RESEARCH COMMUNICATION

# Survival of Patients with Transitional Cell Carcinoma of the Urinary Bladder in Indonesia: A Single Institution Review

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## Abstract

**Objective: To describe for the first time the survival of bladder transitional cell carcinoma (TCC) in Indonesia, according to clinicopathological characteristics. Materials and Methods: Retrospective study of bladder TCC survival in a single institution, Cipto Mangunkusumo Hospital, Indonesia's national tertiary referral centre, between the years 1995 and 2005. The Kaplan-Meier method was used to determine the overall survival (OS). Results: The evaluable data covered 254 cases of primary bladder TCC, in which 95 (37.4%) were non muscle-invasive bladder cancer (NMIBC), and 159 cases (62.6%) were muscle-invasive (MIBC). Of these, 105 cases (41.4%) with a follow-up period up to five years were eligible for survival analysis. The mean age was 56.5 +/- 12.1 years old, with a male to female ratio of 6:1. The 5-year OS for all bladder TCC was 27.6%, with a mean survival time of 32.6 months. For NMIBC, the 5-year OS was 53.8% with a mean survival of 54.5 months. For MIBC, the 5-year OS was 19% with a mean survival of 25.4 months. Regarding pathological stage, the 5-year OS for stage 0, I, II, III, and IV was 83.3%, 45%, 30%, 18.8%, and 9.1%, respectively. Conclusion: The overall survival of bladder TCC in Indonesia is low compared to other countries. Possible explanations include the high number of advanced-stage tumours at initial presentation, under-staging, significant number of treatment refusal by our patients, and the non-standardized use of adjuvant therapy in our centre.**

**Keywords:** Long term survival - treatment modalities - muscle invasive bladder cancer - Indonesia

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## Introduction

Bladder cancer belongs to the top ten most common primary male cancers in Indonesia, with an increasing incidence of 15% per annum in the last decade (Umbas, 2007). This is similar to the rest of the world, in which bladder cancer is the 9th most common malignancy and the 13th most common cause of cancer death worldwide, with an estimated 357,000 new cases and 145,000 deaths annually. The global incidence of bladder cancer has also been increasing steadily in the past ten years (Parkin, 2008).

Transitional cell carcinoma of the urinary bladder (bladder TCC) represents the most common histological type, accounting for 80% of all bladder cancers in Indonesia (Umbas, 2007), and over 90% in other countries (Ries, 2007; Matalka et al., 2008; Gupta et al., 2009; Kong et al., 2010). However, to date there is no published data on the survival of bladder TCC in Indonesia. We therefore undertook a study to assess the survival of bladder TCC patients in our institution, Cipto Mangunkusumo Hospital, which is Indonesia's national tertiary referral centre.

## Materials and Methods

This is a retrospective study of all primary bladder TCC cases treated at the Cipto Mangunkusomo Hospital, Jakarta, Indonesia, between January 1995 and December 2005. Survival analysis was performed on all bladder TCC cases with a follow-up period up to five years. Individual patient data was collected on a standardised medical form and a database was compiled. The data included the patient's age, gender, tumour type, pathological stage, tumour grade, treatment and status at follow up.

Diagnosis of the bladder tumour type was determined by histopathological examination of tissue samples from transurethral resection of bladder tumour (TURBT) or bladder biopsy. Bladder tumours were graded histologically according to World Health Organisation (WHO) / International Society of Urological Pathology consensus classification of transitional cell neoplasms of the urinary bladder (Epstein et al., 1998).

Pathological stage was classified by the TNM system and grouped according to the American Joint Committee on Cancer (AJCC) sixth edition (Greene et al., 2002). Tumour (T) staging was determined by performing bimanual palpation before and after TURBT, evaluating the depth of tumour penetration on histology, or from the results of radical cystectomy. Nodal (N) staging was determined by CT-Scan or lymph node dissection. Evaluation for distant metastasis (M) included chest radiographs, abdominal-pelvic ultrasonography and

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computed tomography. Radioisotope bone scan was performed in advanced stage tumours with suspicion of bone metastasis.

