# Distant Metastasis of Urothelial Tumors of the Renal Pelvis and Ureter

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Autopsy reports on urothelial tumors of the renal pelvis and ureter in 602 cases were analyzed to investigate the mode of metastasis. Seventy one cases, or 12%, showed no metastasis. Metastasis-free cases occurred with significantly high frequencies in cases of tumors of the ureter and papillomatosis, and less frequently in squamous cell carcinoma cases and in females. Lymph nodes were the most frequent site of dissemination, especially the retroperitoneal and para-aortic lymph nodes. Metastases to the lungs, peritoneum and ipsilateral adrenal were significantly more frequent in cases of tumors of the renal pelvis than in those of tumors of the ureter. Metastases to the retroperitoneal lymph nodes and peritoneum were frequent in cases with metastasis to one organ. Radical nephrectomy with regional lymphadenectomy and/or radiation therapy is indicated for tumors of the renal pelvis. Palliative surgery or nephroureterectomy with a cuff of bladder wall is indicated for tumors of the ureter or papillomatosis, and radical nephroureterectomy with regional lymphadenectomy and/or radiation therapy in cases where a pronounced tendency of down-growth invasion is suspected.

(Key Words: Kidney, Ureter, Urothelial Tumor, Metastasis)

## INTRODUCTION

It has been reported that the mode of dissemination of urothelial tumors of the renal pelvis and ureter differs from that of renal adenocarcinoma (19). Either simple nephrectomy or nephroureterectomy with a cuff of bladder wall is generally indicated for urothelial tumors of the renal pelvis and ureter, while radical nephrectomy is indicated for renal adeno-carcinoma (19). Johansson has noted, however, that radical nephrectomy is needed even in cases of urothelial tumors on account of the high incidence of local recurrence of the tumors after nephrectomy (9, 10).

The authors have studied the mode of dissemination and the chain of events in metastatic processes of cancer by means of an autopsy survey (13, 14, 15, 16). Cases without organ involvement were classified as those in a relatively early stage, and cases with involvement of more than two organs were classified as those in the advanced or terminal stage. This classification was used to compared the mode of metastasis in the two groups. The methods of treating patients with primary and metastatic lesions are discussed. This report presents results concerning urothelial tumors of the renal pelvis and ureter.

Materials studied were all autopsy cases and it was not known whether

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invasion or metastasis was involved. Metastasis has been used as a general term throughout this paper.

## MATERIALS AND METHODS

Six hundred and two autopsied cases of urothelial tumors of the renal pelvis and ureter recorded in the 1958 to 1979 issues of the Annual of Pathological Autopsy Cases in Japan (8), published by the Japanese Pathological Society, were investigated.

The location of the tumors was the renal pelvis in 194 cases or 32% (hereinafter referred to as pelvic tumors) and the ureter in 178 cases or 30% (ureter tumors). The remaining 230 cases or 38% had multiple lesions in two or more of the organs, i.e. the renal pelvis, ureter and urinary bladder, unilaterally or bilaterally (others). However, no information was available concerning whether the multiple lesions were primary or metastatic based on these materials. There were 26 cases or 4% of combinations of involvements in the unilateral renal pelvis, ureter and bladder (perhaps unilateral papillomatosis). There were 56 cases or 9% of bilateral lesions, including a single case of bilateral papillomatosis.

