

CARCINOMA OF THE BLADDER

A REVIEW OF TREATMENT*

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While on a recent visit to Great Britain and the Continent of Europe I had the opportunity of visiting numerous clinics. I was impressed by the large number of bladder tumours I saw, the incidence of which appears to be greater than in South Africa. In Manchester the Christie Hospital specializes in the treatment of cancer and consequently cases are referred to them from all over England; moreover, the I.C.I. maintains a large dye works in Manchester, and bladder tumours amongst dye workers being notifiable, routine cystoscopy and a complete follow-up is possible.

The treatment of bladder tumours differed in almost every clinic I visited, and if one refers to the literature during the last 25 years innumerable methods of treatment of bladder tumours have been advocated, most of which have proved very disappointing. To what can this be attributed? The answer is that cases are referred for treatment too late; either the patient does not seek advice or the patient's doctor is foolish enough to prescribe some form of treatment for the haematuria without establishing a diagnosis.

The success of treatment depends on 3 factors: (1) Degree of invasion or infiltration, (2) type of tumour, and (3) metastases.

1. Degree of Invasion

In 1946 Jewett published a most interesting paper on the relation of the depth of penetration of the bladder wall to the incidence of local extension and metastases. This was a review of a large number of cases of infiltrating tumours of the bladder upon which autopsies had been performed at the Johns Hopkins Hospital during the previous 25 years. Jewett divided the cases into groups viz.

- Group A—submucosal infiltration.
- Group B1—superficial infiltration of muscular layer.
- Group B2—deep infiltration of muscular layer.
- Group C—perivesical infiltration.
- Group D—lymphatic and distal metastases.

He showed that group-A cases are theoretically 100% curable. Group-B cases are 88.8% curable, but as soon as the tumour reaches the perivesical tissues the curability drops to 26%. This is not surprising when one studies the variation in size and distribution of the lymphatics of the bladder wall, so beautifully demonstrated by Powell. Of the group-C cases 58% had glandular and distant metastases, 37% had lymphatic-gland involvement only, and in only 7.7% with perivesical infiltration were there no glandular or distant metastases or, to put it more forcibly, if perivesical infiltration has occurred 92% have metastases. In cases with glandular and distant metastases 26% showed no fixation to

surrounding structures; it thus follows that if any fixation exists the percentage of curability is extremely low. Tumours of the anterior and lateral walls of the bladder metastasize earlier than those of the posterior wall.

2. Type of Tumour

The following classification introduced by Dukes and Masina is simple and easily followed:

- (a) Simple transitional-cell papilloma
- (b) Malignant tumours:
 - (i) Papillary transitional-cell carcinoma
 - (ii) Solid transitional-cell carcinoma
 - (iii) Transitional-cell carcinoma with metaplasia
 - (iv) Pure squamous-cell carcinoma
 - (v) Pure adenocarcinoma
 - (vi) Anaplastic spheroidal-cell carcinoma

The histology of these different types of tumours is as follows:

(a) *Simple transitional-cell papilloma*. Central vascular connective-tissue cord covered by transitional epithelium, which may be several cells deep, sharply defined, regularly arranged, with basic membrane intact, and with no sign of invasion or infiltration of the vascular core.

(b i) *Papillary transitional-cell carcinoma*. Similar in structure to (a) but the cells have a disorderly arrangement, irregularity in shape and size of nuclei, sometimes a typical mitosis, and a tendency to metaplasia. Invasion and infiltration seen as a breaking through the basement membrane and clumps of carcinoma cells in the connective-tissue core.

(b ii) *Solid transitional-cell carcinoma*. Most bladder growths in the early stages show a papillary pattern; as infiltration takes place they become more solid, the cells being arranged in more compact clusters. The less malignant tumours tend to remain papillary in structure.

(b iii) *Transitional-cell carcinoma with metaplasia*. A peculiarity of bladder tumours is the tendency of the epithelium to undergo metaplasia with the formation of squamous or glandular epithelium in those tumours of a high grade of malignancy. Scattered islands of squamous epithelium often resemble the cell nests of a cutaneous epithelioma, and glandular epithelium may present a typical picture of an adenocarcinoma.

(b iv) *Pure squamous-cell carcinoma* is a rare tumour and is almost invariably associated with a previous leucoplakia. It is probable that these tumours are less malignant than transitional-cell carcinoma with squamous metaplasia.

(b v) *Pure adenocarcinoma*. While metaplastic glandular epithelium may be present in a bladder carcinoma, a pure adenocarcinoma is rare and arises either from the remnants of a urachus or in epithelium which has previously undergone glandular metaplasia, as in

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extroversion of the bladder; otherwise the adenocarcinoma is probably an extension or metastasis from the bowel.

(b vi) *Anaplastic spheroidal cell carcinoma.* Tumours of undifferentiated spheroidal or polygonal cells are very invasive, grow rapidly, and metastasize early. The histology varies greatly and is sometimes indistinguishable from sarcoma.