The standard therapy for superficial bladder TCC was TURBT followed by intravesical instillation of Mitomycin C within six to twelve hours post-operatively. This therapy was continued for 8 times, once every week, for patients with pTa grade 2-3 or pT1 grade 1-2 disease. Radical cystectomy was the treatment of choice for superficial high grade tumours (pT1 grade 3) and muscle-invasive tumours (pT2- pT3) as well as those with more advanced stages requiring palliation.

Radiotherapy was the alternative for patients who refused surgery or for those unsuitable for surgery due to other comorbidities. Systemic chemotherapy alone or in combination with external beam radiotherapy (EBRT) was administered in patients with regional or distant metastatic disease (pT4, or any N+, or M1). The chemotherapy regimen consisted of platinum-based combination of cytostatic drugs including Methotrexate, Vincristine, Adriamycin, and Cisplatin (MVAC).

Data were analysed using SPSS software version 16 (SPSS, Chicago, IL, USA). The Kaplan-Meier survival analysis was used to calculate the overall survival rate (OS) and the mean survival time. Log-rank (Mantel-Cox) test was used for survival comparisons between each pathological stage and the degree of muscle-invasion of the tumour. A p value of 0.05 or less was considered statistically significant.

## Results

Between 1995 and 2005, there were 254 bladder TCC patients. The mean age was 56.5 +/- 12.1 (range 30 to 90) years old. There were 219 males (86.2%), with a male to female ratio of 6:1. The mean follow-up period for all patients was 32.5 months. Of these, 105 cases (41.4%) with a follow-up period of up to five years were eligible for survival analysis.

**Table 1. Clinicopathological Characteristics**

| Characteristics | No.(%) Patients |
|---|---|
| Age(Mean Years ± SD) | 56.5 ± 12.1 |
| Range | 30 - 90 Years |
| Gender | |
| Male | 219 (86.2%) |
| Female | 35 (13.8%) |
| Male to female ratio | 6:1 |
| Muscle-invasion | |
| NMIBC (Stage 0, I) | 95 (37.4%) |
| MIBC (Stage II, III, IV) | 159 (62.6%) |
| Pathological Stage | |
| Stage 0 (Ta, Tis) | 25 (9.8%) |
| Stage I (T1) | 70 (27.6%) |
| Stage II (T2a,T2b) | 61 (24.0%) |
| Stage III (T3a,T3b,T4a) | 49 (19.3%) |
| Stage IV (T4b / any N+ / M1) | 49 (19.3%) |
| Histological Grade | |
| Grade 1 (Low) | 62 (24.4%) |
| Grade 2 (Intermediate) | 81 (31.9%) |
| Grade 3 (High) | 107 (42.1%) |

NMIBC, Non muscle-invasive bladder cancer (Stage 0-I); MIBC, Muscle-Invasive Bladder Cancer (Stage II-IV)