The case material consisted of 400 males, 201 females and one subject of unknown sex, for a sex ratio of 2:1 (M:F). Cases between 60-69 years of age were the most frequent in the distribution by age in all cases of pelvis, ureter and other tumors (Fig. 1). According to the Annuals' protocol, the location of the tumor was in the left urinary tract in 269 cases or 44%, right in 250 cases or 42%, bilateral in six cases or 1% and unknown in 77 cases or 13%. Therefore, the left to right ratio of tumor incidence was 1.1:1. The incidence of bilateral cases differed from that mentioned above.
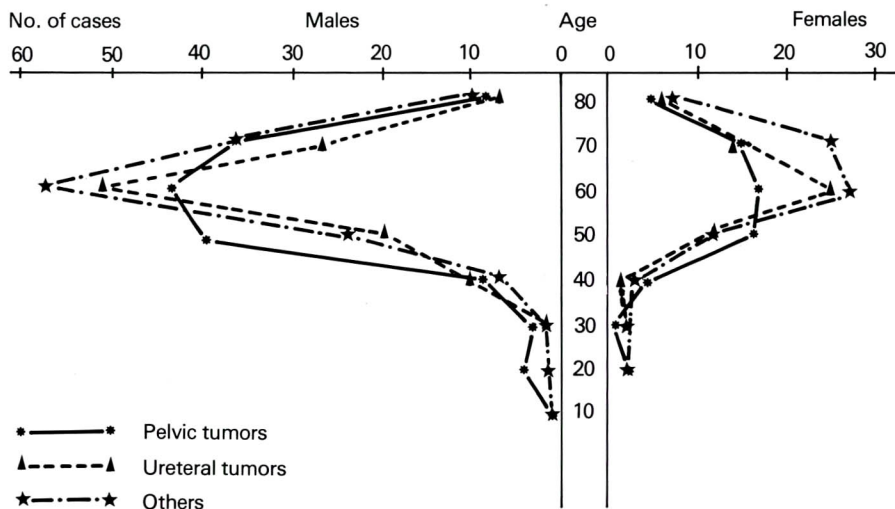


Fig. 1    Age and sex incidences of urothelial tumors of the renal pelvis and ureter

Histologically, tumors were transitional cell carcinomas in 445 cases or 74%, squamous cell carcinomas in 83 or 14%, adenocarcinomas in 15 or 2% and unknown in 59 or 10%. There were no significant differences

in the frequencies of these histological types between pelvic and ureter tumors, and between males and females.

Materials studied were all autopsied cases and no information was available concerning tumor size, number, grade or stage. Also, types and time of surgery perormed were not known.

A comparison was made in frequencies of metastasis in various organs with respect to location of the tumors, histological types, number of organs involved and a history of surgery (chi-square test).

All cases were classified according to the number of organs involved: 0 was observed in 71 cases or 12%, one in 28 cases or 5%, two in 46 cases or 8%, and three or more in 456 cases or 75%.

## RESULTS

1. Seventy one cases or 12% had no metastasis. They were significantly more frequent in cases of ureter tumors and in papillomatosis. The single case with bilateral papillomatosis had no metastasis. However, they were significantly less frequent in squamous cell carcinoma cases and in females (Talbe 1).

2. Lymph nodes especially the retroperitoneal and para-aortic lymph nodes, were the most frequent site of metastasis in both pelvic and ureter tumor cases (Tables 2 and 3)

3. The incidence of metastatic involvement of organs varied among pelvic, ureter and other tumors. In a comparison of incidences between pelvic and ureter tumors, the lung, peritoneum and ipsilateral adrenal were more frequently involved in pelvic tumor cases, whereas the ovaries were not involved in cases of pelvic tumors. Tumor thrombus and brain metastasis were both infrequent (Table 2).

4. Among the lymph node metastasis cases, the inguen was the most frequent site of metastasis in the ureter tumor cases (Table 3).

Table 1    Urothelial tumors of the renal pelvis and ureter

| Urothelial tumors | No. of cases | without metastasis |
|---|---|---|
| Pelvis (P) | 194 | 19 (10) |
| Ureter (U) | 178 | 37 (21)* |
| Others | 230 | 15  (7) |
| P + U | 52 | 3  (5) |
| P + U + Bladder (B) | 26 | 8 (31)* |
| P +    B | 41 | 0 |
| U + B | 55 | 3  (5) |
| Bilateral | 56 | 1  (2) |
| Males | 400 | 55 (14)* |
| Females | 201 | 16  (8) |
| Transitional cell carcinoma | 445 | 53 (12) |
| Squamous cell carcinoma | 83 | 2  (2)* |
| Adenocarcinoma | 15 | 2 (13) |
| Total cases | 602 | 71 (12) |

