Proposal for changes in cystoscopic follow up of patients with bladder cancer and adjuvant intravesical chemotherapy

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A famous surgeon observed that the most important instrument for the management of superficial bladder cancer was a typewriter because it facilitated the organisation of the regular follow up examinations that are so important in controlling this disease. Cystoscopic follow up must be lifelong, and the cost, in the broadest sense, to both patient and health service is considerable. A recent study has suggested that the conventional frequency of bladder examinations may not be necessary and that most patients could be spared many cystoscopies. Instillation of cytotoxic drugs in the bladder has been shown to reduce the recurrence of tumours destroyed endoscopically and the development of new tumours elsewhere in the bladder. Because intravesical instillations are inconvenient, expensive, and may be toxic they have been reserved for patients thought to be at greatest risk of recurrence. However, two clinical trials have shown that a single cytotoxic instillation may be beneficial for low risk patients. If this is verified in everyday practice, the routine use of intravesical chemotherapy for all patients at the time of initial treatment could reduce the need for cystoscopies even further. Such changes should improve the quality of life of the 7000 new patients with superficial bladder cancer each year in England and Wales and allow savings to be made in the NHS.

The management of superficial bladder cancer accounts for a considerable proportion of urologists' workload. At the time of initial diagnosis most of these tumours are confined to the superficial layers of the bladder wall and are described by the tumour, node, metastases (TNM) classification as either Ta (papillary but not invading beneath the basement membrane of the urothelium) or T1 (invading the connective tissue core of papillary fronds or the submucosa but not the underlying detrusor muscle).[1] Initial treatment is by transurethral resection, but most of the work results from the frequent follow up cystoscopies that are considered to be necessary for the detection of recurrent disease and the endoscopic resection of any tumours so found. Many urologists follow a defined pattern for follow up cystoscopy: every three months for one year, every six months for the second, and then annually unless tumours recur, in which case the sequence starts again. Others consider this to be unnecessarily intensive and reduce the frequency of examinations, using a variety of clinical and pathological criteria to make this judgment in a manner that is little more than a "seat of the pants" process.

Intravesical chemotherapy has been shown to reduce the frequency of tumour recurrence by 30%-50%,[2,3] but, because of the associated inconvenience, cost, and toxicity, such treatment is usually reserved for patients with multiple or frequent recurrences that are a nuisance for the patient or difficult for the urologist to manage endoscopically. Like the pattern of cystoscopic follow up, the application of intravesical chemotherapy is still largely arbitrary. Although clinical acumen is laudable, it is preferable to base treatment decisions on scientific observations. We therefore propose changes to the routine management of patients with Ta or T1 bladder cancer that should benefit all those concerned—patients, urologists, and those responsible for the provision of health care. These proposals are based on three studies: an analysis of prognostic factors in patients with Ta and T1 bladder cancer treated in two Medical Research Council trials,[4] a trial of a single instillation of epirubicin by the European Organisation for Research and Treatment of Cancer,[5] and an MRC trial of one or five instillations of mitomycin in patients with solitary or newly diagnosed Ta and T1 bladder cancer.[3,6]

The clinical relevance of these trials does not seem to have been appreciated by urologists, and in our following discussion we try to combine the outcome of these trials to improve the future management of Ta and T1 bladder cancer. Our discussion also relies on the results of other clinical trials that have been summarised by Bouffioux.[7]

Prognostic factors

The time at which follow up cystoscopy is deemed necessary is based on our understanding of prognostic factors such as the size, number, and histological grade of tumours, the depth of invasion, associated urine cytology, random mucosal biopsies, and DNA ploidy. Some of these are easier to judge than others but no single observation or combination of features has enabled the separation of Ta and T1 tumours into clear prognostic groups that are of practical relevance. Even a recent detailed analysis of prognostic factors failed to offer unequivocal guidance.[8]

In contrast, Parmar *et al* for the MRC concluded that the likelihood of tumour recurrence, and hence the need for follow up cystoscopy, could be predicted simply and accurately by counting the number of tumours at initial presentation and observing whether any tumours had recurred at the first follow up cystoscopy three months later.[4] No other prognostic factors added significantly to this information, and the authors recommended a simple programme for the follow up of patients with Ta and T1 bladder cancer. They separated patients with Ta and T1 tumours into three risk groups that appear to be relevant to daily practice and could be exploited. These three prognostic groups are defined as follows: group 1—solitary tumour at presentation and no tumours at cystoscopy three months later; group 2—solitary tumour at presentation and tumour recurrence at three months or multiple tumours at presentation and no tumours at three months; and group 3—multiple tumours at presentation and recurrence at three months.