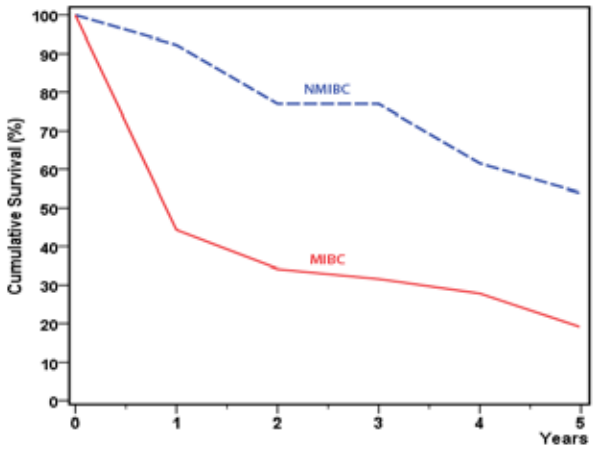


**Figure 1. Overall Survival of Bladder TCC by Tumour Invasion**

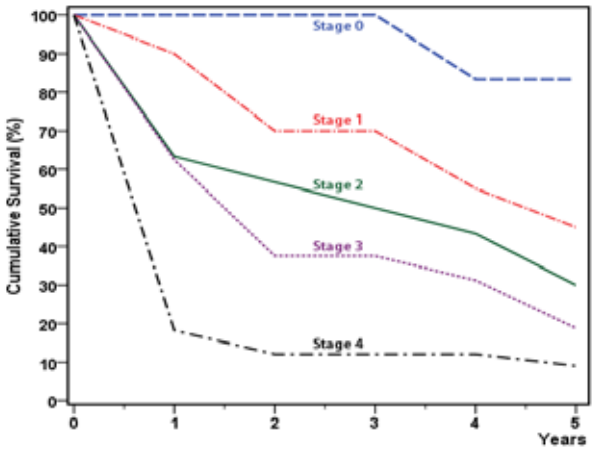


**Figure 2. Overall Survival of Bladder TCC by Pathological Stage**

At the time of presentation, there were 95 cases (37.4%) of non-muscle invasive bladder cancer (NMIBC)

**Table 2. Distribution of Histological Grade by Pathological Stage**

| Stage | Grade, No. (% within Stage) | | | Cases |
|---|---|---|---|---|
| | 1. Low-grade | 2. Intermediate | 3. High-grade | |
| Stage 0 | 23 (92.0%) | 1 (4.0%) | 1 (4.0%) | 25 |
| Stage I | 27 (38.6%) | 28 (40.0%) | 15 (21.4%) | 70 |
| Stage II | 6 (10.2%) | 20 (33.8%) | 33 (55.9%) | 59 |
| Stage III | 4 (8.3%) | 17 (35.4%) | 27 (56.3%) | 48 |
| Stage IV | 2 (4.2%) | 15 (31.3%) | 31 (64.6%) | 48 |

**Table 3. Treatments for Bladder Transitional Cell Carcinoma**

| Treatment | NMIBC(%) | MIBC(%) |
|---|---|---|
| Radical Cystectomy | 1 (1.1%) | 15 (9.4%) |
| Palliative Cystectomy | - | 4 (2.5%) |
| Partial Cystectomy | | 1 (0.6%) |
| EBRT | 7 (7.4%) | 38 (23.9%) |
| Chemoradiation | - | 2 (1.3%) |
| Adjuvant Chemotherapy | - | 3 (1.9%) |
| Intravesical Mitomycin C | 58 (61.1%) | 1 (0.6%) |
| TURBT only | | |
| Patient refusal of treatment | 17 (17.9%) | 80 (50.3%) |
| Other reasons(Comorbidities) | 12 (12.6%) | 15 (9.4%) |
| Total | 95 (100%) | 159 (100%) |

NMIBC, Non Muscle--Invasive; MIBC, muscle-invasive bladder cancer; EBRT, external beam radiotherapy; TURBT, transurethral resection of bladder tumour

**Table 4. Overall Survival of Bladder TCC by Tumour Invasion**

| Tumour Invasion | Cases | Overall survival rate(%) | | | Mean survival time (months) |
|---|---|---|---|---|---|
| | | 1-Year | 3-Year | 5-Year | |
| NMIBC | 26 | 92.3% | 76.9% | 53.8% | 54.5 |
| MBIC | 79 | 44.3% | 31.6% | 19.0% | 25.4 |
| Total | 105 | 56.2% | 42.9% | 27.6% | 32.6 |

Kaplan-Meier Suvival Distribution Log Rank (Mantle-Cox) p<0.0001; NMIBC, Non Muscle-Invasive Bladder Cancer; MIBC, muscle invasive bladder cancer

**Table 5. Overall Survival of Bladder TCC by Pathological Stage**

| Stage | Cases | Overall survival rate(%) | | | Mean survival time (months) |
|---|---|---|---|---|---|
| | | 1-year | 3-year | 5-year | |
| Stage 0 | 6 | 100.0% | 100.0% | 83.3% | 74.0 |
| Stage I | 20 | 90.0% | 70.0% | 45.0% | 48.6 |
| Stage II | 30 | 63.3% | 50.0% | 30.0% | 40.0 |
| Stage III | 16 | 62.5% | 37.5% | 18.8% | 29.3 |
| Stage IV | 33 | 18.2% | 12.1% | 9.1% | 10.2 |
| Total | 105 | 56.2% | 42.9% | 27.6% | 32.6 |

Kaplan-Meier Survival Distribution Log Rank (Mantle-Cox) p<0.0001

and 159 cases (62.6%) of muscle-invasive bladder cancer (MIBC). According to the pathological stage, Stage 0 disease were identified in 25 cases (9.8%), Stage I in 70 cases (27.6%), Stage II in 61 cases (24%), Stage III in 49 cases (19.3%), and Stage IV in 49 cases (19.3%) (Table 1).