3. Metastases

This classification is based on autopsy findings and microscopic examination of pathological material removed by partial or total cystectomy. In what way can we apply the knowledge so gained to our clinical investigation? Initially the diagnosis is established by cystoscopy, and where possible the following observation should be made:

(a) Gross characteristics of the tumour

- (i) Whether single or multiple, and exact situation
- (ii) Size
- (iii) Shape
- (iv) Appearance of surface—villous or cauliflower, and whether sloughing
- (v) Appearance of surrounding mucosa
- (vi) Whether bladder distension causes bleeding

(b) *Biopsy.* This should always be taken as complete as possible, including the base of the tumour and as much musculature as possible. A resectoscope punch or biopsy rongeur should be used.

(c) *Bimanual examination.* This is of paramount importance. While a large papillary tumour may be palpable any degree of infiltration and fixation indicates a hopeless prognosis.

(d) *Cystogram.* This is of value, for a series of pictures may indicate more accurately the size of the tumour and the degree of invasion of the bladder wall.

(e) *Intravenous pyelography.* This should always be done, for dilatation of one or other ureter indicates infiltration of bladder wall.

TREATMENT

Assessment of Case

While the degree of infiltration of the bladder wall is the most important factor in prognosis, it is obvious that the less differentiated and more malignant types of growth infiltrate and metastasize more rapidly. In recent articles Chapman and others have indicated the clinical significance of biopsy examinations, and statistics show that more drastic methods of treatment have to be adopted in tumours of a high degree of malignancy.

Methods of Treatment

These include the following:

1. Transurethral fulguration
2. Open fulguration and electro-coagulation
3. Diathermy excision and implantation of radon seeds, needles of radium or radioactive cobalt, tantalum wire, or gold grains
4. Intracavitary radiation
 - (a) Solid central source, e.g. radium or cobalt
 - (b) Radioactive solution, e.g. sodium bromide or cobalt
5. Radioactive gold solution
6. Partial cystectomy or segmental resection
7. Complete cystectomy, simple or radical

8. Deep X-ray therapy.

- (a) Contact therapy.
- (b) Deep X-ray therapy (250-500 kv. machines)
- (c) Supervoltage X-ray therapy—1-million to 20-million-volt machines

Transurethral fulguration. All simple papillomata should be treated by this method and theoretically should be 100% curable. Many urologists advocate diathermy resection and electro-coagulation in malignant tumours of grade A and grade B1 according to Jewett's classification. At the Mayo Clinic, of 1,222 cases, 961 were treated by transurethral resection and fulguration, with 88% 5-year cures. Milner and Flocks using conservative methods quote the following percentages of 5-year cures in cases classified by Jewett's method:

	A	B1	B2	C
Milner	70%	57%	23%	1 case
Flocks	77.4%	56%	39%	1.6%

Open fulguration and electro-coagulation. This is, as a rule, only carried out in very large tumours where the size and situation make transurethral resection difficult or impossible, or as a preliminary step before implanting radium etc. Special precautions have to be taken to prevent tumour implants developing in the wound.

Implantation of radon seeds. This treatment has been used for many years and the results are very encouraging. Radon seeds of a strength of not less than 1 millicurie are implanted 1 cm. apart encircling the tumour and in the base of the tumour; this may be done transurethrally, but for accuracy the suprapubic route is preferred. The bladder should then be closed, as radon seeds are not removed. The following are published 5-year-survival results (again according to Jewett's classification):

PUBLISHED RESULTS OF 5 YEAR SURVIVALS

	No. of cases	A	B1	B2	C
Poole Wilson (unclassified)	104		49%		
Poole Wilson (classified)	62	71%	50%		11.6%
Milner (unclassified) ..	90		22%		
Barringer	221	52%		23.6%	
Millen	117	63%		21%	
Dean and Balfour ..		54%		14%	
Emmett & Mayo Clinic	118		29%		

The figures from the Mayo Clinic are of particular interest, because radon-seed implantation was not favoured as a method of treatment and was only used when other methods of treatment were inapplicable, and yet there was a 5-year survival rate of 29%. Emmett states that 'as a result of this study we feel that resection plus implantation of radon seeds merits more frequent use than has been accorded in the past'. In use gold grains are similar to radon seeds, but they lose their activity more rapidly, the 'half-life' being 2.7 days compared with the 3.8 days of radon seeds.

Implantation of radium, radio-active cobalt, or tantalum wire. These substances are favoured by many surgeons. Implantation has to be carried out suprapubically, and it is often difficult owing to the curvature of the bladder wall to place the needles or wire accurately. The dosage is calculated from X-ray photographs. The main disadvantage of this form of treatment is that the bladder cannot be closed, although it is possible to close the bladder and bring the attached threads and a catheter through a urethrostomy opening. Few statistics have been published: Jacobs quotes 110 cases with a 34% 5-year survival rate, Kligerman 91 cases and 38% survival, Catgill 20% survivals.

