The case for conservative management in the treatment of patients with non-muscle-invasive micropapillary bladder carcinoma without carcinoma in situ

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GAYA JM, PALOU J, ALGABA F, ARCE J, RODRIGUEZ-FABA O, VILLAVICENCIO H. The case for conservative management in the treatment of non-muscle-invasive micropapillary bladder carcinoma without carcinoma in situ. The Canadian Journal of Urology. 2010;17(5):5370-5376.

Introduction: *Micropapillary carcinoma is a rare pathologic variant of urothelial cell carcinoma. Intravesical bacillus Calmette-Guérin (BCG) has been reported to be ineffective and to entail an increased risk of development of non-organ-confined, metastatic disease.*

We assess the treatment response and disease progression in patients with micropapillary carcinoma of the bladder.

Materials and methods: *The study comprised 18 patients with micropapillary carcinoma of the bladder who underwent transurethral resection of a bladder tumor and multiple random biopsies between 1997 and 2003.*

We retrospectively analyzed treatment response and clinical and pathological cancer evolution related to cancer stage and the percentage of the micropapillary component of the cancer.

Results: *Seven of the 18 patients (38.8%) had carcinoma in situ. At diagnosis, 8 of the 18 patients had non-muscle-invasive bladder cancer; 6 of these patients were treated with intravesical BCG therapy and were alive and free of disease at a median follow up of more than 5 years. Ten of the 18 patients had muscle-invasive bladder cancer; 8 of these patients underwent radical cystectomy, and 7 of the 8 patients (87.5%) had non-organ-confined disease in cystectomy specimens. Seventy percent of patients with muscle-invasive disease at diagnosis had a micropapillary carcinoma component of more than 50% in transurethral resection of the bladder specimens, compared with only 25% of patients with non-muscle-invasive disease. Patients treated successfully with intravesical BCG therapy had a low micropapillary carcinoma component. The 5-year disease-specific survival rate was significantly lower in patients with muscle-invasive disease (30%) than in patients with non-muscle-invasive disease (87.5%) after a median follow up of 52 months ($p = 0.001$), and it was also significantly lower in patients with a high percentage of the micropapillary component of the carcinoma.*

Conclusions: *This retrospective study of 18 patients with micropapillary carcinoma of the bladder suggests that tumor stage and patient outcome may be related to the percentage of the micropapillary component of the carcinoma. Radical surgery is mandatory in muscle-invasive disease, even though patients with lymph node involvement die from the disease. In non-muscle-invasive disease and in the absence of associated carcinoma in situ, intravesical BCG treatment may be offered when the micropapillary component of the carcinoma component is a small percentage.*

Key Words: micropapillary, bladder neoplasms, muscle-invasive, intravesical, management, treatment

Introduction

Micropapillary carcinoma is an uncommon pathologic variant of urothelial cell carcinoma that was first described by Amin et al in 1994.[1] This carcinoma variant has been identified in other anatomic sites, including the breast, the lung, major salivary glands, and, recently, the ureter.[2,3] It is often associated with other histologic types of cancer that are present in different proportions.[4-6] It has been suggested that the percentage of the micropapillary carcinoma component of a tumor may be a prognostic risk factor.[5] The incidence of micropapillary bladder cancer

Accepted for publication July 2010

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ranges from 0.7% to 2.2%, and it usually presents as a high-grade, aggressive tumor.[4,6] It does not differ clinically from normal transitional cell carcinoma, with hematuria being the most common primary symptom.[6] Because of the low incidence of micropapillary carcinoma, few reports of cases have been published, and at present, the optimal treatment strategy for this rare tumor remains controversial.

It has been suggested that in patients with micropapillary carcinoma and non-muscle invasive disease, intravesical therapy with bacillus Calmette-Guérin (BCG) is ineffective, and instead, radical cystectomy is advocated.[7] In patients with muscle-invasive disease, micropapillary carcinomas are aggressive, and most patients die from the disease.[6]

This study aimed to evaluate treatment response and cancer progression in patients with a histological pattern of micropapillary bladder cancer, and to determine the effect of cancer stage, micropapillary carcinoma percentage, and treatment type.

Materials and methods

Institutional review board approval was obtained to search hospital records to find patients with micropapillary bladder cancer who had been treated at our institution. We found that 18 patients with micropapillary cancer had been treated between January 1997 and January 2003. All of the patients had been diagnosed after transurethral resection of the bladder and multiple random biopsies. Patients were considered to have micropapillary bladder cancer if review of pathological material from transurethral resection at our institution revealed any micropapillary carcinoma component in the tumor.