*$p < 0.05$

**Table 2** Differences in organs involved in metastasis among pelvic, ureter and other tumors

| Metastatic sites | Pelvic T. | Ureter T. | Other | Total |
|---|---|---|---|---|
| Lymph nodes | 144 (82) | 108 (77) | 122 (56)** | 374 (70) |
| Liver | 125 (71) | 89 (63) | 146 (68) | 360 (68) |
| Lungs | 133 (76)** | 82 (58) | 125 (58) | 340 (64) |
| Bones | 75 (43) | 61 (43) | 66 (31)* | 202 (38) |
| Peritoneum | 55 (31)** | 26 (18) | 42 (19) | 123 (23) |
| Intestines | 21 (12) | 28 (20) | 37 (17) | 86 (16) |
| Ipsilateral adrenal | 32 (18)* | 14 (10) | 28 (13) | 74 (14) |
| Contralat. adrenal | 12 (7) | 7 (5) | 15 (7) | 33 (6) |
| Pancreas | 19 (11) | 11 (8) | 28 (13) | 58 (11) |
| Uterus*** | 5 (10) | 9 (10) | 17 (33)** | 31 (17) |
| Heart | 13 (7) | 6 (4) | 7 (3) | |
| Ovaries*** | 0 ** | 11 (13) | 13 (25) | 24 (13) |
| Brain | 6 (3) | 4 (3) | 5 (2) | 15 (3) |
| Tumor thrombus | 9 (5) | 2 (1) | 5 (2) | 16 (3) |
| Total cases with metastasis | 175 | 141 | 216 | 532 |
| Total female cases with metastasis*** | 49 | 84 | 52 | 185 |

*$p < 0.05$, Contralat.: contralateral, T: tumor
**$p < 0.01$, ***: female cases

**Table 3** Metastases to lymph nodes

| Lymph nodes | Pelvic T. | Ureter T. | Others | Total | One organ |
|---|---|---|---|---|---|
| Neck and clavicle | 46 (26) | 31 (22) | 51 (24) | 128 (24) | |
| Trachea | 20 (11) | 19 (13) | 27 (13) | 48 (9) | 1 |
| Hilus of lung | 30 (17) | 18 (13) | 38 (18) | 86 (16) | |
| Mediastinum | 8 (5) | 5 (4) | 12 (6) | 25 (5) | 1 |
| Para-aorta | 48 (27) | 41 (29) | 56 (26) | 145 (27) | |
| Retroperitoneum | 70 (40) | 44 (31) | 63 (29) | 177 (33) | 7 |
| Hilus of liver | 24 (14) | 9 (6) | 21 (10) | 54 (10) | |
| Pancreas | 26 (15) | 16 (11) | 31 (14) | 73 (13) | |
| Mesentery | 14 (8) | 10 (7) | 16 (7) | 40 (8) | 1 |
| Stomach | 6 (3) | 8 (6) | 11 (5) | 25 (5) | |
| Hilus of kidney | 8 (5) | 1 (1) | 4 (2) | 13 (2) | |
| Hilus of spleen | 3 (2) | 1 (1) | 4 (2) | 8 (2) | |
| Inguen | 4 (2) | 13 (9)* | 10 (5) | 27 (5) | |
| Axilla | 2 (1) | 1 (1) | 6 (3) | 9 (2) | |
| Total cases | 175 | 141 | 216 | 532 | 28 |

*$p < 0.05$ T.: tumor

5. Among the bone metastasis cases, no significant difference was seen in frequencies of metastasis among the cases of pelvic, ureter and other tumors (Table 4).

6. In single organ metastasis cases, lymph node metastasis was seen in 36% (10/28), frequently involving in the retroperitoneal lymph nodes (Tables 3 and 5). Peritoneal metastasis was seen in 29% (Table 5).

7. Among 46 cases with metastases to two organs, the retroperitoneal lymph node and liver, and the lung and liver combinations were the most frequent sites of metastasis (six cases or 13% in both cases) (Table 6).

8. The frequency varied depending on the number of organs involved in metastasis. Three basic types of metastases were established (Fig. 2). In Type 1, an increase in metastases was seen in accordance with number of organs involved. Metastases to the liver and lung belonged to this group. In Type 2, the requency was low in cases with metastases to one or two organs but significantly increased when three or more organs were involved. Metastases to the pancreas and ipsilateral adrenal belonged to this group. In Type 3, the frequency of metastasis was not significantly changed regardless of the number of organs involved. Metastases to the retroperitoneal lymph nodes and peritoneum belonged to this group. Metastases to the lymph nodes (overall) and bones (overall) belonged to an intermediate type between Types 1 and 3.

9. Among the histological types, transitional cell carcinomas displayed a significantly higher frequency of metastasis in the liver and pancreas and squamous cell carcinomas a higher frequency in the ipsilateral adrenal and a lower frequency in the lungs (Table 7).

