Metastatic Pattern of Bladder Cancer: Correlation With the Characteristics of the Primary Tumor

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OBJECTIVE. The purpose of this study was to evaluate the metastatic pattern of muscle-invasive bladder cancer and to correlate the findings with the characteristics of the primary tumor.

MATERIALS AND METHODS. From a clinic population of 392 patients with muscle-invasive (pT2–4) bladder cancer seen at our institution from January 2004 through December 2009, we studied the cases of 150 consecutively registered patients with pathologically proven metastatic disease. The metastasis-free intervals and metastatic patterns of different T categories were compared by Kruskal-Wallis test and Freeman-Halton extension of Fisher's exact test. Patients were divided into two histologic categories, those with transitional cell carcinoma and those with atypical histologic features. The metastasis-free interval and metastatic pattern of these two groups were compared by Mann-Whitney test and Fisher's exact test.

RESULTS. The study group consisted of 150 patients (116 men [77%], 34 women [23%]; median age, 64 years). The transitional cell carcinoma group consisted of 94 (63%) patients and the atypical histologic features group of 56 (37%) patients. The most common metastatic sites were lymph nodes (104 patients, 69%), bone (71 patients, 47%), lung (55 patients, 37%), liver (39 patients, 26%), and peritoneum (24 patients, 16%). Patients with tumors of a more advanced T category had shorter metastasis-free intervals ($p = 0.001$, $df = 2$). There was no significant difference in the metastatic patterns of tumors in the different T categories. Patients with atypical histologic features had a shorter median metastasis-free interval (3 months; range, 0–29 months) than patients with transitional cell carcinoma (12 months; range, 0–192 months) ($p = 0.0001$). Patients with atypical histologic features had a significantly higher incidence of peritoneal metastasis ($p < 0.0002$).

CONCLUSION. Lymph nodes, bones, lung, liver, and peritoneum are the most common sites of metastasis from bladder cancer. Tumors in a more advanced T category and those with atypical histologic features metastasize earlier. Tumors with atypical histologic features also have a higher frequency of peritoneal metastasis.

Keywords: bladder cancer, metastasis, pattern, transitional cell carcinoma

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Bladder cancer is the most common malignant disease of the urinary tract. An estimated 70,980 new cases of bladder cancer occurred in 2009 in the United States with 14,330 deaths, and the incidence is increasing [1, 2]. Urothelial carcinoma accounts for 90% of cases of bladder cancer in Western countries, and squamous cell carcinoma is the most common bladder cancer in eastern Africa and the Middle East, where schistosomiasis is prevalent [3]. Since the early 1990s, there have been major advances in the management of bladder cancer. Refined imaging has resulted in more accurate staging, and advances in surgical technique have been coupled with improved chemotherapeutic regimens. Bladder cancer is the second most prevalent malignant disease in elderly men owing to smoking and environmental exposures and the propensity of the urothelium for metachronous malignant tumors [1, 4]. Radical cystectomy is the preferred treatment of patients with operable tumors without evidence of metastatic disease. The importance of timely detection of metastatic disease cannot be overemphasized in view of its influence on treatment selection and patient prognosis.

With advances in imaging, earlier detection of recurrent and metastatic disease is possible. However, there are limited data on the metastatic pattern of bladder cancer. Most of the literature on metastasis from bladder cancer is isolated case reports, and most of the larger series are clinical or autopsy based without

detailed imaging findings [5–26]. Our literature search revealed two imaging studies of the metastatic pattern of bladder cancer [27, 28]. The numbers of patients in these studies were relatively small, and the studies were focused on a single imaging technique for detection of metastasis. In contrast, our study had a large number of patients, included all the commonly used imaging techniques, and incorporated clinical and pathologic assessment. To our knowledge, our study is the first in the radiology literature to involve the large patient population of a tertiary cancer center. The purpose of this study was to describe the metastatic pattern of muscle-invasive (pT2–4) bladder cancer at a tertiary cancer institute and to analyze the correlation between metastatic pattern and tumor category and the histologic features at presentation.