Patient records were retrospectively reviewed for demographic and clinical characteristics, tumor pathological characteristics, treatment type, and cancer progression. The tumor's clinical stage at patient presentation and the pathological stage at cystectomy were classified according to the 2002 tumor, node, metastasis (TNM) system and were graded according to the 2004 World Health Organization (WHO) system by reviewing the radiological, pathological, and surgical reports. In the pathological review, we specifically analyzed the percentage of the micropapillary carcinoma component. Tumors were stratified according to the classification of Samaratunga et al,[8] which is based on the extent of the micropapillary carcinoma component: < 10% is a focal tumor; 10%-49% is moderate micropapillary carcinoma; and > 50% is extensive micropapillary carcinoma.

Survival times were measured from the date of diagnosis to the date of death or last follow up. Survival analysis was performed using the Kaplan-Meier test. The Wilcoxon rank sum test and Fisher's exact test were used to test for statistical differences between continuous variables and between categorical variables, respectively. All p values were two-sided, and statistical significance was set at $p < 0.05$. Analyses were performed using SPSS statistical software, version 13.0.

Results

Clinical presentation, diagnosis, and pathological findings

The study population consisted of 16 males and 2 females. Table 1 provides the baseline characteristics of the patients. The mean patient age was 63 years (range, 46 to 82 years). The primary symptom of the bladder carcinoma was hematuria in 15 of the 18 patients (83%) and irritative voiding symptoms in 2 patients. In one patient, the carcinoma was diagnosed incidentally from ultrasonography performed because of abdominal pain. The tumors were primary tumors in 17 patients, and one patient had been treated before for a T1G2 urothelial carcinoma. In the surgical reports of transurethral bladder resection, 15 cases were described as a single lesion, and 67% of the tumors exceeded 3 cm in diameter.

TABLE 1. **Patient characteristics at baseline**

Characteristic	Number of patients	%
Sex		
Male	16	89
Female	2	11
No. of lesions		
Single	15	83
Multiple	3	17
Tumor size		
> 3 cm	12	67
< 3 cm	6	33
Clinical stage		
Non-muscle-invasive	8	45
Ta	1	6
T1	7	39
Muscle-invasive	10	55
T2	8	44
T3	2	11
Associated carcinoma in situ	7	39

TABLE 2. **Micropapillary carcinoma component of the tumors of the 18 study patients**

Micropapillary carcinoma component	Number of patients	%
Non-muscle-invasive carcinoma		
< 10%	1	12.5
10%-50%	5	62.5
> 50%	2	25
Muscle-invasive carcinoma		
< 10%	1	10
10%-50%	2	20
> 50%	7	70

At presentation, 8 patients had non-muscle-invasive disease, and 3 of these patients had associated multiple carcinoma in situ. The remaining 10 patients had muscle-invasive disease; 4 of these patients had associated carcinoma in situ, and 1 patient had enlarged lymph nodes, seen on a CT scan.

All tumors were high grade (according to the 2004 World Health Organization [WHO] classification) and only 2 were G2 tumors (according to the 1973 WHO classification).

All tumors had a mixed micropapillary carcinoma growth pattern with a variable component of conventional carcinoma. An extensive micropapillary carcinoma component was evident in 70% of patients with muscle-invasive disease and in 25% of patients with non-muscle-invasive disease, Table 2.

Treatment and evolution

Non-muscle invasive disease, Table 3a

Three patients with non-muscle-invasive disease had associated multiple carcinoma in situ. Two patients underwent cystectomy. In one of these two cases the pathology was pT1b high grade + carcinoma in situ; this patient is alive at almost 3 years of follow up. In the other case, the pathology was pT2 high grade + carcinoma in situ; this patient died within 4 years, although not of bladder cancer. The third patient received intravesical BCG therapy with no maintenance therapy and is alive, without recurrences, at 6 years of follow up.

Five patients with non-muscle-invasive disease and without carcinoma in situ were treated with 81 mg Connaught BCG intravesically each week for 6 weeks, with no maintenance therapy. None of these patients had disease progression, and only 2 of them had recurrences. In one case, three recurrences (low-grade urothelial cell carcinoma) were well controlled with intravesical instillations of mitomycin C and BCG. In the other case there were two recurrences, one of them high-grade urothelial cell carcinoma that also responded to BCG therapy. The 5 patients are alive and free of disease at a median of 59 months of follow up (range, 34 to 91 months). Of these 5 patients, only one had an extensive micropapillary carcinoma component in a specimen obtained from tumor transurethral resection of the bladder; the other 4 patients had a tumor with a micropapillary carcinoma component of less than 50%.

