Research Article

Innovation in the Urothelial Urinary Bladder Cancer Management

Wafaa M. Abdel-Latif, Amani S. Guirguis, Hoda M. Abdel-Azeam, and Heba M. Sadek Hassan
Department of Oncology, El-Minia Faculty of Medicine

Abstract
The purpose of this study is to display modalities for early detection of Urothelial Urinary Bladder cancer (UUBC) and give an overview of updates and advances in its diagnosis and management.
Keywords: urinary bladder cancer, review, Epidemiology, Risk factors, prognosis, survival, Treatment.

Introduction
Bladder cancer is the 9th most common cancer worldwide and is the sixth most common cancer in the United State ,it has several pathological types, including urothelial cell carcinoma (UCC), adenocarcinoma, and squamous cell carcinoma. (Siegel et al., 2017). Bladder cancer is three times more prevalent in men than in women in the United States and eighth highest cancer-related mortality rate in American men (Jemal et al., 2010). Urothelial cancer (UC) of the bladder is the second most common genitourinary malignancy and the fifth most common malignancy diagnosed in the United States (Siegel et al., 2017). Risk factors include smoking, chronic inflammatory changes in the bladder (due to persistent bladder stones, recurrent urinary tract infections, indwelling catheters, chemotherapeutic exposure, such as cyclophosphamide and

Schistosoma haematobium: which is associated with the development of squamous cell carcinoma (SCC). (Aldousari and Kassouf, 2010). At diagnosis, 90% of all BC are UCC, and three fourths of them are papillary tumors localized in the urothelium or in the *lamina propria*. Less than 8% are classified as SCC and 2% are adenocarcinomas. Approximately 75 to 85% of patients will have disease confined to the mucosa (Ta) or submucosa (T1), that is, non-muscle invasive bladder cancer (NMIBC), CIS (tumor in situ; Tis) is a high-risk disease for muscle- invasion. (Babjuk et al., 2012).

Diagnosis of urothelial bladder cancer
Haematuria Is the cardinal presenting symptom of bladder cancer.

I. Urine Tests

1. **Urine cytology**: Positive cytology finding should be treated as indicating cancer until proven otherwise even if the cytoscopic examination yields normal findings**.** (Tirsar et al., 2012).

2. Urine tumor marker tests:

- Commercially available tests include the following: (Eissa et al., 2013) : Fluorescence in situ hybridization (FISH): FISH is 42-83% sensitive for detecting pTa and pT1 lesions and 92-100% sensitive for pT2-4 invasive lesions, Nuclear matrix protein (NMP-22), Bladder Tumor Antigen (BTA): Complement factor H-related protein, ImmunoCyt/uCyt+: This test looks at cells in the urine for the presence of substances such as mucin and carcinoembryonic antigen (CEA), which are often found on cancer cells, CertNDx, CxBladder, Fibroblast growth factor receptor 3 (FGFR3), BLCA-4, Survivin: A member of inhibitors of apoptosis gene family, CYFRA 21-1: Cytokeratin 19 (cytoskeletal protein), DD23: 185-kDa tumor associated antigen.

II. Cystoscopy:

- Cystoscopy remains the gold standard for the detection of both new and recurrent bladder cancer**.** (Kamat et al., 2012)

III. Biopsy:

EAU guidelines confirm the clinical evidence that biopsy and resection with (BLC) are more sensitive than conventional (WLC) for detection of malignant tumors, particularly carcinoma *in situ.* (Babjuk et al., 2015).

TURBT with a bimanual examination under anesthesia (EUA) is performed to resect visible tumor and to sample muscle within the area of the tumor to assess proper tumor staging and whether invasion has occurred. With CIS, biopsy of sites adjacent to the tumor and multiple random biopsies may be performed to assess for a field change. A transurethral biopsy of the prostate may also be considered. (Kamat et al., 2012).

EUA guidelines recommend a second TURBT be performed 2-6 weeks after the initial resection in any of the following situations:

- After incomplete initial TURBT
- If there is no muscle in the specimen after initial resection, with exception of Ta low-grade tumors and, possibly, completely resected primary carcinoma in situ (CIS)
- In all T1 tumors
- In all high-grade tumors, except primary CIS; however, it may be beneficial to attempt to resect all CIS lesions at repeat TURBT. (Babjuk et al., 2013).