Materials and Methods

In this institutional review board–approved HIPAA-compliant retrospective study, we reviewed the medical records of 392 patients with pathologically proven muscle-invasive bladder cancer consecutively registered at our institution from January 2004 through December 2009. The inclusion criterion was the presence of radiologically documented and pathologically proven lymph node or distant metastasis. Demographic data such as age and sex were recorded. The T category and histopathologic subtype of the primary tumor were noted. Category pT2 included tumors invading muscularis propria; T3, tumors with extravesical extension; and T4, tumors invading adjacent organs. Nodal status at presentation also was noted. For patients who underwent cystectomy, the pathologic T category was recorded. For patients who did not undergo surgery, the clinically determined category was recorded. This determination included a combination of clinical assessment, biopsy results, and MRI findings in the pelvis. Patients with multifocal urothelial tumors were included if the most advanced tumor was located in the bladder.

The histopathologic subtypes of bladder cancer included transitional cell carcinoma (TCC), various histologic variants of TCC (tumors with squamous, glandular, or sarcomatoid differentiation and poorly differentiated tumors), squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and undifferentiated carcinoma [29]. Immunohistochemical markers, including CK7 and CK20, were used for diagnosis and were especially useful in the diagnosis of poorly differentiated tumors. Prostate cancer was excluded on the basis of immunohistochemical results (prostate-specific antigen and prostate-specific acid phosphatase reactivity) and clinical features. Patients were divided into two histologic groups; those with TCC and with tumors having atypical histologic features. The TCC group included patients with well-differentiated and moderately differentiated TCC. The atypical histologic features group included patients with the aforementioned histologic variants of TCC, squamous cell carcinoma, adenocarcinoma, small cell carcinoma, and undifferentiated tumors.

A systematic retrospective review of all available CT scans, MR images, and bone scintigraphic scans was performed to determine the sites, number, and imaging features of the metastatic lesions and the presence of local recurrence. The images were reviewed in consensus by three radiologists specialized in cancer imaging. Two radiologists had 5–10 years of experience in cancer imaging, and the third had less than 5 years of experience. The radiologists were aware of the diagnosis of bladder cancer in every case. For confirmation, the radiologically detected metastatic lesions were correlated with the pathology reports and the clinical notes. Poorly differentiated metastatic lesions were included if the immunohistochemical results suggested the tumor represented metastasis from bladder cancer. Only patients with pathologic confirmation of at least one metastatic lesion were included in the study. Other lesions were considered metastatic if they exhibited changes paralleling other pathologically proven metastatic lesions. Any indeterminate lesions were excluded. Lymph nodes measuring more than 1 cm in the short axis were considered abnormal. The distribution of the metastatic sites and the interval from diagnosis to detection of first metastatic lesion (metastasis-free interval) were recorded.

The metastasis-free intervals for different T categories were compared by Kruskal-Wallis test. The metastatic patterns for different T categories were compared by Freeman-Halton extension of Fisher's exact test. The metastasis-free intervals of the two histologic groups (TCC and atypical histologic features) were compared by Mann-Whitney test, and the metastatic patterns were compared by Fisher's exact test. Findings were compared with those in the largest available bladder cancer series, a retrospective review of the clinical findings on 240 patients conducted by Sengeløv et al. and published in 1996 [20] and an autopsy study of 367 patients (251 of whom had metastasis) conducted by Wallmeroth et al. and published in 1999 [19]. Differences in the observed metastatic pattern over time were noted.

