Cancer Chemother Pharmacol (1983) 11 (Suppl): S 51–S 58

Cancer Chemotherapy and Pharmacology

Long-term intra-arterial infusion chemotherapy with Adriamycin for advanced bladder cancer

Shori Kanoh[1], Tomokazu Umeyama[1], Shinichi Nemoto[1], Satoru Ishikawa[1], Ryosuke Nemoto[1], Kenji Rinsho[1], Tsunetada Yazaki[1], Kenkichi Koiso[1], Shigeki Takahashi[2], and Ryuichi Kitagawa[2]

[1] Department of Urology, Institute of Clinical Medicine, The University of Tsukuba, Sakuramura, Niiharigun, Ibaragi Prefecture 305, Japan
[2] Department of Urology, Juntendo University, School of Medicine, 2-1-1 Hongo, Bunkyo-Ku, Tokyo, 113, Japan

Summary. *Long-term intra-arterial infusion chemotherapy with Adriamycin (ADM) was performed in cases of bladder cancer prior to total cystectomy. This report describes the effects in 13 cases evaluated more than 3 weeks after infusion of 10 mg ADM once or twice weekly.*

An oblique skin incision approximately 10 cm long was made in the gluteal region to expose the gluteus maximus muscle. A teflon catheter was then inserted into the gluteal artery and fixed; the distal end was brought out from under the skin in the precordial region. A similar procedure was performed on the contralateral side.

The catheter was inserted through the superior and inferior gluteal arteries in five and eight cases, respectively. In the former group, partial response was obtained in two cases, minimal response in two and no response in one, so that primary tumor remission was evident in 40% of the cases. In the latter group, all cases but one attained partial response, i.e., remission was seen in 87.5% of cases treated by inferior gluteal infusion.

Skin erosion of the gluteal, perineal, and anal regions and sciatica-like pain were observed in some cases; however neither myocardial effect nor bone marrow suppression, which have been reported as side-effects of ADM, were observed in any of the cases.

These results suggest that this therapeutic modality could be effective in the preoperative work-up of candidates for total cystectomy, and also that it could be useful in the treatment of patients in whom total cystectomy is contraindicated.

Introduction

Regional intra-arterial infusion of chemotherapeutic agents is a treatment modality designed to obtain a high concentration of the agent in the tumor, to ensure effective treatment while minimizing the systemic side-effects [3].

Methods of internal iliac arterial catheterization infusion include direct catheterization of the internal iliac artery [1, 5], puncture and catheterization of bilateral femoral arteries [2, 6], and insertion from the superior gluteal artery [4].

Since February 1977 we have been examining the effects of long-term intra-arterial infusion in patients with advanced bladder cancer who are candidates for total cystectomy. To retain the possibility of total cystectomy later a skin incision was made in the gluteal region and the catheter was inserted into the internal iliac artery via the superior gluteal artery. Of late we have catheterized the inferior gluteal artery to achieve very highly selective infusion of anticancer agents into the vesical artery.

As an intra-arterial infusion agent we used 10 mg Adramycin (ADM) infused once or twice weekly for 3 weeks or more in 13 cases, and the effects on tumor remission were examined.

Requests for reprints should be addressed to S. Kanoh

Materials and methods

In cases in which total cystectomy was indicated intra-arterial infusion of ADM was performed via the superior gluteal artery in five cases and via the inferior gluteal artery in eight cases (Tables 1 and 2).

In cases 1, 4, and 10 hematogenic metastases to the lungs, liver, and bone were recognized but cystectomy was unavoidable because of bleeding and pain.

In case 5 total cystectomy was impossible due to stenosis of the mitral valve, and partial cystectomy was performed. Case 6 had undergone partial cystectomy and radiation at another institution and underwent bilateral ureterostomy because of recurrence.

Catheterization technique. The distribution and branching of the superior and inferior gluteal arteries were confirmed by pelvic angiography.