IV. Imaging:

1. Computed tomography scan: CT urography can provide detailed information about the size, shape, and position of any tumors in the urinary tract, including the bladder. It can also help show enlarged lymph nodes that might contain cancer, as well as other organs in the abdomen and pelvis. (Kantarci et al., 2010).

2. Magnetic resonance imaging scan: Staging sensitivity ranges from 68% to 80% and specificity from 90% to 93% (Watanabe et al., 2009). Although MRI can detect higher numbers of lymph nodes than CT and nodes <5mm, its ability to identify tumor in normal-size or slightly enlarged nodes is poor. (Saokar et al., 2010).

3. **Positron emission tomography scanning**: In muscle-invasive bladder cancer, it shows a sensitivity of 57–81% and specificity of 88–100% in the detection of pelvic lymph node metastases. (Riches et al., 2010).

4. Bone scan: It is used in MIBC- Sympto-matic, high-risk patients or those with laboratory indicators of bone metastasis and should be performed in NMIBC if elevated levels of alkaline phosphatase are seen in the blood. (Rouprêt et al., 2013).

V. New promising future technology:

_ **Narrow-band imaging** :It enhances the contrast between the bladder mucosa and vascular structures by filtering white light into two narrow bands (415 and 540 nm) without the need for a preoperative instillation of contrast agent. Improved detection of primary and recurrent tumours has been shown in small non-randomised studies, (Cauberg et al., 2010).

_ **Optical Coherence Tomography**: Is an emerging technology that provides noninvasive, real-time high-resolution (10 to 20 μm) imaging of the bladder wall in cross-section,. (Ren et al., 2009). OCT can differentiate bladder cancer from normal bladder mucosa with a sensitivity and specificity ranging from 84-100% and 78-90%, respectively (Ren et al., 2009).

Furthermore, better tumor margin detection using OCT to guide transurethral resection (TUR), which is commonly used for non-muscle-invasive bladder cancer such as TCC, (Cauberg Evelyne et al., 2011). It demonstrated that OCT image can differentiate recurrent TCC from scar or necrosis induced by previous TUR may make it difficult to identify residual or recurrent tumors by WLC. Recently, We used this new system to investigate real-time 3D imaging of excised tissue consisting mainly of the three areas such as cancerous, normal and boundary areas from patients with advanced UC, and compared the images to results from histopathological examination of the same area**.** (Choi et al., 2012).

New ways in bladder cancer research. In the future, other newer assays based on telomerase which is an enzyme that is often found in abnormal amounts in cancer cells, and microsatellite analysis may prove to be a better detection method than urinary cytology. (Balar et al., 2014).

Survival rates for bladder cancer by stage

Stage	Relative 5-year Survival Rate
0	98%
I	88%
II	63%
III	46%
IV	15%

(Smith et al., 2014).

Prognosis: The most significant prognostic factors for bladder cancer are grade, depth of invasion, and the presence of CIS. In patients undergoing radical cystectomy for muscle-invasive bladder cancer, the presence of nodal involvement is the most important prognostic factor. To date, there is no convincing evidence of genetic factors affecting outcome. (Mooso et al., 2015). Prognosis for patients with metastatic urothelial cancer is poor, with only 5-10% of patients living 2 years after diagnosis.The risk of progression, depends primarily on the tumor grade, as follows: Grade I – 2-4%, Grade II – 5-7%, Grade III – 33-64%

Prognosis in carcinoma in situ: CIS in association with T1 papillary tumor carries a poorer prognosis. It has a recurrence rate of 63-92% and a rate of progression to muscle invasion of 50-75% despite intravesical BCG. (Griffiths et al., 2002).

Recurrent bladder cancer: The time interval to recurrence is also significant. Patients with tumor recurrences within 2 years, and especially with recurrences within 3-6 months, have an aggressive tumor and an increased risk of disease progression. (van Rhijn et al., 2009).

Approximate probability of recurrence and progression (Collado et al., 2012).

Pathology	Approximate Probability of Recurrence in 5 years	Approximate Probability of Progression to Muscle Invasion
Ta,lowgrade	50%	Minimal
Ta, high grade	60%	Moderate
T1,low grade (rare)	50%	Moderate
T1, high grade	50%-70%	Moderate-High

Prognostic Interpretation of Positive Lymph Nodes: The presence of lymphatic metastasis is associated with markedly worse prognosis in patients with bladder cancer, although surgical resection and chemotherapy can still provide long-term survival for selected patients.. (Abdollah et al., 2012).