Results

The medical records of 392 consecutively registered bladder cancer patients were reviewed. A total of 150 patients (116 men [77%], 34 women [23%]; age range, 32–85 years; median, 64 years; mean, 64.1 years) met the inclusion criteria and were included in our study. Forty-two patients (28%) were younger than 60 years; the other 108 patients (72%) were 60 years old or older. Fourteen patients were younger than 50 years. A history of multiple urothelial malignant disease or multifocal TCC was noted in 24 patients (16%). Eighty-six patients had undergone cystectomy. The other 64 patients underwent chemotherapy with or without radiotherapy. TCC was the most common histologic subtype, present in 94 patients (63%). Forty-three of the 150 patients had T2 tumors; 66 patients, T3; and 41 patients, T4. Forty-seven patients (31%) had positive lymph node results at presentation. The atypical histologic features group comprised 56 patients (37%). Twenty-seven of these patients had poorly differentiated tumors; 10, squamous differentiation; five, squamous cell carcinoma; five, sarcomatoid variant; five, adenocarcinoma; and four patients, small cell carcinoma.

All patients underwent more than one imaging study. In total, images from 812 CT, 273 MRI, and 183 bone scintigraphic examinations were reviewed. Lymph nodes were the most common site of metastasis (104 patients, 69%), followed by bone (71 patients, 47%), lung (55 patients, 37%), liver (39 patients, 26%), and peritoneum (24 patients, 16%). At least one of these five sites was involved in 97% (145/150) of the patients. The sites and frequency of metastatic lesions are shown in Table 1.

Site of Metastatic Lesions

Among patients with lymphadenopathy, pelvic lymphadenopathy was most common, present in 82 patients (55%), followed by retroperitoneal adenopathy in 67 patients (45%) and enlarged intrathoracic nodes in 30 patients (20%). Supraclavicular adenopathy was present in 15 patients (10%). All but two patients with pathologically enlarged mediastinal and supraclavicular nodes had involved lymph nodes in the pelvis or abdomen. Only one patient had cervical adenopathy.

Thirty-three of 71 patients with osseous metastatic lesions (46%) had lytic metastatic lesions; 28 (39%) had sclerotic metastatic lesions; and 10 (14%) had mixed lytic–sclerotic metastatic lesions. Five patients (3% of the total, 7% of those with osseous metastasis) had spinal cord compression due to vertebral fractures or epidural soft tissue secondary to metastatic involvement.

Thirty-five of the 39 patients with hepatic metastasis (90%) had multiple lesions, but

TABLE 1: Sites and Frequency of Metastatic Lesions of Bladder Cancer (*n* = 150)

Site	No.	%
Lymph nodes	104	69
Bone	71	47
Lung	55	37
Liver	39	26
Peritoneum	24	16
Pleura	17	11
Soft tissue	14	9
Adrenal	10	7
Brain	7	5
Urethra, penis	4	3
Intestine	4	3
Spleen	2	1
Pericardium	2	1
Heart	1	< 1
Kidney	1	< 1
Pancreas	1	< 1
Scrotum	1	< 1
Vagina	1	< 1
Ethmoid sinus	1	< 1

only four (10%) had a solitary hepatic metastatic lesion. The hepatic lesions were of low attenuation on CT images in all instances. Two patients with hepatic metastasis (1% of all patients, 5% of those with hepatic metastasis) had portal venous thrombosis. Both of these patients had poorly differentiated tumors.

Solitary or multiple pulmonary nodules were the usual form of pulmonary metastasis, present in 53 of the 55 patients with pulmonary metastasis (96%). The other two patients had consolidation without discrete nodules. Consolidations (eight patients, 15%), lymphangitic carcinomatosis (two patients, 4%), and endobronchial metastasis (one patient, 2%) were the other forms of pulmonary metastasis.

Peritoneal carcinomatosis was present in 24 of the 150 patients (16%). Peritoneal involvement took the form of peritoneal nodules, thickening of the peritoneal folds, peritoneal stranding, serosal metastasis, and ascites. Two patients with peritoneal carcinomatosis (1% of the total, 8% of those with peritoneal involvement) had intestinal obstruction.