Following the achievement of epidural anesthesia, the patient was placed in a prone position. After disinfection of the gluteal region, an incision was made along the line connecting the superior rim of the greater sciatic foramen with the greater trochanter. Immediately beneath the incision, the gluteus maximus muscle was exposed and separated with the fingers to expose the superior or inferior gluteal artery, and its branch was ligated. An arterial infusion catheter was inserted up to a length of approximately 5–6 cm into one of the branches of the gluteal artery (Fig. 1). The teflon catheter was 1.1 mm in outside diameter, 0.6 mm in inside diameter, and 1.7 m in length. A contrast agent was injected through the catheter to ascertain the correct location of its tip and the catheter was firmly fixed to the artery and then to the adjacent fascia so that it could not be easily removed. The gluteal muscles were approximated and sutured and the skin was closed with a nylon suture with the catheter protruding from the wound (Fig. 2).

From the outer edge of the wound a probe 50 cm in length was inserted, and this was led under the skin to the lateral

Table 1. Superior gluteal artery infusion chemotherapy with Adriamycin

Case no.	Age	Sex	Grade	Stage	Total dose of ADM (mg)	Tumor reduction rate (%)	Effect (Yagoda)	Side-effects	Operation	Survival
1	56	M	G3	$pT_4N_1M_1$	80	64	Partial response		1 week, ileal conduit 6 weeks, total cystectomy	8 weeks Died of sepsis
2	65	M	G2	$pT_3N_0M_0$	70	40	Minimal response	Sciatic pain	3 weeks, total cystectomy, ureterosigmoidostomy	31 months Still living
3	67	M	G2	$pT_3N_0M_0$	60	41	Minimal response		4 weeks, total cystectomy, ureterosigmoidostomy	26 months Still living
4	45	M	G3	$T_4N_xM_1$	370	79	Partial response	Skin necrosis, sciatic pain		4 months Died of sepsis
5	65	M	G3	$pT_3N_xM_0$	560		No response	Atrophy of gluteal muscles	4 weeks, partial cystectomy	10 months Died of cancer

Table 2. Inferior gluteal artery infusion chemotherapy with Adriamycin

Case no.	Age	Sex	Grade	Stage	Total dose of ADM (mg)	Tumor reduction rate (%)	Effect (Yagoda)	Side-effects	Operation	Survival
6	57	M	G3	$pT_4N_1M_0$	260	61	Partial response	Skin erosion	16 weeks, total cystectomy	6 Months Still living
7	60	F	G3	$pT_4N_0M_0$	100	59	Partial response	Skin erosion	8 weeks, total cystectomy, ileal conduit	9 months Still living
8	68	M	G3	$pT_3N_0M_0$	130	63	Partial response		4 weeks, total cystectomy, ureterosigmoidostomy	15 months Still living
9	54	M	G2	$T_3N_2M_0$	130	60	Partial response		6 weeks, total cystectomy, ileal conduit	13 months Died of cancer
10	70	M	G3	$T_4N_4M_1$	100		No response	Skin erosion	5 weeks, ileal conduit	4 months Died of cancer
11	69	F	G3	$T_4N_2M_0$	190	52	Partial response	Skin erosion	7 weeks, ileal conduit	16 months Still living
12	84	M	G3	$T_3N_xM_0$	255	71	Partial response	Skin erosion	12 weeks, TUR-Bt	24 months Still living
13	75	M	G3	$T_3N_xM_0$	425	59	Partial response	Skin erosion	10 weeks, TUR-Bt	22 months Still living

abdominal region. Upon insertion of the teflon catheter into the small opening at the end of the probe, the latter was pulled into the lateral abdomen to guide the catheter (Fig. 3). This was followed as soon as possible by injection of heparinized saline into the catheter to prevent obstruction by formation of thrombi.

The position of the patient was then changed to a supine position. The 50 cm probe was moved from the lateral abdominal position to the subclavian region, where the catheter was brought out of the body and was firmly fixed to the skin with a nylon suture (Fig. 4).

Exposure of the end of the catheter at the subclavian region means that sponge-bathing of the patient is possible and it is easier to prevent infections arising at the point of entry of the catheter, thus enabling the patient to receive long-term intra-arterial infusion therapy in the outpatient clinic. Injection of 6,000 U of urokinase into the catheter makes it possible for it to be left in place for nearly a month without the problem of obstruction by coagulation.