According to the histological grade, 62 cases (24.4%) were low-grade, 81 cases (31.9%) were intermediate-grade, and 107 cases (42.1%) were high-grade tumours (Table 1). The distribution of histological grades by pathological stage are shown in Table 2. Most NMIBC were low-grade tumours and the majority of MIBC were high-grade tumours; 55.9% in Stage II, 56.3% in Stage III, and 64.6% in Stage IV disease.

The treatments for bladder TCC are summarised in Table 3. The majority of NMIBC were treated with intravesical instillation of Mitomycin C (58 patients, 61.1%). Seventeen NMIBC patients (17.9%) refused treatment and 12 patients (12.6%) only had TURBT for reasons including poor comorbidities and those who underwent watchful waiting because of low-grade lesions.

For MIBC, radical cystectomy was performed in 15 patients (9.4%) and external beam radiotherapy (EBRT) in 38 patients (23.9%). Most MIBC patients refused treatment (80 patients, 50.3%); whereas 15 patients (9.4%) only had TURBT due to comorbidities.

The 5-year overall survival (OS) for all bladder TCC cases was 27.6%, with a mean survival time of 32.6 months. For NMIBC, the 5-year OS was 53.8% with a mean survival of 54.5 months. Meanwhile for MIBC, the 5-year OS was 19% with a mean survival of 25.4 months. The survival distribution log-rank test was significant, $p < 0.0001$ (Table 4, Figure 1).

The 5-year OS for each pathological stage 0, I, II, III, and IV was 83.3%, 45%, 30%, 18.8%, and 9.1%, respectively. The mean survival time was 74 months for Stage 0, 48.6 months for Stage I, 40 months for Stage II, 29.3 months for stage III, and 10.2 months for stage IV. The survival distribution log-rank test was significant, $p < 0.0001$ (Table 5, Figure 2).

## Discussion

This study describes for the first time the survival of bladder TCC in Indonesia, according to the clinicopathological characteristics. The survival was retrospectively analysed from a single institution, Cipto Mangunkusumo Hospital, Indonesia's national tertiary referral hospital.

Clinicopathological features of bladder cancer patients in Indonesia have been described previously (Umbas, 2007). The mean age of bladder TCC in this study was 56.5 years old, lower than that reported in other Asian, Middle Eastern and Western countries (60 to 69 years old) (Goonewardena et al., 2004; Ries, 2007; Matalka et al., 2008; Gupta et al., 2009; Kong et al., 2010). The incidence of bladder TCC was higher among males compared to females, with a ratio of 6 : 1. This is higher than the ratio reported in the United States (4:1) (Ries, 2007), but similar to Sri Lanka (6:1) (Goonewardena et al., 2004). The higher male to female ratio may be attributed to fewer female smokers compared to men, lesser female exposure to industrial carcinogens, or other female protective factors that are yet to be identified (Goonewardena et al., 2004; Umbas, 2007; Matalka et al., 2008; Kong et al., 2010). Haematuria was the initial presentation in majority of the patients (88%), and three-quarter of them were painless or intermittent in nature (Umbas, 2007).

The overall survival (OS) of bladder TCC in our centre is lower than that reported in the literature. The 5-year OS for all TCC patients in our centre was 27.6%, with a mean survival of 32.6 months. This is very much lower compared to the United States, in which the observed 5-year survival for non-papillary TCC was 46.6% with a median survival of 50 months (Ries, 2007). In our centre, the 5-year OS for NMIBC was 53.8% with a mean survival of 54.5 months. For MIBC, the 5-year OS was 19% with a mean survival of 25.4 months. This is worse than the mean survival of muscle-invasive tumours reported elsewhere, including Turkey (77.8 months) (Turkolmez et al., 2007) or neighbouring countries like Malaysia (33 months) (Kong et al., 2010).