10. A comparison of patients not subjected to surgery and those subjected to surgery showed that metastasis in the peritoneum was significantly more frequent in surgery cases with both ureter and pelvic tumors. Metastasis to the ipsilateral adrenal was more frequent in non-surgical patients with pelvic tumors and to the ovaries in non-surgical patients with ureter tumors (Table 8).

**Table 4**    Metastases to bones

| Bones | Pelvic T. | Ureter T. | Others | Total |
|---|---|---|---|---|
| Skull | 1 | | | 1 |
| Spine | 28 (16) | 36 (25) | 37 (17) | 101 (19) |
| Ribs | 7 (4) | 6 (4) | 6 (3) | 19 (4) |
| Sternum | 4 (2) | 3 (2) | 5 (2) | 12 (2) |
| Pelvis | 3 (2) | 3 (2) | 9 (4) | 15 (3) |
| Scapula | 1 | | | 1 |
| Humerus | | | 1 | 1 |
| Femur | | | 2 (1) | 2 |
| Tibia | 1 | | | 1 |
| Total | 175 | 141 | 216 | 532 |

**Table 5**   Cases with metastasis to one organ

| Metastatic sites | Pelvic T. | Ureter T. | Others | Total |
|---|---|---|---|---|
| Lymph nodes (overall) | 3 | 1 | 6 | 10 (36) |
| Liver | | 1 | 2 | 3 (11) |
| Lungs | 1 | 1 | 1 | 3 (11) |
| Bones | 1 | | | 1 (4) |
| Peritoneum | 3 | 4 | 1 | 8 (29) |
| Pancreas | 1 | | | 1 (4) |
| Pleura | 1 | | | 1 (4) |
| Skin | | 1 | | 1 (4) |
| Total cases | 10 | 8 | 10 | 28 |

T.: tumor

**Table 6**   Combination of metastases in cases with metastases to two organs (46 cases)

| Combination | Liver | Lungs | Lymph nodes | Total |
|---|---|---|---|---|
| Liver | — | 6 | 9 | 22 (48) |
| Lungs | 6 | — | 6 | 19 (41) |
| Lymph nodes (overall) | 9 | 6 | 4* | 21 (46) |
| Retroperitoneum | 6 | 3 | | 12 (26) |
| Hilus of the kidney | 2 | | | 2 |
| Peritoneum | 4 | 2 | | 8 (17) |
| Bones | 2 | 2 | 1 | 5 (11) |

*Clavicle + retroperitoneum 2 cases
 Clavicle + mesentery 1 case
 Para-aorta + retroperitoneum 1 case

**Table 7**   Difference in organs involved in metastasis among histological types

| Metastatic sites | Transitional cell ca. | Squamous cell ca. | Adenocarcinoma |
|---|---|---|---|
| Lymph node | 276 (71) | 55 (68) | 7 (54) |
| Liver | 274 (70)* | 44 (54) | 6 (46) |
| Lungs | 258 (66) | 45 (56)* | 9 (69) |
| Bones | 146 (38) | 30 (37) | 5 (38) |
| Peritoneum | 95 (24) | 18 (22) | 2 (15) |
| Intestines | 64 (16) | 18 (22) | 0 |
| Ipsilateral adrenal | 46 (12) | 17 (21)* | 1 |
| Contralateral adrenal | 20 (5) | 9 (11) | 1 |
| Pancreas | 49 (13)* | 3 (4) | 1 |
| Uterus** | 17 (15) | 5 (21) | 1 |
| Heart | 14 (4) | 8 (10) | 1 |
| Ovaries** | 15 (13) | 5 (21) | 1 |
| Brain | 13 (3) | 2 (2) | 0 |
| Tumor thrombus | 9 (2) | 4 (5) | 0 |
| Total cases with meta. | 389 | 81 | 13 |
| Total female cases with metastasis ** | 114 | 24 | 5 |