To allow observation of the distribution of the drug infused from the catheter, $^{99m}TcO_4$ (pertechnetate) was injected through the catheter and RI angiography was carried out

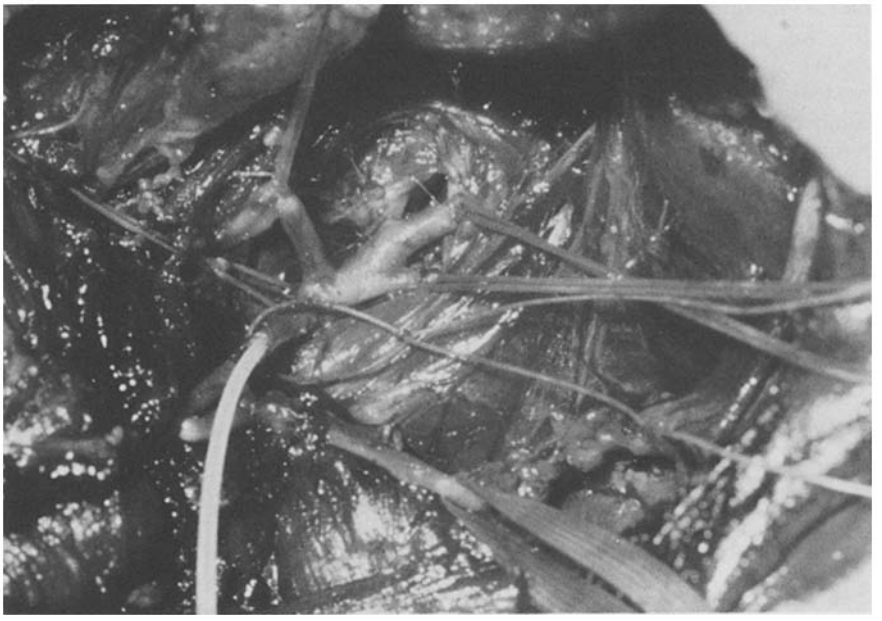

Fig. 1. A teflon catheter was inserted into one of the branches of the inferior gluteal artery, and the other branches were ligated

routinely (Fig. 5). The drug used for intra-arterial infusion was ADM in single doses of 10 mg, once or twice a week. Occasionally three 10-mg doses were administered in a single week. Tables 1 and 2 describe the surgical procedures: total cystectomy was performed in seven cases 3–16 weeks after commencement of infusion treatment.

In stage T_4 cases 10 and 11 only, an ileal conduit was constructed 5 and 7 weeks after commencement of infusion. In cases 12 and 13, in whom total cystectomy could not be performed because of age, TUR-Bt was performed at 10 and 12 weeks after commencement of treatment.

Criteria for response. Since intra-arterial infusion is a local treatment method, changes in the size of the tumor as a result of treatment were measured by CT and ultrasonography to investigate the tumor reduction rate. Tumor size was calculated by multiplication of the length and width as recorded in the image in which it appeared largest.

The criteria for evaluation of effectiveness were based on those of Yagoda [7]:

Complete response (CR) required complete disappearance of clinical, radiological, and biochemical evidence of tumor.

Partial response (PR) was defined as greater than 50% reduction in the sum of the products of the dimensions of measurable tumors.

Minimal response (MR) was defined as any unequivocal shrinkage of measurable tumors which was less than 50%.

Results

To make it possible to observe the distribution of the drug infused from the catheter, $^{99m}TcO_4$ pertechnetate was injected via the catheter and RI angiography was carried out (Fig. 5). The angiogram showed practically no trace of the drug in the bladder region when the drug was infused from the aorta. On the other hand, when the drug was infused from the superior gluteal artery most of the drug flowed into the gluteal muscles

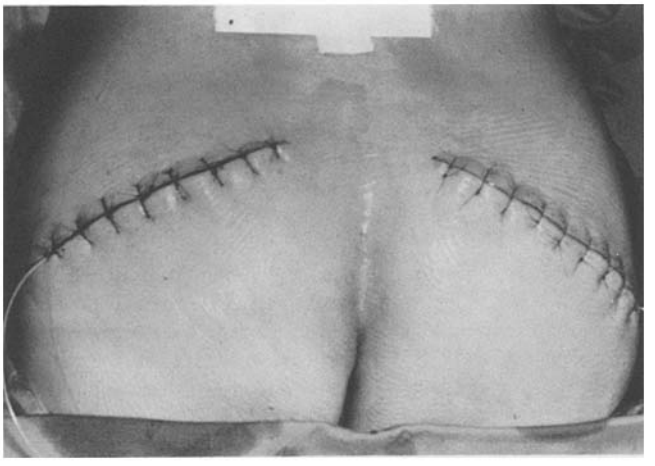

Fig. 2. The skin incision in the gluteal region was closed with nylon sutures, with the catheter protruding from the wound

Fig. 3. From the outer edge of the incision, a 50-cm probe was inserted, which was led under the skin to the lateral abdominal region

via the inferior gluteal artery, although some portion of the drug was also observed in the bladder region.