TABLE 3a. **Pathological characteristics, initial therapy, survival, and percentage of micropapillary carcinoma in patients with non-muscle-invasive disease**

Clinical stage	Treatment	Pathological stage	Follow up	MPC %
T1HG + multifocal CIS	BCG		Alive at 72 mo	100
T1HG + multifocal CIS	RC	pT1bHGN0 + CIS	Alive at 34 mo	20
T1HG + multifocal CIS	RC	pT2HGN0 + CIS	Died in 43 mo	40
T1HG	BCG		Alive at 91 mo+	30
T1HG	BCG		Alive at 47 mo	10
TaHG	BCG		Alive at 34 mo*	60
T1HG	BCG		Alive at 82 mo	40
T1HG	BCG		Alive at 59 mo*	30

+Recurrent tumor, previously CCT G2T1
*Presented recurrences, without progression; well controlled with intravesical treatments
BCG = bacillus Calmette-Guérin; HG = high-grade; RC = radical cystectomy; mo = months
MPC % = percentage of micropapillary component in the TURB specimen
TURB = transurethral resection of bladder tumor

Muscle-invasive disease, Table 3b

Eight patients with muscle-invasive disease underwent radical early cystectomy. Seven of them had non-organ-confined disease (> pT2, or positive nodes at lymphadenectomy). All patients with positive lymph nodes despite adjuvant chemotherapy died within 3 years. Of the patients with negative nodes, one died at 66 months from metastatic disease diagnosis and the remaining 3 patients are still alive at 3, 5, and 7 years of follow up.

Two of the patients in the muscle-invasive-disease group did not undergo cystectomy: one because we found positive nodes on the CT scan and the other because of refusal of radical surgery. Both were treated with chemotherapy and radiotherapy but died at 17 and 18 months.

Seven of the 10 patients (70%) who underwent radical surgery had non-organ confined disease in the cystectomy specimen. Of these 7 patients, 6 patients (85.7%) were found to have an extensive micropapillary carcinoma component at prior transurethral resection of bladder tumor. In the group with organ-confined disease, none of the 3 patients had an extensive micropapillary carcinoma component at prior transurethral resection of bladder tumor. With a cut-off value of a 50% micropapillary carcinoma component, there were significant differences between patients with organ-confined disease and patients with non-organ-confined disease ($p = 0.03$).

Survival results

At a median follow up of 52 months (95% CI, 10 to 98 months) from diagnosis of micropapillary carcinoma, 8 of 18 patients (44.4%) had died and 7 of 18 patients (38.9%) had no evidence of disease. In 7 of the 8 patients who died (87.5%) the cause of death was bladder tumor. Seven of 10 patients (70%) with muscle-invasive disease died, and in all these patients the cause of death was bladder tumor. No patient with non-muscle-invasive disease died because of bladder cancer.

Six of the 7 patients who died because of bladder cancer (85.7%) had a micropapillary carcinoma component > 50% in the transurethral resection of the bladder tumor specimen, Figure 1; the seventh patient had a moderate micropapillary carcinoma component of 10%-50%. Neither of the 2 patients (out of the 18 patients) with a focal micropapillary carcinoma component < 10% died.

Of the 5 patients with non-muscle-invasive disease and without carcinoma in situ who were treated successfully with BCG therapy, only 1 of 5 patients (20%) had an extensive micropapillary carcinoma component.

Overall, the 5-year, disease-specific survival rate was 65.4%. The 5-year, disease-specific survival rate was significantly lower in patients with muscle-invasive disease (30%) than in patients with non-muscle-invasive disease (87.5%), after a median follow up of 52 months ($p = 0.001$), as shown in Figure 2. The 5-year,

TABLE 3b. **Pathological characteristics, initial therapy, survival, and percentage of micropapillary carcinoma in patients with non-muscle-invasive disease**