*$P < 0.05$, **: female cases, ca.: carcinoma, meta.: metastasis

**Table 8** Difference in organs involved in metastasis between non-surgical and surgical cases

| Metastatic sites | Ureter tumor | | Pelvic tumor | |
|---|---|---|---|---|
| | Non-surgical cases | Surgical cases | Non-surgical cases | Surgical cases |
| Lymph nodes | 60 (78) | 48 (75) | 66 (80) | 78 (85) |
| Liver | 46 (60) | 43 (67) | 59 (71) | 66 (72) |
| Lungs | 43 (56) | 39 (61) | 65 (78) | 68 (74) |
| Bones | 31 (40) | 30 (47) | 36 (43) | 39 (42) |
| Peritoneum | 14 (18) | 22 (34)* | 17 (20) | 36 (39)* |
| Intestines | 11 (14) | 17 (27) | 7 (8) | 14 (15) |
| Ipsilateral adrenal | 9 (12) | 5 (8) | 25 (30)** | 7 (8) |
| Contralat. adrenal | 5 (6) | 2 (3) | 4 (5) | 8 (9) |
| Pancreas | 5 (6) | 6 (9) | 11 (13) | 8 (9) |
| Uterus*** | 5 (15) | 4 (27) | 1 (4) | 4 (13) |
| Heart | 2 (3) | 4 (6) | 7 (8) | 6 (7) |
| Ovaries*** | 10 (29)* | 1 (7) | 0 | 0 |
| Brain | 0 | 4 (6) | 4 (5) | 2 (2) |
| Tumor thrombus | 2 (3) | 0 | 3 (4) | 6 (6) |
| Total cases with metastasis | 77 | 64 | 83 | 92 |
| Total female cases with metastasis*** | 34 | 15 | 28 | 31 |

*p < 0.05 **p < 0.01 ***: female cases
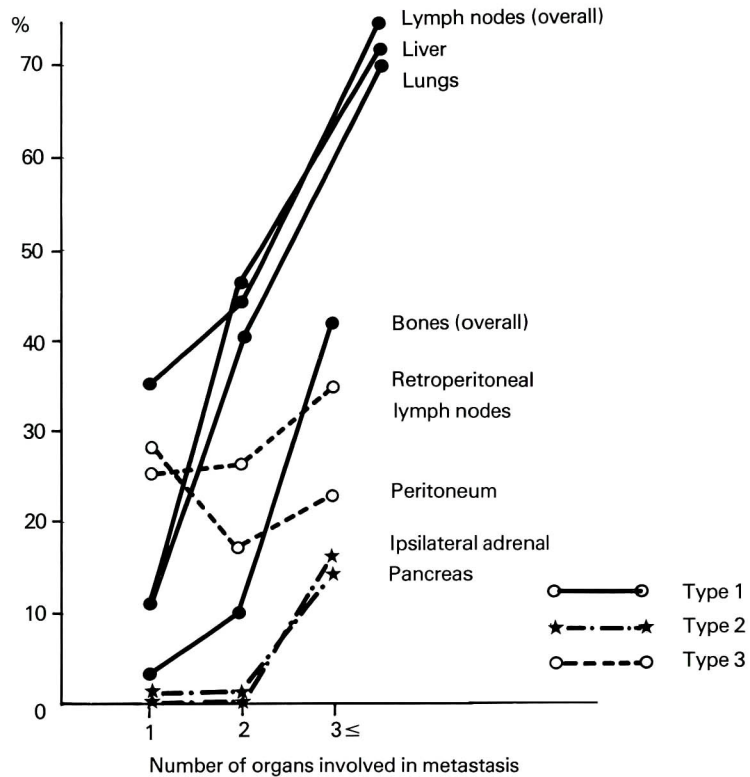


**Fig. 2** Frequency of metastasis in accordance with the increase in the number of organs involved in metastasis

DISCUSSION

It has been reported that urothelial tumors of the urinary tract tend to occur in multiplicity since the urinary tract epithelium is continual from the renal pelvis to the ureter and the bladder (23). Thirty eight percent of the present cases showed multiple involvement in two or more organs among the pelvis, ureter and bladder (others).

Twelve percent of the cases had no metastasis, and this incidence is comparable to that for renal adenocarcinomas (14%) (15). Metastasis-free cases were more frequent in cases of ureter tumors than in cases of pelvic tumors and multiple involvement in two or more organs among the pelvis, ureter and bladder (others). However, in papillomatosis, the rate of metastasis-free cases was significantly higher i.e. as much as 31%. The single case of bilateral papillomatosis was also metastasis-free.