When the drug was infused from the inferior gluteal artery, most of the drug was seen to flow into the bladder region. However, in different cases the drug was also distributed in the perineum, scrotum, and penis via the internal pudendal artery.

Case 4 had undergone partial cystectomy 8 months previously at another institution, but as is shown in the CT in Fig. 6, a large tumor in the left bladder wall extended to the pelvic wall and metastases were recognized in the ribs and pelvic bone. After 10 mg ADM had been administered three times per week for a total dosage of 370 mg, extensive necrosis of the tumor was recognized, as shown in Fig. 7; due to necrosis of the tumor in the pelvic wall extravasation of urine into the posterior peritoneal cavity occurred, followed by septicemia and death 4 months later.

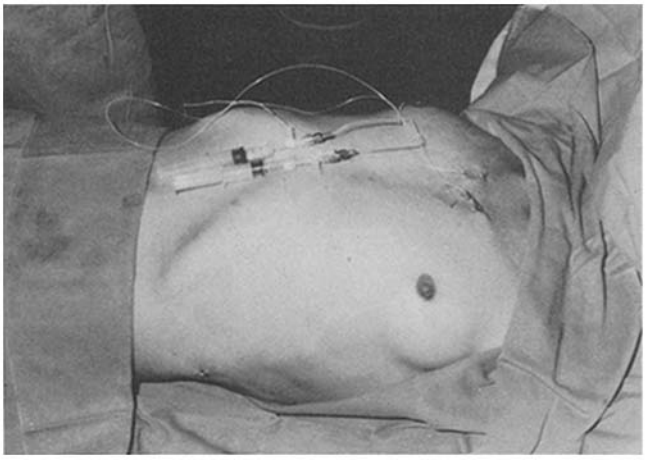

Fig. 4. The catheter was brought out of the body in the subclavian region, and was firmly fixed to the skin with nylon sutures

Case 1 was also a stage T4 case in which an ileal conduit was first made 1 week after intra-arterial infusion, after which the treatment was continued. However, as in case 4, extravasation of urine to the posterior peritoneal cavity developed due to tumor necrosis and the patient died of sepsis although total cystectomy was performed 6 weeks later.

Partial cystectomy was performed 4 weeks after commencement of intra-arterial infusion in case 5, but the resected specimen failed to reveal any effects histologically, and although treatment was continued after surgery there was striking atrophy of the gluteal muscles and RI angiography revealed flow into the gluteal muscles only and none into the bladder.

In the five cases of superior gluteal artery infusion therapy, partial and minimal responses were seen in two cases each and no response in one, giving an overall response rate of 40% (Table 1). The side-effects of the drug included sciatica-like pain in two cases and skin necrosis in one.

As shown in Figs. 8 and 9, the papillary broad-based bladder cancer occupied about half the vesical lumen. Biopsy was performed and total cystectomy was indicated in this grade 3 stage T_3 case. However, because of respiratory disturbance due to bronchial asthma and also the age of the patient (75 years), chemotherapy with ADM 5 mg per dose twice weekly, infused via the inferior gluteal artery, was commenced.