Other sites of metastasis were soft tissue including muscle and subcutaneous tissue (14 patients, 9%), the adrenal glands (10 patients, 7%), and brain (seven patients, 5%). The intestine, urethra, pericardium and heart, spleen, pancreas, kidney, scrotum, vagina, and ethmoid sinus were the uncommon metastatic sites. Local recurrence in the pelvis was found in 36 patients (24%).

Metastatic involvement of a single organ site was present in 47 patients (31%). The isolated organs of involvement, in descending order of frequency, were lymph nodes (19 patients, 13%), bone (11 patients, 7%), lung (eight patients, 5%), peritoneum (four patients, 3%), liver (three patients, 2%), and brain (two patients, 1%). Two organs were involved in 35 patients (23%). Three or more sites were involved in 68 patients (45%).

Metastasis-Free Interval

The median metastasis-free interval for the entire study sample was 8 months (range, 0–192 months). For T2 tumors the median interval was 16 months (range, 0–192 months); T3, 8 months (range, 0–73 months); and T4, 4 months (range, 0–37 months). Patients with tumors in the more advanced T categories had shorter metastasis-free intervals (p = 0.001, df = 2, Kruskal-Wallis test). Figure 1 shows the metastasis-free intervals for three T categories and for the two histologic groups. The metastatic patterns of the T categories were compared according to the incidence of involvement of the five most common metastatic sites: lymph nodes, bones, lung, liver, and peritoneum. There was no significant difference in the involvement of these sites with respect to T category.

The median metastasis-free interval was 12 months (range, 0–192 months) for the TCC group and 3 months (range, 0–29 months) for the atypical histologic features group. The metastasis-free interval was significantly shorter for the atypical histologic features group than for the TCC group (p = 0.0001, Mann-Whitney test). The metastasis-free interval of the atypical histologic features group was shorter than that of the TCC group for T2 (p = 0.04) and T3 (p = 0.004) tumors. No statistically significant difference was found for T4 tumors (Fig. 1).

Metastatic Pattern

The difference between the TCC and atypical histologic features groups with respect to metastatic pattern was determined by comparing the number of metastatic sites and the incidence of involvement of the five most common metastatic sites. There was no significant difference in mean number of metastatic sites of TCC or tumors with atypical histologic features (TCC, 2 sites; atypical histologic features, 3 sites). Lymph nodes, bones, and lung were the three most common sites of metastasis in both groups. The fourth most common metastatic site was liver for the TCC group and peritoneum for the atypical histologic features group. No significant difference was found between the TCC and atypical histologic features groups in incidence of involvement of lymph nodes, bone, lung, and liver. The incidence of peritoneal involvement, however, was significantly higher for the atypical histologic features group than for the TCC group (p < 0.0002, Fisher's exact test) (Table 2). There was no significant difference between the rate of local recurrence of TCC and that of tumors of atypical histologic features.

Importance of Peritoneal Involvement

In further evaluation of the influence of peritoneal involvement, metastasis-free interval and the number of metastatic sites in all the patients with peritoneal involvement were compared with those of the patients without peritoneal involvement. The metastasis-free interval of the patients with peritoneal involvement (median, 2 months;

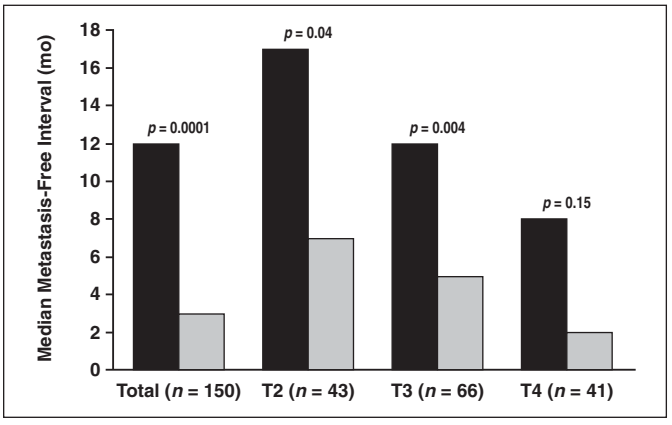

Fig. 1—Graph shows statistical association between metastasis-free interval and T category of transitional cell carcinoma (*dark gray*) and tumors with atypical histologic features (*light gray*).