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The validity of this categorisation lies in the statistical strength of the two prognostic factors that have been selected—namely, the number of tumours at presentation and the presence or absence of tumours at the first follow up cystoscopy three months later. These two factors are better than all others because of the certainty of their observation: either there is one tumour at first cystoscopy or there are more than one, and at the first follow up cystoscopy tumour is either present or absent. All other factors are open to varying degrees of doubt. Measurement of tumour size is fairly accurate, but histopathologists may differ in their assessment of both tumour grade and depth of invasion (Ta or T1).[9,10] Also the problems of interpreting random mucosal biopsies have been documented.[11]

Thus, for practical purposes there are three types of patient with Ta and T1 bladder tumours. In group 1 patients have solitary initial tumours that do not recur at three months. These patients have a low risk of recurrence (20% at one year) and could be followed safely by flexible cystoscopy at annual intervals only. They account for about 60% of all new patients presenting with Ta and T1 bladder cancer. Patients in group 3 have the worst prognosis; they present with multiple tumours that recur at three months and account for about 10% of all patients with Ta and T1 tumours at initial diagnosis. Half are likely to have recurrence by six months and 90% by one to two years. For this reason they warrant frequent cystoscopies and some form of adjuvant treatment such as intensive schedules of intravesical chemotherapy, immunotherapy, or possibly cystectomy. Patients in group 2 (about 30%) of all new cases), have a 40% risk of recurrence at one year and 60% at two years. For these patients the conventional pattern of cystoscopic follow up of every three months for the first year would seem appropriate, albeit with the flexible instrument if possible—that is, with topical anaesthesia. Some form of adjuvant intravesical treatment also seems desirable provided that the toxicity, inconvenience, and cost are not too high.

pT1G3 TUMOURS

The particularly poor prognosis of many patients with pT1G3 transitional cell carcinoma is cause for concern,[12] and it may be asked how such patients fit into the above plan of management. In the first MRC trial 14 of the 379 patients were considered by the local pathologist to have pT1G3 tumours[4]: seven were in group 1, six in group 2, and one in group 3. This confirms clinical impressions that these sinister tumours are often solitary and may not recur quickly but do recur within a few years as muscle invasive cancers. In this study 29% (4/14) of the pT1G3 tumours progressed to muscle invasion, metastasis, or cancer death within five years compared with only 3% of the remaining 365 patients (unpublished data). Despite the variation among pathologists in separating Ta from T1 tumours and agreeing grade 3 histological differentiation,[9,10] the diagnosis of a pT1G3 tumour is important, and we suggest that such patients should be excluded at the outset from the recommended plan of management and regarded as a separate group in need of special treatment.

Role of intravesical chemotherapy

PATIENTS AT LOW RISK (GROUP 1)

In keeping with current common practice, we initially considered endoscopic resection at the time of initial diagnosis to be sufficient treatment for those patients with the lowest risk of recurrence (group 1). However, we now suggest otherwise because of results from recent clinical trials.

The trial reported by Oosterlinck *et al* showed that a single instillation of epirubicin 80 mg/40 ml normal saline given within 24 hours of the first transurethral resection more than halved the rate of tumour recurrence in low risk patients from 0·31 to 0·15.[5] These patients had solitary Ta or T1 transitional cell tumours and, although the outcome of cystoscopy at three months was not determined, the rate of recurrence in control patients (who received sterile water in place of epirubicin) was similar to that of group 1 patients. Recurrence after a median follow up of 23·4 months was 41% with an annual rate of recurrence of 0·32 (that is, developing a recurrent tumour every 3·1 years). Although this may not pose a great threat, the chance to reduce recurrence from 41% to 29% at two years and to extend the average time to recurrence from three years to nearly six years should not be overlooked given the simplicity and lack of toxicity of the treatment.