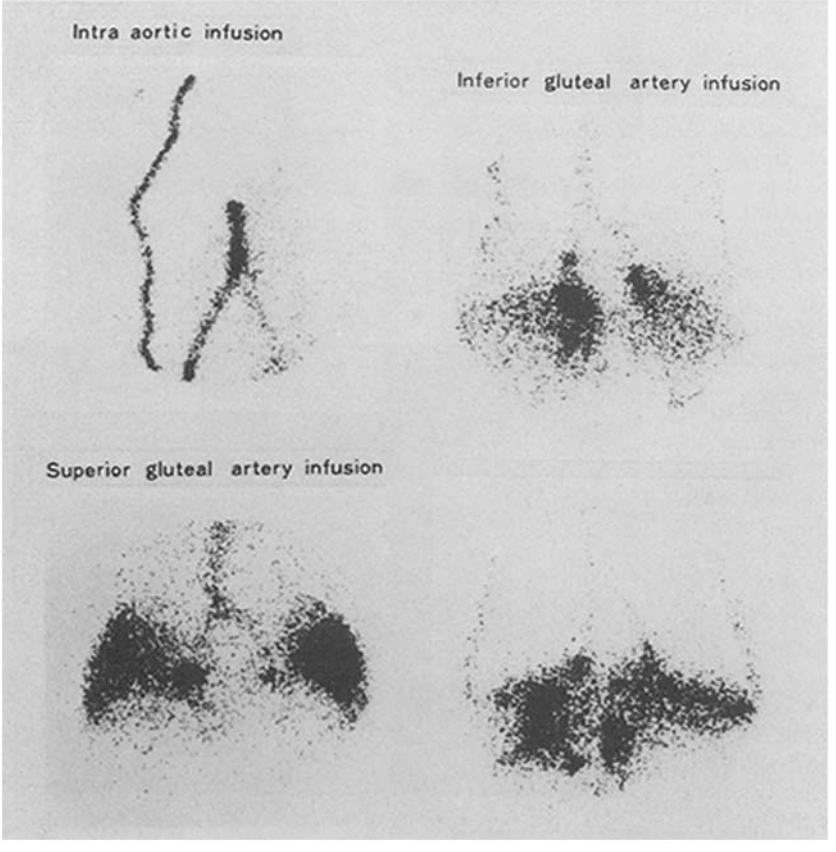

Fig. 5. RI angiography through the arterial infusion catheter with $^{99m}TcO_4$ pertechnetate

After 2 months and a total dose of 105 mg, the tumor showed remarkable regression (Fig. 10). TUR performed at that juncture revealed residual tumor, and therefore it was decided to continue with weekly injections of 10-mg doses of ADM. IVP revealed an improvement after 5 months, as shown in Fig. 11. One year later the tumor had completely disappeared. The intra-arterial injection therapy was halted and the patient is now alive, disease-free 22 months later.

Case 12 was also an elderly patient (84 years) to whom 10 mg ADM was administered twice weekly for 13 doses, followed by 5 mg once per week; TUR was performed after 3 months. Intra-arterial injections were continued thereafter and complete disappearance of tumor was recognized at a total dosage of 255 mg, whereupon treatment was halted. This patient is also still alive with no evidence of recurrence, 2 years later.

Concerning the short-term effects, within 2 months of intra-arterial injection of ADM from the inferior gluteal artery partial response was seen in seven cases and no response in one, yielding a good overall response rate of 87.5%.

In terms of the side-effects of the treatment, mild skin erosions in the gluteal, perineal, and anal regions were seen in six of the eight cases, but the symptoms disappeared on reduction of dosage either to 5 mg per dose twice weekly or to one dose of 10 mg per week. When ADM was limited to less than 20 mg/week it did not cause myocardial disturbances or bone marrow suppression in any of our subjects, but this dosage appeared to be adequate to produce positive responses in these patients.