Further survival analysis for each pathological stage revealed that our 5-year OS for Stage 0, I, II, III, and IV was 83.3%, 45%, 30%, 18.8%, and 9.1%, respectively. This is lower compared to the United States where the 5-year OS for non-papillary TCC was 93.9%, 80.9%, 61.1%, 43.8%, and 13.7% for each respective stage (Ries, 2007). The low survival rates in our study, especially in the early stage disease, may be partly explained by initial under-staging. It is known that tumour invasion into the lamina propria could be missed on pathological examination and result in under-diagnosis (Matalka et al., 2008). Furthermore, patients in our centre rarely agree to have a re-resection of tumour base in cases of high grade TCC.

Survival of bladder cancer is known to be significantly affected by the tumour stage, grade, and size at initial evaluation (Narayana et al., 1983; Flamm and Havelec, 1990; Takashi et al., 2002). The low survival in this study could be explained by the fact that most our TCC cases presented at an advanced stage and with poorly

differentiated high-grade tumours. Our number of muscle-invasive or advanced stage tumours at initial presentation was 62.6%, which is very much higher compared to other centres around the world (15 to 25%) (Messing et al., 1995; Lee and Droller, 2000). Late presentation may also be caused by the patient's lack of awareness and their tendency to seek alternative traditional therapies before seeking professional healthcare advice (Umbas, 2007). In addition, the non-specific symptoms of bladder cancer including painless and intermittent haematuria may often be misdiagnosed by primary care givers, resulting in further delays in diagnosis (Matalka et al., 2008).

Refusal of treatment by the patient may also be a contributory factor for our low survival rates. A total of 17.9% NMIBC patients and 50.3% of MIBC patients only had TURBT and rejected further treatment. In general, the issue of treatment refusal significantly hinders cancer treatment in Indonesia. The underlying cause is not only due to socioeconomic and financial issues but also the lack of knowledge and trust in 'Western Medicine' (Umbas, 2007; Eriksen et al., 2008). However, some patients received no treatment due to very poor comorbidities that precludes optimal treatment, or because a watchful waiting approach was adopted in cases of superficial low-grade tumours.

The type of treatment determines the survival outcome. The treatment of choice for bladder TCC depends on the stage and grade of the tumour. Radical cystectomy is the 'gold standard' for muscle-invasive or high-grade tumours, with reported 5-year survival of 66-68% in Asian and Western countries (Gaitonde et al., 2002; Nishiyama et al., 2004; Shariat et al., 2006). However, the potential complications associated with radical cystectomy along with the cost of stoma bags and aftercare discouraged most of our patients, who thus opted for radiotherapy despite being informed of the inferior survival outcome (Shelley et al., 2002). Neo-adjuvant and adjuvant chemotherapy have also been shown to improve overall survival by 5 to 6% at five years (Ruggeri et al., 2006; Rosenberg, 2007; Calabro and Sternberg, 2009). Nevertheless, adjuvant regimens have not become a part of our standard care due to cost considerations and therefore not routinely administered.

The limitations of this study include all those inherent in a retrospective single-institution analysis. Although all data elements were prospectively collected and follow-up were done periodically every time the patient visits for control, there were a lot of lost cases after five years. The remaining sample eligible for analysis may result in overestimation or underestimation of survival. Mortality ascertainment is likely to be inaccurate with passive follow-up, especially if the data is not backed by a reliable death registration system (Sankaranarayanan et al., 2010). However, to our knowledge, this is the first report on long term survival of bladder cancer patients from Indonesian centres. Further prospective studies should address the limitations of follow-up by means of coordinated active surveillance recorded accurately in a uniform hospital-based cancer registry.

In conclusion, the overall survival of bladder TCC in Indonesia is lower compared to other countries. Possible explanations for this survival pattern include the high number of advanced-stage tumours at initial presentation, under staging, significant number of treatment refusal by our patients, and non-standardized use of adjuvant therapy in our centre.

## References


Calabrò F, Sternberg CN (2009). Neoadjuvant and adjuvant chemotherapy in muscle-invasive bladder cancer. *Eur Urol*, **55**, 348-58.

Epstein JI, Amin MB, Reuter VR, et al (1998). The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Bladder consensus conference committee. *Am J Surg Pathol*, **22**, 1435-48.