Treatment Protocols; Non-Muscle-Invasive Disease

Treatment according to stage

cTa, Low-Grade Tumors: TURBT is the standard treatment for cTa, low-grade tumors. Although a complete TURBT alone can eradicate cTa low-grade tumors, these tumors have a relatively high risk for recurrence. Therefore, after TURBT, the panel recommends observation and to strongly consider administering a single dose of immediate intravesicular chemotherapy within 24 hours of resection. (Gudjonsson et al., 2009).

cTa, cT1 High-Grade Tumors: Tumors staged as cTa, high-grade lesions are papillary tumors with a relatively high risk for recurrence and progression towards more invasiveness. Repeat resection is recommended if there is incomplete resection, or is strongly considered if there is no muscle in the specimen. (Babjuk M et al., 2011). Afterr TURBT, in addition to obser-

vation, patients with Ta, high-grade tumors may be treated with intravesical BCG or mitomycin c The NCCN Bladder Cancer Panel Members recommend BCG as the preferred option over mitomycin C for adjuvant treatment of high-grade lesions**.**

Posttreatment Recurrent or Persistent cTa, cT1, and Tis Disease Following Intravesical Treatment. Patients, who show a documented recurrence by positive cystoscopy results, that responded to induction intravesical therapy, should undergo another TURBT followed by a second induction course of BCG or mitomycin C induction therapy. No more than two consecutive induction courses should be given (Babjuk et al., 2011). If a second course of BCG is given and residual disease is seen at the second 12-week (3-month) follow-up, TURBT is performed. For patients who have Tis or cTa disease after TURBT, intravesical therapy with a different intravesical agent is an alternative to cystectomy. Valrubicin has been approved for CIS that is refractory to BCG. In a recent study of non-muscle-invasive bladder cancer that recurred following 2 courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk non-muscle-invasive bladder cancer**. (**Skinner et al., 2013) It had some activity in the high-risk group, and may be an option if a candidate is not eligible for a cystectomy; however, the study results indicate that cystectomy is preferred when possible. Malmstrom et al., performed a meta-analysis including 9 trials in 2820 patients with non-muscle-invasive bladder cancer. They report that mitomycin C is superior to BCG without maintenance in preventing recurrence, but inferior to BCG in trials with maintenance. (Malmstrom et al., 2009), While the optimal maintenance regimen has not been established, most patients undergo maintenance for 1 to 3 years. The duration is often limited by toxicity as follows: (Oddens et al., 2013)

- 1 year for intermediate-risk patients.
- In high-risk patients, 3-year maintenance BCG reduced recurrence compared to 1-year maintenance, but did not impact progression or survival.

Muscle-Invasive Disease

T2, T3, and T4a Tumors : TURBT is the initial treatment for all muscle-invasive disease. The goal of the TURBT is to correctly identify the stage; therefore, bladder muscle must be included in the resection biopsies. (Verma et al., 2012). Further treatment following initial TURBT is required for muscle-invasive tumors. These include radical cystectomy, partial cystectomy, neoadjuvant or adjuvant therapy, bladder-preserving approaches, and chemo-therapy for advanced disease. (Verma et al., 2012).

Radical Cystectomy; Radical cystectomy is the primary treatment for T2 and T3 tumors, with consideration for neoadjuvant chemo-therapy. A pelvic lymph node dissection (PLND) is considered an integral part of the surgical management of bladder cancer. A more extensive PLND, which may include the common iliac or even lower para-aortic or para-caval nodes**,.** (Wright et al., 2008).

Neoadjuvant Chemotherapy: Neoadjuvant chemotherapy is preferred over adjuvant-based chemotherapy on a higher level of evidence data.The use of neoadjuvant chemotherapy (NC) before open radical cystectomy (RC) for invasive urothelial carcinoma of the bladder demonstrating 5% survival benefit compared with RC alone that can help determine the sensitivity of the carcinoma to the selected chemotherapeutic agents. (Gerullis et al., 2010).

