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Size and location of tumors influencing the effect of bladder instillation therapy

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Summary. The clinical results obtained in 81 cases of bladder tumor are used as a basis for discussion of factors influencing the effect of bladder instillation therapy. The following conclusions are derived: 1) If bladder instillation therapy aims only at complete remission (CR), tumors over 1 cm in diameter should be excluded, because this is the theoretical size limit beyond which instillation therapy cannot lead to CR. 2) At least 40 ml of drugs may be needed for instillation therapy for tumors located in area B, the limited part posterior to the trigonum.

Introduction

The effect of bladder instillation of anticancer drugs on bladder tumors is not completely predictable. This treatment causes pronounced shrinkage of the tumor in some cases but has an entirely negative result in others.

The primary factor influencing the effect is of course the sensitivity of the tumor to the anticancer drugs. However, since this kind of therapy works through absorption, the effect is also influenced by other factors. We found a second factor, the physicochemical property of the drugs, made up of the ionization constant, partition coefficient and molecular size, and published details in 1985 [5]. This factor relates to the drugs. In this presentation I would like to postulate a third factor influencing the effect of instillation therapy on bladder tumors; this one relates to the actual tumors.

Materials and methods

The study group comprised 81 patients with bladder tumor, these being all the patients treated by bladder instillation therapy with mitomycin C (MMC) or adriamycin (ADM) in our clinic in a 6-year period from January, 1980 to December, 1985 (Table 1). The course of therapy consisted in instillation of 20 mg MMC [3] or 20 mg ADM [4] in 20 ml distilled water on 20 occasions in the vast majority of cases, but 200 mg cytosine arabinoside (CA) [1] was also given in a limited number of cases.

Cystoscopy was performed immediately before the course of therapy in each case, and the size of the tumor was determined macroscopically. The tumors were then divided into two groups: (a) below 1 cm and (b) 1–3 cm in maximum diameter. No tumor larger than 3 cm was noted.

At the same time, the location of the tumor was also recorded, the bladder being considered in three areas: the trigonum (area A), the lower half of the posterior wall of the bladder, adjoining the trigonum (area B), and areas other than A and B (area C) (Fig. 1).

Immediately after the completion of instillation therapy, cystoscopy was again performed and the effect of the therapy was judged, three categories being used: complete remission with the disappearance of the tumor (CR); partial remission with a reduction in the diameter of the tumor by over 50% (PR); and no change in the size or reduction by less than 50% (NC).

In some patients with multiple bladder tumor, the largest tumor was used to assess the effect of treatment.

Table 1. Drugs instilled for treatment of bladder tumor (Jan. 1980 to Dec. 1985)

Instillation	Cases
MMC	23 (28%)
ADM	14 (17%)
MMC + CA	30 (37%)
ADM + CA	14 (17%)
Total	81

Results

In 45 cases with bladder tumors smaller than 1 cm in diameter (Table 2) CR was observed in 10 (22%), PR in 20

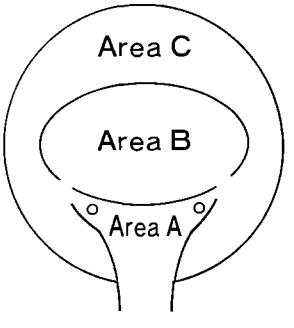

Fig. 1. Areas in the new mapping

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(44%) and NC in 15 cases (33%). The tumors in which CR was achieved were located exclusively in area A ($P<0.05$) or area C ($P<0.1$). No tumor in area B showed CR ($P<0.01$).

In 36 cases with tumors 1–3 cm in diameter (Table 3) PR was observed in 11 (31%) and NC in 25 cases (69%). No case of CR was found. In 12 cases with tumors located in area B only 1 case showed PR ($P<0.05$) and the remaining 11 cases were categorized as NC.

Discussion

From these results it became evident that CR was only observed in tumors smaller than 1 cm in diameter. This means that the maximum volume of tumor that can be reduced by bladder instillation therapy may be equal to the volume of a tumor 1 cm in diameter. When a tumor of this size is simulated as a sphere 1 cm in diameter, its volume is 0.52 ml and its surface area, 3.1 cm^2. If we suppose that the reduction volume is proportional to the surface area, the reduction volume per 1 cm^2 of the surface area is approximately 0.2 ml.