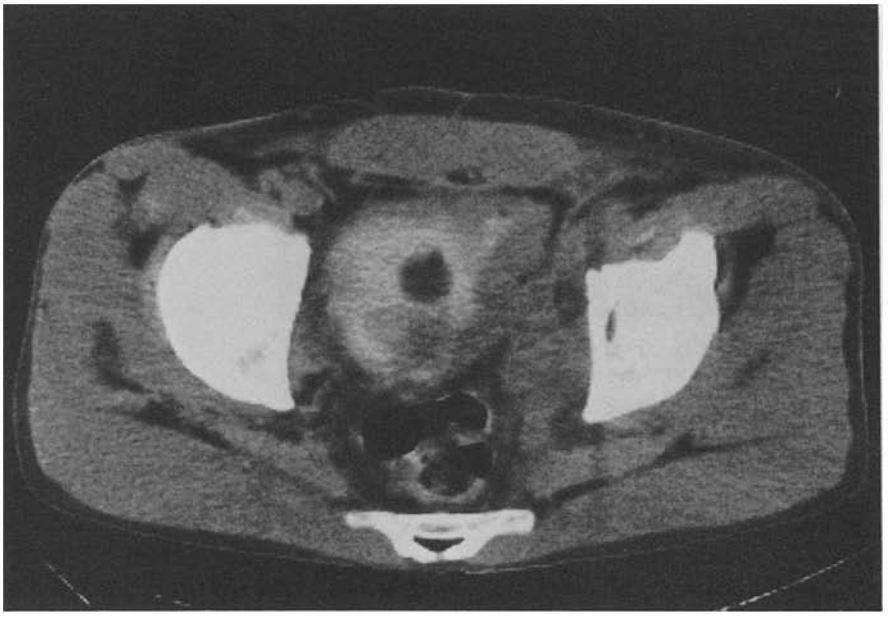

Fig. 6. CT scan of case 4 before treatment

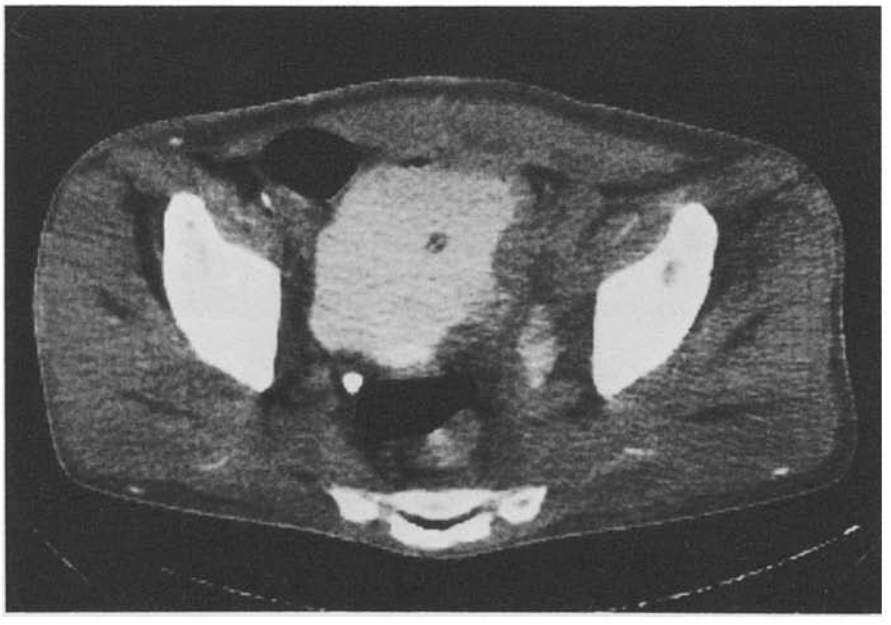

Fig. 7. The CT scan of case 4 after superior gluteal artery infusion chemotherapy showed reduction in the size of the tumor; however, infiltration of urine into the retroperitoneal cavity due to necrosis of the tumor infiltrating into the pelvic wall was observed