TABLE 2: Comparison of Metastatic Pattern of Transitional Cell Carcinoma and Tumors With Atypical Histologic Features

Site	Transitional Cell Carcinoma (n = 94)	Atypical Histologic Features (n = 56)	p[a]
Lymph nodes	66	38	0.76
Bone	46	25	0.61
Lung	33	22	0.60
Liver	25	14	0.83
Peritoneum	6	18	< 0.0002

[a]Fisher's exact test.

range, 0–28 months) was significantly shorter than that of patients without peritoneal involvement (median, 10 months; range, 0–192 months) (p = 0.003, Mann-Whitney test). The number of metastatic sites also was higher among patients with peritoneal involvement (mean, 4 sites) than patients without peritoneal involvement (mean, 2 sites) (p = 0.0002, Mann-Whitney test).

Discussion

Bladder cancer is commonly a disease of older age and is more prevalent among men than women. It is one of the most common malignant diseases, and data on its metastatic pattern are limited. Timely detection of metastasis is important for appropriate treatment. Bladder cancer has variable metastatic potential, and almost any organ can be involved by metastasis. In our study, lymph nodes, bones, lungs, liver, and peritoneum were the most common sites of metastasis from bladder cancer. Only five patients (3%) had metastatic disease elsewhere without metastasis at one of these five sites.

The lymph nodes are the most common site of metastasis from bladder cancer. Identification of nodal involvement is important because the presence of nodal metastasis advances the disease to stage IV. We found a sequentially decreasing incidence of involvement of more distant nodes. In our study, the intrathoracic and supraclavicular lymph nodes were rarely involved in the absence of pelvic and abdominal adenopathy. Pelvic and abdominal lymphadenopathy therefore should always be carefully excluded. It can also be postulated that prominent thoracic or supraclavicular lymph nodes in the absence of pelvic or abdominal adenopathy are less likely to represent metastatic disease. Although it does not hold in every case, this postulate can be a useful guide in the care of patients with equivocal enlargement of more distant nodes, which is a common challenge faced by radiologists.

Bone was the most common site of distant metastasis in our study. In previous studies liver [19] and lungs [27] were identified as the most common sites of distant metastasis. The higher incidence of osseous metastasis in our study might have been due to the higher sensitivity of bone scintigraphy and MRI in the detection of osseous metastasis. The higher incidence also may be partly related to the overall longer survival time, even in advanced disease, due to improved management.

Pulmonary nodules are the most common form of pulmonary metastasis, followed by consolidation. Lymphangitic spread and endobronchial metastasis may occasionally be seen. Bladder cancer usually involves multiple hypoattenuating hepatic metastatic lesions. Peritoneal involvement was seen in the form of peritoneal nodules, thickening of the peritoneal folds, peritoneal stranding, serosal metastasis, and ascites. Other common metastatic sites included soft tissue, the adrenal glands, and the brain, although almost any organ can be involved. Most of the patients in this study (69%, 103/150) had more than one organ involved.

We compared our findings with those of the most extensive clinical study, to our knowledge, of the metastatic pattern of urothelial cancer. In that study, Sengeløv et al. [20] studied clinical data from 1976 to 1991. Chest radiographs were used to detect pulmonary metastasis and bone radiographs to detect skeletal metastasis. Compared with those findings, our study showed a higher incidence of metastasis at all sites (Table 3). Sengeløv et al. noted that 20% of patients had three or more metastatic sites; we found that 45% of patients had three or more sites of metastasis. These differences are indicative of our improved ability to detect metastasis as a result of advances in imaging. Compared with that of Wallmeroth et al. [19], our study showed a lower incidence of metastasis at almost all sites (Table 3). However, Wallmeroth et al. conducted an autopsy study. The differences in the findings can be explained in part by the fact that imaging techniques do not depict metastatic lesions at a very early stage and in part by the use of autopsy findings to describe the status of metastasis at a more advanced stage, the end of life.