Clinical stage	Treatment	Pathological stage	Follow up	MPC %
T2bHG	CT + RT		Died at 17 mo	100
T2aHG	CT + RT		Died at 18 mo	20
T3aHG	RC	pT3HGN2 + CIS	Died at 35 mo	80
T2aHG + CIS	RC	pT3aHGN2 + CIS	Died at 16 mo	100
T3bHG	RC	pT3bHGN1	Died at 10 mo	100
T2aHG	RC	pT3HGN0	Died at 66 mo	90
T2bHG + CIS	RC	pT3HGN0	Alive at 63 mo	90
T2aHG + CIS	RC	pT2HGN1	Died at 28 mo	80
T2aHG + CIS	RC	pT3aHGN0	Alive at 96 mo	20
T2aHG	RC	pT0N0	Alive at 36 mo	10

HG = high-grade; RC = radical cystectomy; mo = months
MPC % = percentage of micropapillary component in the TURB specimen
TURB = transurethral resection of the bladder tumor
CT = chemotherapy; RT = radiotherapy

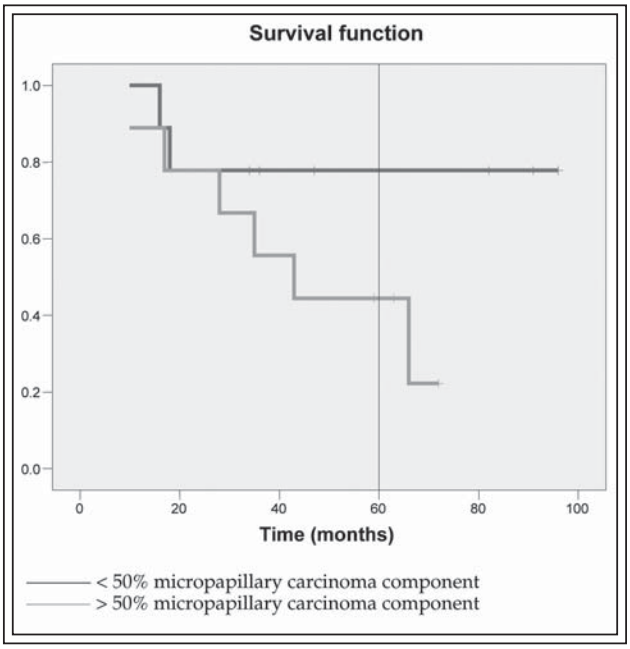

Figure 1. Disease-specific survival according to a cut-off value of 50% for the micropapillary carcinoma component.

disease-specific survival rate was also significantly lower in patients with an extensive micropapillary carcinoma component (33.3%) in the transurethral resection of bladder tumor specimen than in the two groups of patients with a moderate micropapillary carcinoma component (71.4%) or a focal micropapillary carcinoma component (100%), p = 0.025.

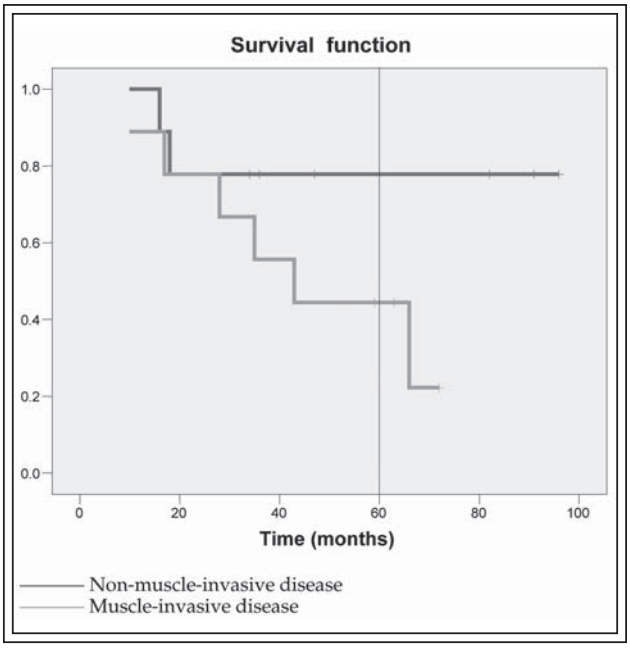

Figure 2. Disease-specific survival according to the presence of muscle-invasive disease or non-muscle-invasive disease at transurethral resection of the bladder.

Discussion

Micropapillary urothelial carcinoma is recognized as a rare and aggressive variant of urothelial carcinoma that often presents at a high stage.[1,6,9] In previously reported series of cases, at presentation, most patients had locally advanced disease and lymphatic invasion. Most series of cases and case reports have included patients with muscle-invasive disease at presentation[10-12] in whom cystectomy failed because of micrometastasis present at the time of surgery.[13] Despite the small number of patients in our series, we obtained similar results in patients with muscle-invasive disease: only 3 of 10 patients (30%) are alive, with 2 patients free of disease at more than 5 years of follow up.

