et al. [52], in a study involving very few patients reported the use of cyclophosphamide and adriamycin, both singly and in combination. They quote objective response rates of 52.3% for cyclophosphamide alone; 10% for adriamycin alone; and 50% for the combination of cyclophosphamide and adriamycin. Cross [18] reported the use of adriamycin and 5-fluorouracil in 24 patients with advanced transitional cell carcinoma of the bladder and claim a 35% objective response rate in 24 patients 20 of whom were evaluated. In this small series three patients had complete remissions.

In a preliminary study, Collier has used cyclophosphamide, adriamycin, and 5-fluorouracil in combination [14]. This study has demonstrated that the toxicity of this regime was acceptable in patients whose mean age was 64 years. The assessment of response to this particular combination requires the study of many more patients. More recently, several authors have reported the use of *cis*-platinum in combination. Of these reports, that of Williams and his co-workers [99] deserves mention. This group studied 19 patients with advanced bladder cancer, treating them with *cis*-platinum, adriamycin, and 5-fluorouracil. The mean age of these patients was 63 years, with a range of 51–76 years. Seventeen of the patients were evaluable; nine had received previous radiotherapy and six, previous surgery. Initial chemotherapy consisted of *cis*-platinum 20 mg/m^2 IV on days 1 through 5, adriamycin 50 mg/m^2 IV on day 1, and 5-fluorouracil 500 mg/m^2 IV on day 1. This regimen was repeated at 3-week intervals for three courses, and maintenance chemotherapy was continued every 4 weeks with single injections of adriamycin and 5-fluorouracil in the doses described and a 1-day infusion of *cis*-platinum 50–75 mg/m^2 in combination with the other two drugs. The mean number of courses per patient for this group was 4.5. Toxic effects seen in this group of patients were vomiting (100%), alopoecia (100%), nephrotoxicity (11%), hearing loss (3 patients; 16%). No patient in this group had a complete response, but there were 11 out of 17 patients who showed a partial response (65%) with a median duration of response of 28 weeks. Two of the 17 patients (12%) showed stable disease, and in four of the 17 patients (23%) the disease progressed. All the nonresponders died, while six of the responding patients are alive at between 9 and 51 weeks. This study is an encouraging preliminary report, but as with many studies further evaluation with larger numbers of patients is urgently required for accurate assessment of the response rate.

Table 7. Combination chemotherapy in advanced bladder cancer

Drugs	No. of patients	Ave objective response (%)	References
Cyclophosphamide + Adriamycin	3/18	17 50	[104, 105] [52]
Cyclophosphamide + *Cis*-platinum	11/18	61	[104, 105]
Cyclophosphamide + Adriamycin + 5-FU	2/3	–	[14]
Adriamycin + 5-FU	7/20	35	[18]
Cis-platinum + Adriamycin + 5-FU	11/17	67	[99]

Irradiation and Concurrent Chemotherapy

Between 1962 and 1973 many groups reported studies in which 5-fluorouracil (5-FU) was used concomitantly with radiation therapy [45, 83, 101, 102]. In all these studies chemotherapy was used as an adjunct to irradia-

tion. With two exceptions these studies are characterised by small nonrandomised groups of patients, short follow-up, and a diversity of treatment methods. In most cases 5-FU was given as a single agent, continuously or 2–3 times weekly, for the duration of radiation therapy only. Edland and his co-workers [23] reported a small randomised prospective series of patients in which one group was treated with irradiation alone and the second group was treated with 5-FU for the duration of the radiation therapy. Only 36 patients were randomised, and from the results the authors concluded that survival was uninfluenced by 5-FU given at the same time as radiation therapy. The overall survival rate was 17%. However, in the group that received irradiation only, clinical metastases were noted in 10 of 18 patients (56%), whereas in the group receiving concomitant 5-FU, only 18 patients had clinically demonstrable metastases (22%).

Regional Perfusion and Intravesical Therapy

There are a few reports in the literature of the use of regional perfusion [57] (Table 8). Sullivan [85] first used intra-arterial methotrexate in 1962, and noted a sustained clinical benefit and decrease in tumour size. More recently, Nevin has reported the use of intra-arterial infusion of 5-FU via the internal iliac arteries as an adjunct to radiation therapy [60]. These approaches require a high degree of expertise and staff training, and have therefore not been widely used. In addition, there is no good evidence that this approach is superior to conventional systemic therapy. Intravesical cytotoxic drug therapy has rarely been used for invasive bladder cancer. Most experience has been obtained with noninvasive tumours.

Adjuvant Chemotherapy

After effective treatment for primary malignant disease in a situation where tumour body burden is minimal, chemotherapy is known to be much more effective experimentally and clinically in man in delaying recurrence (metastasis) and prolonging survival than when it is used against massive advanced disease [11].

In bladder, cancer adjuvant chemotherapy might reasonably be expected to reduce the incidence of methastatic disease, although its effect on residual local disease, is likely to be less marked [50, 51, 52, 74]. In human bladder cancer the only controlled study of adjuvant chemotherapy has been conducted by Prout and co-workers [69, 70]. This group used chemotherapy with 5-fluorouracil (5-FU) as an adjunct to cystectomy (± radiation therapy), and concluded that although the number of patients was small, survival was not improved. The conclusion of Prout's group may be reexamined in the light of more recent approaches with adjuvant chemotherapy. In his chemotherapy schedule he used 5-FU alone, daily for 5 days and subsequently on alternate days, for a total period of no greater than 30 days. More recent experience with adjuvant chemotherapy in other human solid tumours suggests that improved results were obtained with combinations of effective drugs used for periods of 1–2 years.

Evidence reviewed here in invasive carcinoma of the bladder suggests that irrespective of its effect on local residual disease, early effective adjuvant chemotherapy has the potential for improving survival rates in the 50% of patients who die early from disseminated metastatic disease.

Table 8. Results of arterial infusion of cytotoxic agents in bladder cancer

Agent	Responses	Technique	References
5-FU	6/10	Hypogastric artery	[60]
Methotrexate	3/3	Internal iliac	[85]
	2/6		[10]
Mitomycin C	3/5	Hypogastric artery (iliac artery)	[62]

Conclusions

In invasive bladder cancer, local treatments have achieved 5-year survival rates of approximately 30%. Of the 70% of patients who die of their disease within 5 years, half will die of metastases and half of uncontrolled primary disease. Evaluation of local invasion and lymphatic spread are of the greatest importance in predicting prognosis. Data on the efficacy of cytotoxic agents in advanced bladder cancer are scant and poorly documented. Recent evidence suggests that drug combination such as cyclophosphamide, adriamycin, 5-FU and cis-platinum may be used within the limits of acceptable toxicity.

There is a clear need for more data from well-constructed studies on the use of single agents and combinations in advanced disease to allow identification of the most active agents and the combinations that can be used with greatest efficacy and least toxicity. New approaches using radiation-sensitising agents may prove to be important in improving local control, and effective systemic adjuvant chemotherapy has the potential for decreasing therapeutic failure that results from the supervention of metastatic disease.

Combined-modality treatments using radiation therapy, surgery, and chemotherapy have produced im-

proved results in several solid tumours (e.g., Wilm's tumour, breast cancer, and lymphomas). Similar approaches have yet to be tested in adult patients with invasive bladder cancer. This review suggests that a combined approach may be of value in improving the poor survival rates in this disease.

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