Eriksen KT, Petersen A, Poulsen AH, et al (2008). Social inequality and incidence of and survival from cancers of the kidney and urinary bladder in a population-based study in Denmark, 1994-2003. *Eur J Cancer*, **44**, 2030-42.

Flamm J, Havelec L (1990). Factors affecting survival in primary superficial bladder cancer. *Eur Urol*, **17**, 113-8.

Gaitonde K, Goyal A, Nagaonkar S, et al (2002). Retrospective review and long-term follow-up of radical cystectomy in a developing country. *BJU Int*, **89**, 57-61.

Goonewardena SA, De Silva WA, De Silva MV (2004). Bladder cancer in Sri Lanka: experience from a tertiary referral center. *Int J Urol*, **11**, 969-72.

Greene F, C Balch, D Haller, et al (2002). AJCC Cancer Staging Manual (6th Edition), Springer.

Gupta P, Jain M, Kapoor R, et al (2009). Impact of age and gender on the clinicopathological characteristics of bladder cancer. *Indian J Urol*, **25**, 207-410.

Kong CH, Singam P, Hong GE, et al (2010). Clinicopathological features of bladder tumours in a single institution in Malaysia. *Asian Pac J Cancer Prev*, **11**, 149-52.

Lee R, Droller MJ (2000). The natural history of bladder cancer. Implications for therapy. *Urol Clin North Am*, **27**, 1-13.

Matalka I, Bani-Hani K, Shotar A, et al (2008). Transitional cell carcinoma of the urinary bladder: a clinicopathological study. *Singapore Med J*, **49**, 790-4.

Messing EM, Young TB, Hunt VB, et al (1995). Comparison of bladder cancer outcome in men undergoing hematuria home screening versus those with standard clinical presentations. *Urology*, **45**, 387-96; discussion 396-7.

Narayana AS, Loening SA, Slymen DJ, et al (1983). Bladder cancer: factors affecting survival. *J Urol*, **130**, 56-60.

Nishiyama H, Habuchi T, Watanabe J, et al (2004). Clinical outcome of a large-scale multi-institutional retrospective study for locally advanced bladder cancer: a survey including 1131 patients treated during 1990-2000 in Japan. *Eur Urol*, **45**, 176-81.

Parkin DM (2008). The global burden of urinary bladder cancer. *Scand J Urol Nephrol*, Suppl(218), 12-20.

Ries LAG (2007). Cancer survival among adults : U.S. SEER program, 1988-2001, patient and tumor characteristics, 276 p. pp., U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Bethesda, MD.

Rosenberg JE (2007). Current status of neoadjuvant and adjuvant chemotherapy for muscle-invasive bladder cancer. *Expert Rev Anticancer Ther*, **7**, 1729-36.

Ruggeri EM, Giannarelli D, Bria E, et al (2006). Adjuvant chemotherapy in muscle-invasive bladder carcinoma: a pooled analysis from phase III studies. *Cancer*, **106**, 783-8.

Sankaranarayanan R, Swaminathan R, Brenner H, et al (2010). Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol*, **11**, 165-73.

Shariat SF, Karakiewicz PI, Palapattu GS, et al (2006). Outcomes of radical cystectomy for transitional cell carcinoma of the bladder: a contemporary series from the bladder cancer research consortium. *J Urol*, **176**, 2414-22; discussion 2422.

Shelley MD, Barber J, Wilt T, et al (2002). Surgery versus radiotherapy for muscle invasive bladder cancer. *Cochrane Database Syst Rev*, CD002079.

Takashi M, Wakai K, Hattori T, et al (2002). Multivariate evaluation of factors affecting recurrence, progression, and survival in patients with superficial bladder cancer treated with intravesical bacillus Calmette-Guerin (Tokyo 172 strain) therapy: significance of concomitant carcinoma in situ. *Int Urol Nephrol*, **33**, 41-7.

Türkölmez K, Tokgöz H, Reşorlu B, et al (2007). Muscle-invasive bladder cancer: predictive factors and prognostic difference between primary and progressive tumors. *Urology*, **70**, 477-81.

Umbas R (2007). Bladder cancer: 10 years experience from two tertiary care hospitals in Indonesia. *Indonesian J Surg*, **35**, 17-22.