These findings appear to be conflicting, but the high rate of metastasis-free cases in papillomatosis is in no way strange, providing that the multiplicity and down-growth invasion outside of the urinary tract can be interpreted as representing patterns of tumor growth in different directions.

The frequencies of histological types of urothelial tumors of the renal pelvis and ureter in the present series are consistent with the report of Latham (1974) (11). In conformity with reports that the prognosis was unfavorable in squamous cell carcinoma of the renal pelvis and ureter (5, 18, 22), the present group of squamous cell carcinoma cases showed a significantly lower rate of metastasis-free cases, 2%, than that in the transitional cell carcinoma group (12%). In females, metastasis-free cases were less frequent than in males although the reason was not known.

Pelvic tumors showed more frequent metastases to the lung (76%), peritoneum (31%) and ipsilateral adrenal (18%) than ureter tumors. Compared with renal adenocarcinomas, the frequencies of metastases to the lung and ipsilateral adrenal were almost the same (76% and 17%, respectively, in renal adenocarcinoma), but those to the peritoneum were higher, i.e. 31% for pelvic tumors compared with 12% for renal adenocarcinomas (14).

Lymph nodes were the most frequent site of metastasis in all cases with metastasis (70%) and also in cases of single organ involvement (36%), frequently involving the retroperitoneal and para-aortic lymph nodes. The frequency of metastasis to the lymph nodes was higher, i.e. 82% for pelvic tumors compared with 64% for renal adenocarcinomas (14), a significant difference.

In cases with metastasis to one organ, lung and liver metastases were rather infrequent (11% in both cases), but metastasis to the peritoneum was frequent (29%).

In addition to the increase in the number of organs involved in metastasis, the frequency of metastasis to each organ varied. One possible explanation may be that there are three basic different modes of dissemination (14):

1) Invasion of the retroperitoneal lymph nodes and peritoneum. Frequency of the involvement was unchanged in accordance with increases

in the number of organs involved (Type 3). Invasion of these organs does not seem to be correlated with the other organs involved.

2) Metastases to the lung and liver. Metastases to these organs seem to be correlated with the other organs involved. They tend to develop into multiple metastases (Type 1).

3) Metastases to the ipsilateral adrenal and pancreas may involve a multi-step or cascade process (3, 4, 14, 22) (Type 2).

The ipsilateral adrenal was more frequently involved in patients with pelvic tumors, in those not subjected to surgery and in those with squamous cell carcinomas than in those with ureter tumors, in those with pelvic tumors who underwent surgery and in those with transitional cell carcinoma.

The peritoneum showed a higher incidence of metastasis in patients with pelvic tumors and in those subjected to surgery than in those with ureter tumors and in those not subjected to surgery. The influence of the surgery is conceivable, but no confirmation is available.

It has been generally agreed that nephroureterectomy with a cuff of bladder wall is indicated for urothelial tumors of the renal pelvis since they as a rule arise in multiplicity in the urothelium of the urinary tract (2, 6, 17 20), but Johansson has proposed that radical nephrectomy including ipsilateral adrenalectomy is more advisable on accout of the high incidence of local recurrence after nephrectomy (9, 10).

Although cancer in its advanced stage is difficult to cure, patients with metastasis to one organ and occasionally to two organs have a potential indication for surgery and/or radiation therapy for metastatic lesions. Five percent of patients had only one organ involved in metastasis. This fact emphsizes the potential cure of some patients with metastasis by surgery and/or radiation therapy as follows.

Radical nephrectomy with regional lymphadenectomy and/or radiation therapy is considered necessary in patients with pelvic tumors, as in those with renal adenocarcinomas, because of high frequencies of metastases to the retroperitoneal lymph nodes and peritoneum in cases with metastasis to one organ. The authours agree with the view of Johansson in this respect.

Ureter tumors and papillomatosis, on the ohter hand, are relatlively less prone to down-growth invasion than to multiple growth with a high frequency of metastasis-free cases. Palliative or conservative operations or, in cases of multiple lesions or papillomatosis, nephroureterectomy with a cuff of bladder wall should be undertaken (1, 7, 12, 21). Radical nephroureterectomy with regional lymphadenectomy and/or radiation therapy may be necessary in cases where a pronounced tendency of down-growth invasion is suspected.

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