Neoadjuvant radiotherapy: The rationale is to prevent intraoperative seeding of tumor cells in the operative field and to sterilize micro-scopic extensions in the perivesical tissues.For invasive tumors, (T2–T4a) without evidence of distant metastasis. consider low-dose pre-operative radiation therapy prior to segmental cystectomy. Pelvic nodal metastasis is not a contraindication for preoperative radiotherapy. (McBain and Logue, 2005)

Adjuvant radiation: Patient Selection for Postoperative Radiotherapy who underwent RC with ileal conduit within 3–6 weeks and belonged to pathological stages pT2b–pT4a, with or without pelvic nodal involvements and with good performance status with doses in the range of 45 to 50.4 Gy. Involved resection margins and areas of extranodal extension could be boosted to 54-60 Gy if feasible based on normal tissue constraints. (Huddart et al., 2013). Because of local recurrence rates are high after

cystectomy (32% for pT3-T4 patients and 68% for patients with positive surgical margins, adjuvant radiation therapy is reasonable to consider in these patients. (Herr et al., 2004). For patients with stage Ta, T1, or Tis, external beam radiation therapy (EBRT) alone is rarely appropriate.

Bladder-Preserving Options: First, an endoscopic resection that is as complete as possible is performed. Incomplete resection is an unfavorable prognostic factor for the ability to preserve the bladder and for survival. (Efstathiou et al., 2012). Radiotherapy with concurrent cisplatin-based chemotherapy or concurrent 5-fu and mitomycin c in patient with low or moderate renal function. as a radiosensitizer is the most common and well studied chemoradiation method used to treat muscle-invasive bladder cancer and often referred to as Trimodality Therapy. After this induction phase, an endoscopic re-evaluation is performed. The overall tumor status should be reassessed 2 to 3 months after treatment. If tumor remains, cystectomy is the preferred choice if feasible. Patients who are not surgical candidates should consider completion of radiation with alternative radiosensitizing chemotherapy and/or alternative chemotherapy. (James et al., 2012). If no disease is visible and the cytology and biopsy are negative (T0), an additional 25 Gy of consolidation external-beam radiotherapy is administered along with one additional dose of cisplatin. (Efstathiou et al., 2012). After maximal TURBT, chemotherapy alone, radiotherapy alone, or chemotherapy combined with radiotherapy (all followed by close cystoscopic observation and further treatment, if necessary) are potential treatment options..(James et al., 2012).

Survival Outcomes: Adjuvant sequential chemotherapy plus radiation therapy and adjuvant radiation therapy alone significantly improved local tumor control compared with adjuvant chemotherapy alone in locally advanced bladder cancer. Postoperative radiation is known to improve local control, and evidence from Egypt suggests that it can improve survival, while the benefit of postoperative chemotherapy is controversial. (Zaghloul et al., 2006). A prospective controlled randomized trial was performed in order to test the tolerability and efficacy of adding adjuvant chemotherapy (gemcitabine and cisplatinum) to PORT in a Phase III study. This regimen, administered with hyper fractionated PORT (4500 cGy/3 weeks/30 fractions) as an adjuvant combination to surgery proved to be tolerable, and the percentage of grade III and IV toxicities were minimal. Preliminary results showed improvement in 2-year DFS in the adjuvant chemoradiotherapy group although this did not reach statistical significance. Patients with one risk factor, lower pathological stage or no nodal involvement appeared to benefit more from the added chemotherapy. A better DFS was reported for chemoradiotherapy. The locoregional recurrence was the main cause of failure in the adjuvant chemotherapy arm. In the other two arms, local recurrences were much lower (Zaghloul et al., 2016).

Several newer types of treatment are now being studied for use against bladder cancer.

Surgery: Some surgeons are using a newer approach to cystectomy in which they sit at a control panel in the operating room and maneuver robotic arms to do the surgery. This approach, known as a robotic cystectomy, lets the surgeon operate through several small incisions instead of one large one. This may help patients recover more quickly from surgery**.** (Howlader N. et al., 2015).

Photodynamic therapy: A light-sensitive drug is injected into the blood and allowed to collect in the cancer cells for a few days. Then a special type of laser light is focused on the inner lining of the bladder through a cystoscope. The light changes the drug in the cancer cells into a new chemical that can kill them. An advantage of PDT is that it can kill cancer cells with very little harm to nearby normal cells. One drawback is that the chemical must be activated by light, so only cancers near the surface of the bladder lining can be treated in this way. (Feldman et al., 2015).