Fig. 8. Pretreatment IVP of case 13

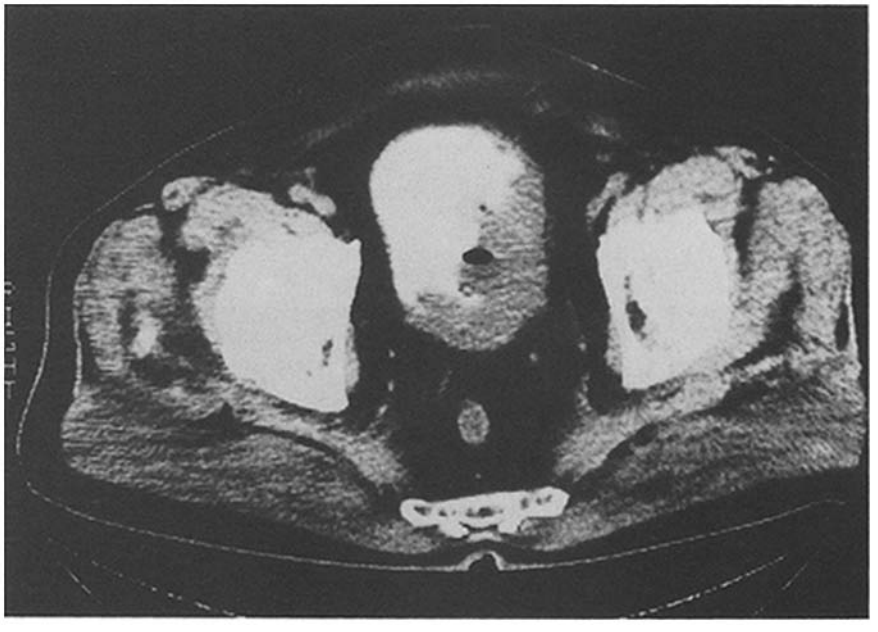

Fig. 9. Pretreatment CT scan of case 13

Discussion

RI angiography revealed that the flow of drug into the bladder upon intra-aortic infusion via the indwelling catheter in the femoral artery was extremely low (Fig. 5). On infusion via the superior gluteal artery some of the drug reached the bladder via the internal iliac artery, but most of it went to the gluteus muscles from the inferior gluteal artery.

We therefore devised this method for very highly selective infusion of anticancer agents via the inferior gluteal artery (Fig. 5).

We examined this method using bleomycin, which was considered to have minimal toxic effects on normal tissue. This study confirmed the safety of the method, but the effectiveness rate was only about 10% according to histological studies. Mitomycin C was also employed but it was observed to damage

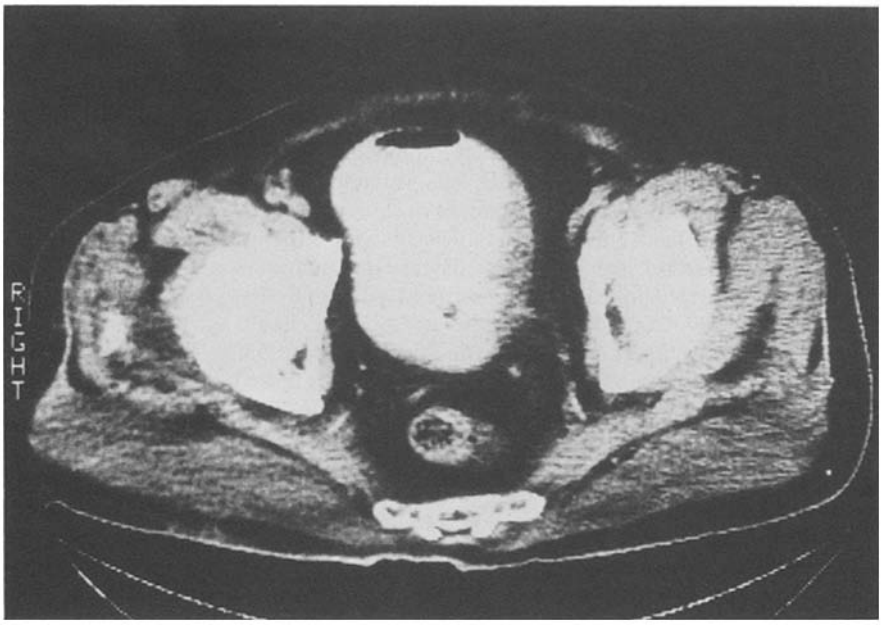

Fig. 10. CT scan of case 13 after 2 months of inferior gluteal artery infusion chemotherapy revealed marked regression of the tumor