Intracavitary radiation. Specially constructed balloon catheters have been used for this purpose. Generally speaking the results have been disappointing. Sufficient penetration cannot be obtained to destroy growths of B1 & B2 group, without causing severe bladder irritation and fibrosis. It is probably most useful in generalised papillomatosis. The handling of radioactive solutions such as Radioactive Sodium and Bromine requires elaborate apparatus and the results have been disappointing.

Radio-active liquid gold. This method is most suitable for papillomatosis, but it is impossible to estimate the dosage and the method is unsuitable for infiltrating tumours.

Partial cystectomy or segmental resection. This method of treatment has been carried out for many years, and is still advocated by many surgeons. The results have been disappointing and published results do not compare favourably with other methods of treatment. Five-year survival rates: Milner 28%, Mayo Clinic 27%, Jewett 23.7% (Groups A and B 68%, groups B2 and C 7%), Kligerman 22%, Riches 21.7%, Jacobs 20%. It is generally accepted that partial cystectomy should be carried out in all tumours of the vault or upper half of the bladder.

Total cystectomy. During the last decade there has been a wave of enthusiasm for the operation of total cystectomy. At the beginning the mortality rate was very high, in some instances over 50%; with more experience and improved technique the mortality rate has been reduced as low as 5%. Inasmuch as most surgeons reserve this operation for cases unsuitable for any other form of treatment, viz. penetrating tumours (when the penetration has reached the perivascular tissues 93% have glandular or distal metastases) the results have not been very encouraging. Published statistics of 5-year survivals: Mayo Clinic 19%, Kerr and Colby 10%, Riches 9%, Jewett 19%, but all show severe renal damage secondary to the ureteric transplant. Marshall, who extended the operation to include all grades of carcinoma and so-called simple papillomata, had even more disappointing results, only 26% 5-years survivals. More recently radical cystectomy, including the prostate and all the pelvic lymphatics, and in the female pan-hysterectomy, has been advocated. Few statistics of this procedure are available; Emile Sayegh published a review of 106 cases which is of interest: Of 21 cases which had palliative uretero-colic amastomosis, 18 died within 18 months and only 1 survived 2 years,

and then died. Of 23 cases which had bilateral uretic transplant and total cystectomy, 18 died during the first year and only 1 survived longer than 2 years. Of 62 patients who had radical cystectomy and pelvic adenectomy, 8 or 13%, have survived for longer than 3 years, with no sign of recurrence.

The enthusiasm for total cystectomy is on the wane because of poor results, renal damage following uretero-colic amastomosis, and electrolytic imbalance. The following types of lesion, however, are best treated by cystectomy: (1) Leucoplakia of the bladder, (2) diffuse papillomatosis, (3) irradiation cystitis and uncontrollable bleeding following irradiation, and (4) extensive superficial lesions. Some surgeons advocate cystectomy as a palliative measure, it will not prolong the patient's life, but may relieve his suffering.

Deep X-ray therapy. For contact therapy the lesion has to be exposed by open cystostomy and irradiated by direct X-ray therapy by means of a sterilized applicator. It is thus a 'single shot' treatment, and there are few lesions which cannot be more adequately dealt with by other forms of irradiation. *Deep and supervoltage X-ray therapy* have usually been employed in the treatment of invasive carcinomata which were too advanced for any other form of treatment. The results, however, have been very encouraging. The following are the 5-year survival results of deep X-ray therapy at the Christie Hospital and Holt Radium Institute, Manchester:

	No. of cases	% of total no. of cases (289)	5-year Survival
<i>Radical X-ray Therapy</i>			
Diffuse Papillomatosis	17	6%	8 (47%)
Gross infiltrating carcinoma	66	23%	17 (25%)
<i>Palliative X-ray Therapy</i>			
Gross infiltrating carcinoma	48	17%	3 (6%)

Bloomfield, at the United Sheffield Hospitals, after deep X-ray therapy had 14% alive and apparently free of tumour for 2 years. Better results followed the use of supervoltage therapy, 44% being alive after 2 years.

CONCLUSION

From the above analysis the following conclusions may be drawn regarding the best methods of treatment of bladder tumours:

Simple papillomata and grade-A and grade-B carcinomata should be treated by fulguration, resection and electro-coagulation, grading of the tumour being determined by cystoscopy, a carefully-taken biopsy, and bimanual examination. In grade-B1 and grade-B2 tumours the best results are obtained by resection and radon-seed implantation. Sequential resection should be reserved for tumours of the vault or upper half of the bladder. Should cystectomy be contemplated, it should be a radical cystectomy with complete pelvic adenectomy. The radio-active isotopes can be used effectively where radon seeds are not available. Cobalt needles and tantalum wire will no doubt be used extensively in South Africa. There is undoubtedly a place for X-ray therapy in the treatment of vesical carcinoma, more particularly supervoltage X-ray therapy, and the results would be considerably better if this treatment were not reserved for the hopelessly inoperable cases.