Let us imagine that proportional reduction occurs in a tumor 1.5 cm in diameter. In this case, the final diameter of the tumor after reduction can be calculated as 0.9 cm, i.e., 40% reduction in diameter. Since the general definition of PR is a reduction of the diameter by over 50%, this result would be judged as NC, although the same reductive effect has surely occurred as in a tumor originally 1 cm in diameter for which CR is recorded.

Many reports have indicated that intravesicular instillation therapy is ineffective in tumors larger than 1 cm in diameter [3]. However, this assessment seems incorrect in light of the simple calculation worked here. In fact, the therapy is not ineffective but its results simply cannot be classified in the conventional three categories for tumors over 1 cm in diameter.

Another striking observation recorded in this study is that the effect of the therapy depends to a considerable extent on the location of the tumor. We found that tumors located in a particular limited area (area B) just posterior to the trigonum responded much less well to treatment that those located in the other areas (areas A and C).

Table 2. Effect of instillation therapy on tumors smaller than 1 cm in diameter

Area / Effect	A	B	C	Total
CR	5	0	5	10 (22%)
PR	0	12	4	20 (44%)
NC	5	11	3	15 (33%)
Total	10	23	12	45

Table 3. Effect of instillation therapy on tumors 1–3 cm in diameter

Area / Effect	A	B	C	Total
CR	0	0	0	0
PR	3	1	7	11 (31%)
NC	8	11	6	25 (69%)
Total	11	12	13	36

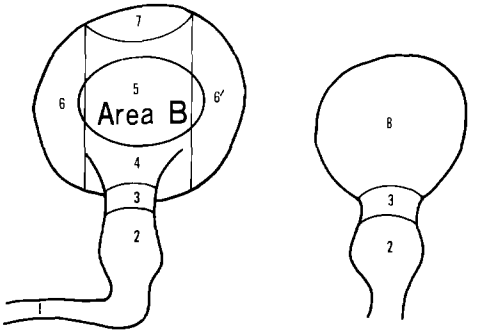

Fig. 2. Sections in the conventional mapping

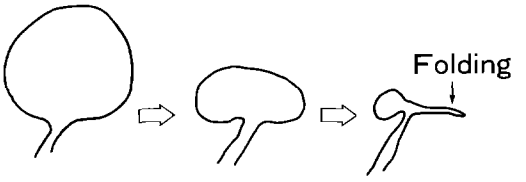

Fig. 3. Contraction of the bladder

For our own purpose we devised a new mapping system for the bladder, which is different from the conventional mapping in eight sections (Fig. 2) [2]. In terms of the conventional mapping system, our area A corresponds to section 4. Area B is mostly covered by section 5, but is narrower and includes a small part of sections 6 and 6'. Area C is the rest of the bladder not included in areas A & B (Fig. 2).

This new mapping is based upon the physiology of bladder contraction. When the bladder is full its shape is spherical. As the bladder contracts the spherical shape is maintained until the content approaches a critical point. Once this critical point is passed the spherical form is lost and the bladder wall is folded by abdominal pressure. The folding is most pronounced at the part just posterior to the trigonum, while the trigonum itself is rather stretched until complete contraction has occurred. In our mapping, the folding part corresponds to area B and the stretched parts to area A. The bladder content at the critical point when folding starts is around 20–30 ml in adults (Fig. 3).

A serial cystogram in a man with 10, 20, 40, and 100 ml of contrast medium instilled demonstrates the contracting status (Fig. 4). With a content of 10 ml or 20 ml the bladder wall is folded intensively at the part posterior to the trigonum. When the content increases to 40 ml, the folding is cancelled and the shape of the bladder is basically similar to that with a content of 100 ml.