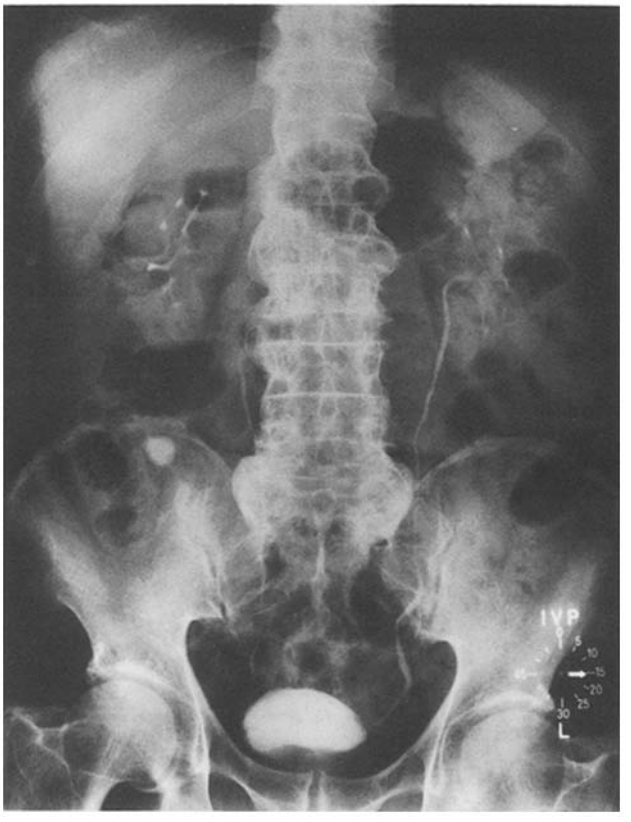

Fig. 11. The IVP of case 13 after 5 months of arterial injection showed marked reduction in tumor size

blood vessels and cause rapid obstruction of the gluteal artery.

It was therefore decided to employ ADM, whose effect is dose-dependent, in this very highly selective intra-arterial injection method for bladder cancer cases of stage T_3 or more according to the UICC classification.

Initially 20 mg ADM was administered thrice weekly but this was reduced to 10 mg once or twice a week, due to the appearance of marked skin erosion in the gluteal region and perineum. With this reduction hardly any significant side-effects appeared, yet significant effectiveness was obtained.

Long-term (e.g., 1 year) intra-arterial infusion chemotherapy with minimal danger of infection was made possible by passing arterial catheters subcutaneously, bringing them out, and fixing them to the anterior thoracic wall. This method demonstrated that it was possible to cure bladder tumors

without surgery or side-effects by long-term administration of anticancer agents. The results indicate that in the future curative treatment of inoperable stage T_4 bladder tumors may be possible if this method is combined with radiotherapy and hyperthermia.

The effectiveness of this method was examined in terms of the tumor reduction rate when it was administered as preoperative chemotherapy for 4–9 weeks in cases in stage T_3 or more: 40% effectiveness was recognized with superior gluteal artery injection. This is not a satisfactory rate, but when inferior gluteal artery injection was performed a rate of 87.5% effectiveness was obtained. This was as good as the results obtained by Jacobs and Lawson [2], who administered ADM through a Harvard pump for 48 h via arterial catheters placed at the trifurcation of the hypogastric arteries distal to the origin of the superior gluteal artery in combination with local bladder hyperthermia.

With bilateral internal iliac artery infusion [6] most of the drug flows out through the superior and inferior gluteal arteries, with the result that effectiveness is low and side-effects frequent.

However, the method proposed in this paper is also not without its drawbacks. One of these is that since the branching of the inferior gluteal artery and internal pudendal artery are extremely close, reflux of most of the drug into the internal pudendal artery, with resultant formation of erosion in the scrotal, rectal, and anal regions and no tumor response, as in case 10, can occur. Also, in the presence of severe arterial sclerosis intra-arterial injection can cause obstruction, with the result that the drug does not reach the tumor, as in case 5. One other point is that the branching of the inferior gluteal artery to the gluteal muscle is proximal to the site at which the catheter is inserted, so that unless it is ligated drug will flow from that bifurcation into the gluteal region, causing skin erosion. It is therefore necessary to evaluate angiogram findings carefully to establish the condition of the vascular branching and confirm the position of the tip of the catheter.

The results suggest that long-term inferior gluteal artery injection chemotherapy with ADM will be possible for curative treatment in the outpatient clinic, without significant side-effects, of bladder cancer in stage T_3 or more. Furthermore, in stage T_4 cases of bladder cancer in which it is necessary to infuse the drug through the internal pudendal artery, it is possible to insert the catheter from the superior gluteal artery, ligate the inferior gluteal artery distal to the vesical artery, and administer long-term intra-arterial infusion, thereby reducing the stage of the disease.

The present study was limited to the effects of this local treatment on the bladder tumor itself. Investigations are in progress to study its effectiveness in combination with systemic therapeutic modalities in cases with distant metastases and its effect on the prognosis of bladder cancer cases.

In conclusion, since favorable local therapeutic effects were obtained in 87.5% cases treated by this modality, the long-term intra-arterial infusion of ADM from the inferior gluteal artery appears to be useful as preoperative treatment in candidates for total cystectomy, and it appears to be the treatment of choice in cases in which surgery is contraindicated due to age or cardiopulmonary disorders.

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