We used nonparametric tests for statistical analysis of the metastasis-free interval to avoid the influence of few outlying values. Our sample size was large enough for detection of statistically significant differences, even with nonparametric tests. The metastasis-free interval was progressively shorter for tumors in more advanced T categories (Fig. 1). We did not find differences in the metastatic patterns of tumors of different T categories. This result is consistent with the theory that the metastatic potential of bladder cancer depends on the presence or absence of certain biologic properties, such as expression of certain genes and proteins, including p53, the insulinlike growth factor binding protein 2 gene, E-cadherin, and Bcl-2. In addition, tumors with metastatic potential usually metastasize early in the clinical course [19, 30–33].

It is not clear whether the prognosis of the tumors with atypical histologic features is different from that of pure TCC. Previous studies have had conflicting results [19, 34]. We found that tumors with atypical histologic features metastasized earlier than did TCC. This difference also was noted for T2 and T3 tumors (Fig. 1). Compared with TCC, tumors with atypical histologic features are significantly more likely to have peritoneal metastasis (p < 0.0002, Fisher's exact test).

TABLE 3: Comparison of Findings With Those of Previous Studies

Site	Current Study	Wallmeroth et al. [19]	Sengeløv et al. [20]
Lymph nodes	69	90	26
Bone	47	32	35
Lung	37	45	20
Liver	26	47	13
Peritoneum	16	19	NA

Note—Values are percentages. NA = data not available.

We tried to determine which subset of tumors with atypical histologic features accounted for the higher incidence of peritoneal carcinomatosis. We found that 18% (27/150) of patients had poorly differentiated tumors. We believe these tumors caused the observed difference between the metastatic patterns of TCC and the tumors of atypical histologic features. When we combined the poorly differentiated tumors with the TCCs, as was done in some previous studies [19], we found no difference in the incidence of peritoneal metastasis. We then separately compared the poorly differentiated tumors and tumors with other atypical histopathologic subtypes with the TCCs. Both of these subgroups of atypical histologic features, even separately, had a higher incidence of peritoneal carcinomatosis than did the TCC group (poorly differentiated tumors, $p < 0.0002$; other atypical tumors, $p = 0.02$). This finding indicates that all the tumors with atypical histologic features, especially poorly differentiated tumors, have a predilection to peritoneal carcinomatosis. We believe that the poorly differentiated tumors account for the conflicting results between our study and some previous studies.

The clinical significance of peritoneal involvement is that patients with peritoneal carcinomatosis tend to have a shorter metastasis-free interval (median, 2 months). Another clinical significant factor is that patients with peritoneal involvement probably are more prone to development of intestinal obstruction. In our study, two patients had intestinal obstruction; both had peritoneal carcinomatosis. There was no significant difference in the incidences of metastasis at other sites, that is, lymph nodes, bones, lungs, and liver. We found a much smaller incidence of intestinal and renal metastasis than that reported in the most extensive autopsy study [19]. Our finding suggests that these metastatic lesions are not being effectively detected at imaging.

The limitations of our study were the retrospective design and the selection of patients from a tertiary cancer center, who may differ from patients treated in a community hospital. This bias was the reason we did not calculate the overall incidence of metastasis to individual sites and instead used all patients with bladder cancer as the denominator. In this study, all the tumors with atypical histologic features were grouped together because the numbers of individual atypical histopathologic subtypes were small, and meaningful comparison between them was not possible. It is possible that there are differences in the behavior of these subtypes, and studies with larger samples are needed to identify these differences, if any. To our knowledge, ours is the first large-sample study in the radiology literature in which the metastatic pattern of bladder cancers and the clinical and pathologic correlations are described in detail.