Micropapillary carcinoma of the bladder does not differ clinically from normal transitional carcinoma of the bladder, in that hematuria is the most common sign.[6] Micropapillary carcinoma can grow below normal mucosa and sometimes may not be identifiable by routine follow up cystoscopy or urine cytology.[4,8] It can also be difficult to detect by CT scan, because it cannot be described as a mass lesion.

Micropapillary carcinoma is usually associated with other histologic types of cancer; transitional cell carcinoma and carcinoma in situ have been noted in 85% and 65% of patients with micropapillary carcinoma, respectively.[6] There are some aspects that could explain the aggressive behavior of this type of tumor. In our series, 7 of the 18 patients (39%) had associated carcinoma in situ; this finding is similar to that in the first series of patients described by Amin et al,[1] who reported that 10 of 18 patients with micropapillary carcinoma of the bladder had associated carcinoma in situ.

It has previously been reported that survival time is related to differentiation type.[14] Patients with a more than 80% classic urothelial cell carcinoma pattern had a favorable prognosis; the survival rate increased further with increasing percentages of this differentiation type. On the other hand, non-conventional differentiation, especially with greater extension and a greater number of differentiation types, appeared to entail a worse prognosis. It was also reported that the number of non-conventional differentiation types increased in the presence of a sarcomatoid, an undifferentiated, a nested,

or a micropapillary pattern. A highly aberrant expression of MUC1,[15] a glycoprotein that is normally located in the apical cell surface of normal glandular epithelium, has been described in invasive micropapillary carcinoma, where it is localized predominantly in the stroma-facing surface of the cells. This may be one of the key factors responsible for the distinctive morphology of this tumor type, i.e., detachment of the neoplastic cells from the stroma, enhancing their spread and leading to early dissemination to lymph nodes. Studies with p53 were not conclusive.[5]

Samaratunga et al[8] were the first to report that the prognosis of micropapillary carcinoma is related to the proportion and location of the micropapillary carcinoma component. Subsequently, Alvarado-Cabrero et al[5] investigated 38 patients with micropapillary carcinoma and a control group of 76 patients with high-grade urothelial carcinoma and found that patients with a micropapillary carcinoma component of more than 50% had a relative mortality risk of 2.4 (range, 1.3-4.2), whereas patients with a micropapillary carcinoma component of less than 50% did not have a significantly different disease-specific survival. These findings are similar to our findings.

To our knowledge, only Kamat et al[7] have published results from a study that evaluated non-muscle invasive micropapillary bladder carcinoma behavior and the response to different treatments. They did a retrospective study of 44 cases of non-muscle invasive micropapillary bladder carcinoma. The cancer stage at presentation was Ta in 5 patients (11%), carcinoma in situ in 4 patients (9%), and T1 in 35 patients (80%). They did not report whether or not there was an association of Ta/T1 tumors with carcinoma in situ. They treated 27 patients (61%) with BCG therapy; 18 of these 27 patients (67%) had disease progression and only 19% of these 27 patients remained disease-free. Because of the ineffectiveness of BCG therapy and the increased risk of non-organ-confined disease and node-positive disease at the time of cystectomy, they did not recommend a conservative approach.

Maranchie et al[4] obtained a good response in only 2 of 5 patients treated with BCG therapy plus interferon alpha therapy. Neither Kamat et al or Maranchie et al analyzed the response in relation to carcinoma in situ or the micropapillary carcinoma component.

In our series of 8 patients with non-muscle-invasive micropapillary bladder cancer, 3 of the 8 patients (37.5%) had associated multifocal carcinoma in situ, 1 patient had a stage Ta tumor, and 7 patients had stage T1 tumors. Six patients were treated with intravesical BCG therapy; none of these 6 patients had disease progression, and all were alive and free of disease after a median follow-up of more than 5 years. Despite the small number of patients in our series, we observed that patients with a low micropapillary carcinoma component in tumors were successfully treated with BCG therapy without maintenance therapy, which is not yet established as standard treatment. In the last few years patients with high grade non-muscle-invasive bladder cancer are treated with BCG and maintenance treatment according to the European Guidelines in non-muscle-invasive bladder cancer.[16]

At present the optimal treatment strategy for this rare tumor non-muscle-invasive micropapillary bladder carcinoma remains unclear. The results of our small series, suggest that patients with non-muscle-invasive disease who have undergone a complete transurethral resection, who do not have carcinoma in situ, and who have a low (< 50%) micropapillary carcinoma component, are good candidates to be treated with a conservative approach.