In support of this an MRC trial showed that a single dose of mitomycin (40 mg/40 ml normal saline) instilled at the time of initial transurethral resection similarly reduced rates of recurrence by 40% for up to five years.[3,6] This effect was not initially analysed according to the risk categories outlined above, but 60% of the patients in this trial were in group 1 and subsequent analysis showed that the benefits of giving mitomycin were similar for all types of patients. This trial also showed a trend in favour of additional instillations of mitomycin given at the time of each three month cystoscopy for the first year. However, since low risk patients do not require three monthly cystoscopy it is inappropriate to recommend three monthly chemotherapy instillations, especially as the additional benefit for patients with the best prognosis would probably be small.

PATIENTS AT MEDIUM RISK (GROUP 2)

A 60% probability of tumour recurrence within two years is not inconsiderable, and most patients would welcome treatment that would significantly reduce this risk. Conventional regimens of intravesical chemotherapy (weekly instillations for eight weeks and monthly instillations for several months thereafter) are inconvenient, costly, and sometimes toxic and might be considered excessive for medium risk patients. In the MRC trial[3,6] these disadvantages were largely avoided while the benefit achieved was roughly equivalent to that of more intensive regimens.[13,14] Although a single treatment was effective, a trend for greater benefit was observed with five instillations at intervals of three months.[3,6] Since patients in group 2 warrant three monthly follow up cystoscopy for the first year, it would be appropriate to give an instillation of mitomycin (or other intravesical drug) at the same times. For those patients who remain free of tumours annual flexible cystoscopy would be appropriate thereafter.

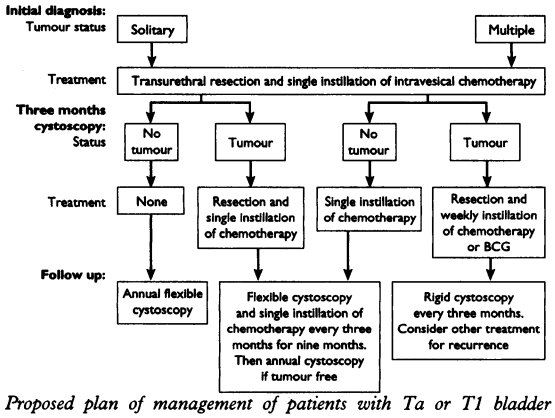
PATIENTS AT HIGH RISK (GROUP 3)

Intensive, weekly intravesical treatment with BCG (bacille Calmette-Guerin), epirubicin, mitomycin, or thiotepa is appropriate for patients at high risk of tumour recurrence since many trials have shown that such patients experience a halving of tumour recurrence by instillation of these drugs. However, the effect of treatment on progression to muscle invasion, metastasis, or cancer death remains uncertain. Some urologists might recommend cystectomy without delay, but the need for this is not proved.

Proposed treatment and follow up

The figure outlines our proposed plan of management of patients with Ta or T1 bladder cancer.

At the initial diagnosis of bladder cancer—All patients should undergo cystoscopy, bimanual palpation, and



Proposed plan of management of patients with Ta or T1 bladder cancer

an endoscopic resection that includes underlying detrusor muscle to remove all visible tumour in the bladder and establish whether muscle invasion has occurred. If carcinoma in situ is suspected appropriate mucosal biopsy specimens and bladder washes should be examined, and if it is confirmed appropriate treatment should be implemented. Those patients without carcinoma in situ or muscle invasion should receive a single instillation of intravesical chemotherapy as soon as possible after the transurethral resection, preferably within 24 hours. No other investigation or treatment is indicated at this time.