Patients receiving bladder instillation therapy are usually requested to reduce their fluid intake and to void before the instillation. The usual volume of vehicle used for the drugs is 20 ml, which allows intensive folding to persist in the part posterior to the trigonum. It is possible that tumors situated in the folding part are not adequately immersed in the drug solution. It is emphatically suggested that there is a causal connection between this insufficient immersion in the drugs instilled and our observation that

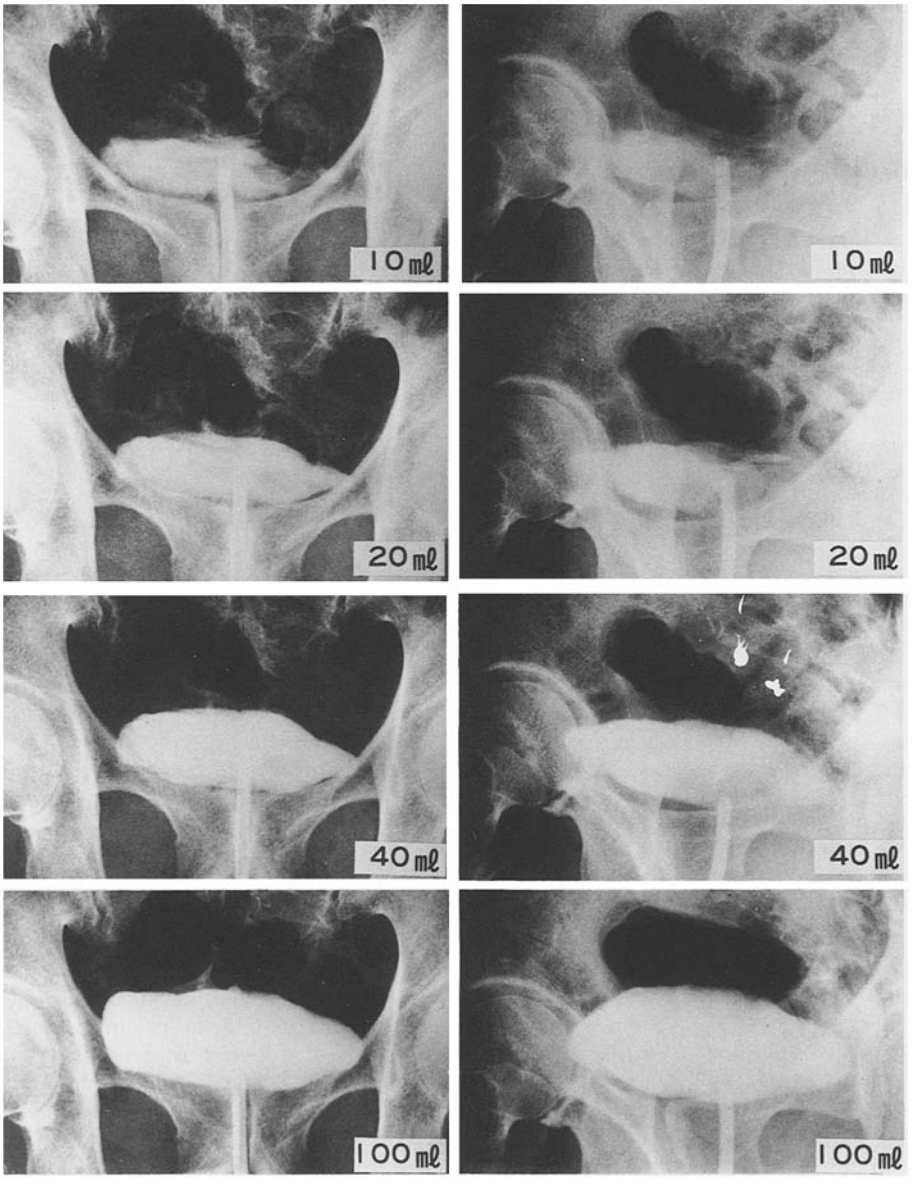

Fig. 4. Serial cystogram in 2 directions with 10, 20, 40, and 100 ml instilled medium

tumors located in area B showed very poor response to therapy.

If this suggestion is true, it is advisable that the amount of the drug and the volume of the solvent should be doubled (volume of at least 40 ml with the same concentration of drug) for instillation therapy directed at tumors located in area B.

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