Immunotherapy: Newer drugs that target checkpoint molecules such as PD-1 and PD-L1 hold a lot of promise as bladder cancer treatments. For example, atezolizumab (which targets PD-L1) and pembrolizumab (which targets PD-1), have been shown to shrink some advanced bladder cancers in early studies. (Efstathiou et al., 2015)

Targeted therapies: Some of these drugs are now being studied for use against bladder cancer as well, including lapatinib (Tykerb) and erlotinib (Tarceva). Other drugs target the blood vessels that allow tumors to grow. These are known as *anti-angiogenesis drugs*. Examples include bevacizumab (Avastin), sorafenib (Nexavar), cabozantinib (Cometriq), and pazopanib (Votrient), which are already used for some other types of cancer. They are now being studied for use against bladder cancer, usually combined with chemotherapy. **(**Smith et al., 2014)

Gene therapy :One approach to gene therapy uses special viruses that have been modified in the lab. The modified virus is put into the bladder and infects the bladder cancer cells. When this infection occurs, the virus injects a gene into the cells for GM-CSF, an immune system hormone that can help immune system cells to attack the cancer. This and other approaches to gene therapy are still in the early stages of development. (Feldman et al., 2015).

Summery

Bladder cancer is the commonest malignancy of the urinary tract. Narrow-band imaging and photodynamic diagnosis/blue-light cystoscopy have shown promise in improving detection and reducing recurrence of bladder tumors, by improving the completion of bladder resection when compared with standard resection in white light.

Bladder cancer is a chemosensitive disease, and systemic chemotherapy plays a role in its management. Cisplatin-based combination chemotherapy prolongs survival in the metastatic setting.

With the advancement in radiotherapy techniques as a direct result of the great advancement in computer science and communication revolution, radiotherapy can improve the tumor control probability and decrease the normal tissue complication probability. The image-guided and adaptive radiotherapy ensure the precise dose delivery.

References

1. Siegel RL, Miller KD and Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017; 67:7-30.
2. Aldousari S and Kassouf W. (2010): Update on the management of non-muscle invasive bladder cancer Can Urol Assoc J.; 4(1): 56–64.
3. Eissa S, Motawi T, Badr S, Zaghlool A, et al., (2013). Evaluation of urinary human telomerase reverse transcriptase mRNA and scatter factor protein as urine markers for diagnosis of bladder cancer. Clin Lab. 59(3-4):317-23.
4. Babjuk M et al., (2015). European Association of Urology. Guidelines on Non-Muscle-Invasive Bladder Cancer (Ta T1 and CIS).
5. Kamat AM, Dickstein RJ, Messetti F, et al., (2012). Use of fluorescence in situ hybridization to predict response to bacillus Calmette-Guerin therapy for bladder cancer: results of a prospective trial. J Urol;187:862-867.
6. Smith A, Balar AV, Milowsky MI, et al., (2014). Chapter 83: Bladder Cancer. In: Niederhuber JE, Armitage JO, Dorshow JH, Kastan MB, Tepper JE, eds. Abeloff's Clinical Oncology. 5th ed. Philadelphia, Pa. Elsevier:.
7. Cauberg EC, de Bruin DM, Faber DJ, et al., (2010). quantitative measurement of attenuation coefficients of bladder biopsies using optical coherence tomography for grading urothelial carcinoma of the bladder.J Biomed Opt. Nov-Dec; 15(6):066013.
8. Cauberg Evelyne CC, de la Rosette JJ and de Reijke, (2011). Emerging optical techniques in advanced cystoscopy for bladder cancer diagnosis: A review of the current literature. Indian J Urol; 27:245 - 51
9. Rouprêt M, Babjuk M, Compérat E, et al., (2013). European guidelines on upper tract urothelial carcinomas: update. Eur Urol 2013;63:1059-1071.
10. H. Watanabe, M. Kanematsu, H. Kondo, et al., (2009). Preoperative T staging of urinary bladder cancer: does diffusion-weighted MRI have supplementary value?. AJR Am J Roentgenol.; 192:1361-1366.
11. Ren H, Waltzer WC, Bhalla R, Liu J, et al., (2009). Diagnosis of bladder cancer with micro electro mechanical systems-based cystoscopic optical coherence tomography. Urology; 74:1351 - 7;