Further studies are needed to examine the micropapillary carcinoma component among patients who underwent complete transurethral resection of a bladder tumor and had a high incidence of micropapillary carcinoma component at diagnosis.

Conclusions

Micropapillary bladder carcinoma is a rare and aggressive variant of urothelial carcinoma. Its usual presentation is as a high-grade invasive tumor. There is a relationship between the percentage of the micropapillary carcinoma component and the stage at presentation. In muscle-invasive disease, radical surgery is mandatory, even though the majority of patients with lymph node involvement will die from their disease despite radical cystectomy. Although our study is limited by its retrospective nature and small number of patients, it suggests that conservative intravesical treatment with BCG may be offered to patients with non-muscle-invasive bladder carcinoma who do not have associated carcinoma in situ and whose carcinoma has a low (< 50%) micropapillary carcinoma component. □

References

1. Amin MB, Ro JY, El-Sharkawy T et al. Micropapillary variant of transitional cell carcinoma of the urinary bladder. Histologic pattern resembling ovarian papillary serous carcinoma. *Am J Surg Pathol* 1994(12);18:1224-1232.
2. Oh YL, Kim KR. Micropapillary variant of transitional cell carcinoma of the ureter. *Pathol Int* 2000;50(1):52-56.

3. Vang R, Abams A. A micropapillary variant of transitional cell carcinoma arising in the ureter. *Arch Pathol Lab Med* 2000; 124(9):1347-1348.
4. Maranchie JK, Bouyounes BT, Zang PL, O'Donnell MA, Summerhayes IC, DeWolf WC. Clinical and pathological characteristics of micropapillary transitional cell carcinoma: a highly aggressive variant. *J Urol* 2000;163(3):748-751.
5. Alvarado-Cabrero I, Sierra-Santiesteban FI, Mantilla-Morales A, Hernàndez-Hernàndez DM. Micropapillary carcinoma of the urothelial tract. A clinicopathologic study of 38 cases. *Ann Diagn Pathol* 2005;9(1):1-5.
6. Johansson SL, Borghede G, Holmäng S. Micropapillary bladder carcinoma: a clinicopathological study of 20 cases. *J Urol* 1999; 161(6):1798-1802.
7. Kamat A, Gee J, Robinson T, Pisters L. The case for early cystectomy in the treatment of nonmuscle invasive micropapillary bladder carcinoma. *J Urol* 2006;175(3 Pt 1):881-885.
8. Samaratunga H, Khoo K. Micropapillary variant of urothelial carcinoma of the urinary bladder; a clinicopathological and immunohistochemical study. *Histopathology* 2004;45(1):55-64.
9. Ylagan LR, Humphrey PA. Micropapillary variant of transitional cell carcinoma of the urinary bladder: a report of three cases with cytologic diagnosis in urine specimens. *Acta Cytol* 2001; 45(4):599-604.
10. Sugino Y, Negoro H, Iwamura H et al. Micropapillary variant of transitional cell carcinoma of the bladder. *Int J Urol* 2004; 11(9):792-794.
11. Nishizawa K, Kobayashi T, Mitsumori K et al. Micropapillary bladder cancer. *Int J Urol* 2005;12(5):506-508.
12. Baty V, Michalet V, Tamiere P et al. Peritoneal carcinomatosis and hepatic infiltration related to the dissemination of a micropapillary cell carcinoma of the bladder. *Gastroenterol Clin Biol* 2003;27(8-9):828-832.
13. Smith JA, Crawford ED, Paradelo JC et al. Treatment of advanced bladder cancer with combined preoperative irradiation and radical cystectomy versus radical cystectomy alone: a phase III intergroup study. *J Urol* 1997;157(3):805-807.
14. Jozwicki W, Domanieswski J, Skok Z, Wolski Z, Domanowska E, Jozwicka G. Usefulness of histologic homogeneity estimation of muscle-invasive urinary bladder cancer in an individual prognosis: a mapping study. *J Urol* 2005;66(5):1122-1126
15. Nassar H, Pansare V, Zhang H et al. Pathogenesis of invasive micropapillary carcinoma: role of MUC1 glycoprotein. *Mod Pathol* 2004;17(9):1045-1050.
16. European Guidelines. European Association of Urology 2008.