At the first follow up cystoscopy three months later—If the original tumour was solitary and no tumour is present (group 1 patients) no more treatment is needed and the next cystoscopy (flexible) may be scheduled for nine months later (that is, one year after initial diagnosis) and then annually thereafter. If the original tumour was solitary and tumour recurrence is found or if the original tumours were multiple and no tumour is found (group 2 patients) cystoscopy should be accompanied by a single instillation of intravesical chemotherapy, which should be repeated at each of the following three monthly cystoscopies up to and including one year after the initial diagnosis. If the original tumours were multiple and tumour is present (group 3 patients) intensive treatment with weekly instillations of intravesical chemotherapy or immunotherapy should be started. Three monthly cystoscopies thereafter are essential, and indications for other treatments should be considered carefully.

CYSTOSCOPY

Most hospitals now have flexible cystoscopes, which can be used with topical anaesthesia and allow savings to be made in time and in costs (from anaesthesia, use of recovery facilities and day beds, and transport of patients home). For patients with a low risk of tumour recurrence (group 1) there is little argument against using flexible cystocopes for all follow up. Patients in group 2 have a 2:1 chance against finding tumour recurrence within two years, which means a 10:1 chance against finding tumour at any one cystoscopy. This would argue in favour of flexible cystoscopy for these patients as well. Patients in group 3 should continue to undergo rigid cystoscopy under general anaesthesia because of the probability of tumour recurrence, and the need for resection, is much greater.

Cost implications of proposals

The financial implications of our proposals can only be estimated approximately because the actual cost of individual urological procedures in the NHS is not known. The figures suggested are based on our conservative estimates from the limited information available and are considerably lower than the current price of £565 charged by the private sector for a day case cystoscopy with general anaesthesia and use of a bed for six hours. Intravesical drugs tend to be priced similarly, but the individual costs of intravesical chemotherapy will depend upon local purchasing arrangements.

Our estimate is based on 100 patients presenting with Ta or T1 urothelial carcinoma and average costs assumed to be £70 for a single instillation of intravesical chemotherapy, £100 for cystoscopy, and £800 for one attendance or admission for transurethral resection of tumour. The distribution of patients in the three prognostic groups and the expected rates of tumour recurrence are based on the figures given earlier. Thus, for the 60 patients in group 1, a single instillation of an intravesical drug at the time of initial diagnosis would reduce recurrence in three years from 36% to about 22%, giving a saving of eight transurethral resections. For the 30 patients in group 2, single intravesical instillations every three months for the first year would reduce recurrence from 60% to 36%, saving seven transurethral resections. The use of chemotherapy to treat group 3 patients would not change.

The table shows that the financial costs of this extra intravesical chemotherapy would be more than offset by savings in hospital costs from the reduced number of attendances for follow up cystoscopy and for tumour resections over three years. A total saving of £25 300 would be achieved (£26 200 for group 1 less £900 overspend for group 2). In addition, the more widespread use of flexible cystoscopy with topical anaesthesia instead of rigid cystoscopy and general anaesthesia would achieve considerable further savings as well as releasing anaesthetic and nursing staff.

Estimated financial implications of proposed cystoscopy schedule and intravesical chemotherapy for 100 patients with Ta and T1 bladder cancer

	Individual cost (£)	No of procedures	Total cost (£)
Group 1 patients (n=60)			
Extra costs:			
Intravesical chemotherapy at diagnosis	70	60	4 200
Savings:			
Cystoscopies at 6, 9, 18, and 30 months after diagnosis	100	4×60	24 000
Transurethral resections	800	8	6 400
Final saving			26 200
Group 2 patients (n=30)			
Extra costs:			
Three monthly intravesical chemotherapy in first year	70	5×30	10 500
Savings:			
Cystoscopies at 18 and 30 months after diagnosis for 67% of patients tumour free at one year	100	2×20	4 000
Transurethral resections	800	7	5 600
Final extra cost			900

Treatment of group 3 does not change.

Detailed costs will differ between hospitals but it is clear that considerable financial savings could be made by using intravesical chemotherapy and flexible cystoscopy as recommended above. For patients, the reduction in hospital attendance, anaesthesia, endoscopic resections, loss of time from work, anxiety, and other factors are difficult to quantify but should considerably improve quality of life for most patients with superficial bladder cancer.