Bladder cancer is a common malignant disease, and radiologists should be familiar with the common and uncommon sites of metastasis. Detection of metastasis is important to guide appropriate treatment selection and has a marked influence on prognosis. Lymph nodes, bones, lungs, liver, and peritoneum are the most common metastatic sites. Most patients have more than one site of metastasis, and almost any organ can be involved. Advances in imaging and longer survival are the reasons for the higher rate of detection of metastasis at all sites compared with published results in the literature. Of note, the incidence of osseous metastasis was even higher than previously reported, and patients with tumors in a more advanced T category had shorter metastasis-free intervals. We found that tumors with atypical histologic features had a more aggressive phenotype and a shorter metastasis-free interval and predilection for peritoneal involvement. Patients with peritoneal involvement, irrespective of the histologic features of the tumor, had a shorter metastasis-free interval and have multiorgan involvement.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; 59:225–249
2. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005; 55:10–30
3. Ghoneim MA, el-Mekresh MM, el-Baz MA, el-Attar IA, Ashamallah A. Radical cystectomy for carcinoma of the bladder: critical evaluation of the results in 1,026 cases. *J Urol* 1997; 158:393–399
4. Vercelli M, Quaglia A, Parodi S, Crosignani P. Cancer prevalence in the elderly. ITAPREVAL Working Group. *Tumori* 1999; 85:391–399
5. Hadzi-Djokić J, Pejcić T, Aćimović M, Andrejević V, Radosavljević R. Penile metastasis from invasive bladder cancer. *Acta Chir Iugosl* 2009; 56: 101–103
6. Zennami K, Yamada Y, Nakamura K, Aoki S, Taki T, Honda N. Solitary brain metastasis from pT1, G3 bladder cancer. *Int J Urol* 2008; 15:96–98
7. Bonnin N, El Karak F, Droz J, Flechon A. Pleural metastasis in a patient with bladder cancer. *J Clin Oncol* 2008; 26:329–330
8. Perlmutter AE, Zaitoon A, Sparks SS, Zaslau S, Zaitoon M. Isolated cerebellar metastasis in a patient with organ-confined, lymph node negative bladder cancer. *W V Med J* 2006; 102:14–15
9. Pascual I, Alvarez-Gallego M, Herreros MD, Garcia-Olmo D, García-Fernández E. Metastasis in anal mucosa from bladder cancer. *Tech Coloproctol* 2006; 10:255
10. Ishii Y, Itoh N, Takahashi A, Masumori N, Ikeda T, Tsukamoto T. Bladder cancer discovered by ovarian metastasis: cytokeratin expression is useful when making differential diagnosis. *Int J Urol* 2005; 12:104–107
11. Petković M, Muhvić D, Zamolo G, et al. Metatarsal metastasis from transitional cell cancer of the urinary bladder. *Coll Antropol* 2004; 28:337–341
12. El-Tabey NA, Shoma AM. Port site metastases after robot-assisted laparoscopic radical cystectomy. *Urology* 2005; 66:1110
13. Breul J, Block T, Breidenbach H, Hartung R. Implantation metastasis after a suprapubic catheter in a case of bladder cancer. *Eur Urol* 1992; 22:86–88
14. Kawamura J, Tsukamoto K, Yamakawa K, Tazima K, Tochigi H. Diabetes insipidus due to pituitary metastasis from bladder cancer. *Urol Int* 1991; 46:217–220
15. Fujita K, Sakamoto Y, Fujime M, Kitagawa R. Two cases of inflammatory skin metastasis from transitional cell carcinoma of the urinary bladder. *Urol Int* 1994; 53:114–116
16. Gordon HL, Munro R. Ocular metastasis of bladder cancer. *South Med J* 1974; 67:745–746
17. Spiliotopoulos K, Argiriou M, Argyrakos T, et al. Solitary metastasis of urothelial carcinoma of the urinary bladder to the heart: an unusual clinical manifestation. *J Thorac Cardiovasc Surg* 2008; 136:1377–1378
18. Babaian RJ, Johnson DE, Llamas L, Ayala AG. Metastases from transitional cell carcinoma of urinary bladder. *Urology* 1980; 16:142–144
19. Wallmeroth A, Wagner U, Moch H, Gasser TC, Sauter G, Mihatsch MJ. Patterns of metastasis in muscle-invasive bladder cancer (pT2–4): an autopsy study on 367 patients. *Urol Int* 1999; 62:69–75
20. Sengeløv L, Kamby C, von der Maase H. Pattern of metastases in relation to characteristics of primary tumor and treatment in patients with disseminated urothelial carcinoma. *J Urol* 1996; 155: 111–114
21. Friedell GH, Mcauley RL. Untreated bladder cancer: 31 autopsy cases. *J Urol* 1968; 100:293–296
22. Taher AN, Kotb MH. Bone metastases in muscle-invasive bladder cancer. *J Egypt Natl Canc Inst* 2006; 18:203–208
23. Maltry E Jr. Carcinoma of the bladder. *J Urol* 1968; 99:165–171
24. Fetter TR, Bogaev JH, McCuskey B, Seres JL.