12. Feldman AS, Efstathiou JA, Lee RJ, et al., (2015). Chapter 65: Cancer of the Bladder, Ureter and Renal Pelvis. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. 10th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; Efstathiou JA, Spiegel DY, Shipley WU, et al., (2012) Long-term outcomes of selective bladder preservation by combined-modality therapy for invasive bladder cancer: the MGH experience.EurUrol;61:705-711.
13. Mooso BA, Vinall RL, Mudryj M, et al., (2015). The role of EGFR family inhibitors in muscle invasive bladder cancer: a review of clinical data and molecular evidence. J Urol. Jan. 193 (1):19-29.
14. Choi DH, Hiro-Oka H, Shimizu K, et al., (2012). Spectral domain optical coherence tomography of multi-MHz A-scan rates at 1310 nm range and real-time 4D-display up to 41 volumes/second. Biomed Opt Express., 3: 3067-3086. 10.1364/ BOE.3. 003067.
15. van Rhijn BW, Burger M, Lotan Y, et al., (2009) .Recurrence and progression of disease in non-muscle-invasive bladder cancer: from epidemiology to treatment strategy. Eur Urol. Sep. 56(3):430-442.
16. Zaghloul MS. (2016). In Regard to Reddy et al., *International Journal of Radiation Oncology*Biology*Physics* 95:2, 854. Online publication date: 1-Jun-2016.
17. Zaghloul MS, Nouh A, Nazmy M, et al., (2006). Long-term results of primary adenocarcinoma of the urinary bladder: a report on 192 patients. Urol Oncol.; 24(1): 13–20.
18. James ND, Hall E, Jenkins P, et al., (2012); BC2001 Investigators (2012): Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med, 366(16):1477-88.
19. Howlader N, Noone AM, Krapcho M, et al (2015). SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, based on November 2014 SEER data submission, posted to the SEER web site, April.
20. McBain CA, Logue JP .(2005): Radiation therapy for muscle-invasive bladder cancer: treatment planning and delivery in the 21st Century. Semin. Radiat. Oncol. 15(1), 42–48.
21. Herr HW, Faulkner JR, Grossman HB, et al., 2004. Surgical factors influence bladder cancer outcomes: a cooperative group report. J Clin Oncol;22:2781-2789.
22. Gerullis H., Wishani K, Otto T, et al., (2010): What happens if nothing happens History of untreated Uroothelial carcinoma of the bladder . J. Egypt. Soc. Parasitol., 40 (3),789 – 796.
23. Huddart RA, Hall E, Hussain SA, et al., (2013). Randomized noninferiority trial of reduced high-dose volume versus standard volume radiation therapy for muscle-invasive bladder cancer: results of the BC2001 trial (CRUK/01/004). Int J Radiat Oncol Biol Phys;87:261-269.
24. Verma S, Rajesh A, Prasad SR, et al., (2012) Urinary bladder cancer: role of MR imaging. Radiographics;32:371-387.Availableat : http://www.ncbi.nlm.nih.gov/pubmed/22411938.
25. Wright JL, Lin DW and Porter MP. (2008). The association between extent of lympha-denectomy and survival among patients with lymph node metastases undergoing radical cystectomy. Cancer; 112:2401-2408.
26. Malmstrom PU, Sylvester RJ, Crawford DE, et al., (2009). An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. EurUrol; 56:247-256.
27. Oddens J, Brausi M, Sylvester R, et al., (2013). Final results of anEORTC-GU cancers group randomized study of maintenancebacillusCalmette-Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3years of maintenance. Eur Urol; 63:462-472.
28. Skinner EC, Goldman B, Sakr WA, et al., (2013). SWOG S0353: Phase II trial of intravesical gemcitabine in patients with nonmuscle invasive bladder cancer and recurrence after 2 prior courses of intravesical bacillus Calmette-Guerin. J Urol;190:1200-1204.
29. Babjuk M, Oosterlinck W, Sylvester R, et al., (2011). EAU guidelines on non-

muscle-invasive urothelial carcinoma of the bladder. Eur Urol 2011;59:997-1008.
30. Babjuk M, Sylvester R, Rouprêt M; et al., (2012). European Association of Urology (EAU) guidelines on non-muscle-invasive bladder cancer. (_TaT1_Bladder_ Cancer_)
31. Gudjonsson S, Adell L, Merdasa F, et al., (2009). Should all patients with non-muscle-invasive bladder cancer receive early intravesicalchemotherapy after transurethral resection? The results of a prospective randomised multicentre study. Eur Urol; 55:773-780.
32. Jemal A, Siegel R, Xu J, et al., (2010): Cancer statistics,. CA Cancer Journal for Clinicians; 60(5):277–300.
33. Saokar, T. Islam, M. Jantsch, et al., (2010). Detection of lymph nodes in pelvic malignancies with computed tomography and magnetic resonance imaging. Clin Imaging;34:361-366.