Conclusion

The proposals in this paper amount to a radical change in the policy and practice of treating patients with Ta and T1 bladder carcinoma. We hope readers will recognise the importance of the data on which our arguments have been based and accept that our

proposals are an attempt to translate logically and realistically the results of clinical trials into urological practice. Although we have no reason to doubt the basis of our recommendations, it should be recognised that they are proposals for discussion. If they are implemented, the outcome should be monitored closely by urologists, hospital management, and health care economists.

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Grand Rounds—Hammersmith Hospital

β Adrenergic agonists and pulmonary oedema in preterm labour

Must be used with care

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Ritodrine and other β adrenergic agonists relax uterine smooth muscle and have been widely used to manage preterm labour. The effect of these drugs on birth weight and perinatal mortality remains controversial. Several side effects, including maternal pulmonary oedema, have been described.

Case history

A 34 year old woman with primary infertility for 10 years had in vitro fertilisation, resulting in a twin pregnancy. She was normally fit and well with no history of cardiac disease. At 24 weeks of pregnancy she developed intermittent vaginal bleeding and was admitted to hospital. Initial assessment showed no evidence of uterine activity, but later the same day she developed contractions and the cervix was found to be 2 cm dilated, although the membranes were intact. Preterm labour was diagnosed and a ritodrine infusion was started at a dose of 200 μg/min, given in 500 ml of normal saline every four hours. She was also given dexamethasone (two 12 mg doses) and thyrotrophin releasing hormone (400 μg eight hourly over 48 hours) to improve fetal lung maturation and reduce the risk of hyaline membrane disease.

Over the next 24 hours the contractions became less frequent and although she had a resting tachycardia, her chest was clinically clear. During the next day the contractions became more frequent and she was given ritodrine in 500 ml of normal saline every four hours. The contractions continued and on the fourth day she became increasingly breathless with a tachycardia of 135 beats/min, bilateral basal crackles, and some peripheral oedema. Pulmonary oedema was diagnosed clinically and she responded to oxygen and a bolus of intravenous frusemide. The ritodrine infusion was stopped and twins were delivered a few hours later.

Thirty minutes after delivery she became acutely breathless and started coughing up pink frothy sputum. She had severe tachycardia with chest crepitations and pulmonary oedema was confirmed by chest radiography (fig 1). An electrocardiogram showed minor ST segment changes. She again improved with oxygen and intravenous frusemide but had a further less severe episode four hours later.

The next day her respiratory symptoms had resolved, and she had a pulse rate of 70 beats/min, normal heart sounds, and a clear chest. An echocardiogram showed no valvular abnormalities, good biventricular function, normal chamber dimensions, and unremarkable Doppler filling velocities (fig 2). An electrocardiogram appeared normal.

The twins were transferred to the neonatal unit. The first twin weighed 780 g and died one week later. The second twin weighed 690 g and was treated with surfactant for the respiratory distress syndrome. He

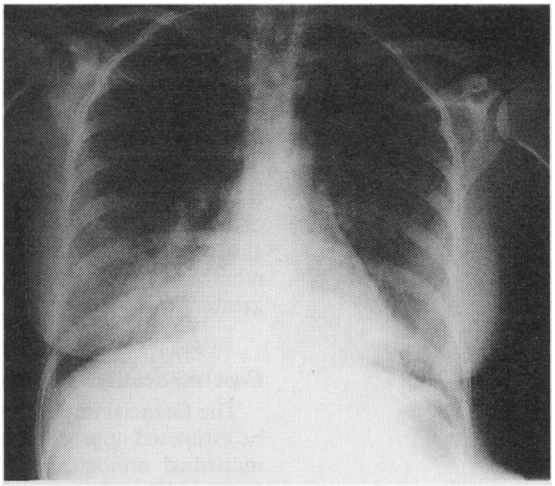

FIG 1—*Chest radiograph taken during episode of acute breathlessness showing upper lobe blood diversion, alveolar shadowing, and septal lines. These signs confirm the diagnosis of acute pulmonary oedema*