Carcinoma of the bladder: sites of metastases. *J Urol* 1959; 81:746–748
25. Sternberg CN, Yagoda A, Scher HI, et al. Methotrexate, vinblastine, doxorubicin, and cisplatin for advanced transitional cell carcinoma of the urothelium: efficacy and patterns of response and relapse. *Cancer* 1989; 64:2448–2458
26. Loehrer PJ, Einhorn LH, Elson PJ, et al. A randomized comparison of cisplatin alone or in combination with methotrexate, vinblastine, and doxorubicin in patients with metastatic urothelial carcinoma: a cooperative group study. *J Clin Oncol* 1992; 10:1066–1073
27. Goldman SM, Fajardo AA, Naraval RC, Madewell JE. Metastatic transitional cell carcinoma from the bladder: radiographic manifestations. *AJR* 1979; 132:419–425
28. Ellis JH, McCullough NB, Francis IR, Grossman HB, Platt JF. Transitional cell carcinoma of the bladder: patterns of recurrence after cystectomy as determined by CT. *AJR* 1991; 157:999–1002
29. National Comprehensive Cancer Network Website. NCCN Clinical Practice Guidelines in Oncology. www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed March 18, 2010
30. Ehdaie B, Smith SC, Theodorescu D. Personalized medicine in advanced urothelial cancer: when to treat, how to treat and who to treat. *Can Urol Assoc J* 2009; 3:S232–S236
31. Miyake H, Hara I, Yamanaka K, Muramaki M, Gleave M, Eto H. Introduction of insulin-like growth factor binding protein-2 gene into human bladder cancer cells enhances their metastatic potential. *Oncol Rep* 2005; 13:341–345
32. Pasqualini ME, Heyd VL, Manzo P, Eynard AR. Association between E-cadherin expression by human colon, bladder and breast cancer cells and the 13-HODE:15-HETE ratio: a possible role of their metastatic potential. *Prostaglandins Leukot Essent Fatty Acids* 2003; 68:9–16
33. Miyake H, Hara I, Yamanaka K, Gohji K, Arakawa S, Kamidono S. Overexpression of Bcl-2 enhances metastatic potential of human bladder cancer cells. *Br J Cancer* 1999; 79:1651–1656
34. Scosyrev E, Yao J, Messing E. Urothelial carcinoma versus squamous cell carcinoma of bladder: is survival different with stage adjustment? *Urology* 2009; 73:822–827