# METASTASIS AND LOCAL INVASION PATTERN OF BLADDER CANCER IN HASAN SADIKIN HOSPITAL

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#### **ABSTRACT**

Objective: The aim of this study is to provide database about local invasion and metastasis pattern, as well as the disease characteristics of bladder cancer in Hasan Sadikin Hospital, Bandung. Material & Methods: Between January 2011 and December 2016 there were 321 cases of bladder cancer recorded in our hospital. Of all cases, 106 patients included in this study, with evident of local invasion or distant metastasis either radiologically (contrast abdominal pelvic CT scan) or pathologically. Results: The study group consist of 106 patients (86 men [81.7%], 20 women [28.3%]); with mean age of 56.78 ± 13.19 (4-76) years old. Histopathology findings of transitional cell carcinoma (TCC) consist of 82 (77.3%) patients and the atypical histology features group of 24 (22.7%) patients. Local invasion was found in 99 patients of 321 (30.8%), with the most common organ invasion to the prostate in male (n=38 [35.8%]). Lymph node metastasis were found in 47 patients (44.3%), with the most common nodal metastasis to obturator lymph nodes (n=21 [19.8%]). Distant metastasis was found in 24 patients (22.6%) with the most common site for distant metastasis was the liver  $(n=12 \lceil 11.3\%]$ ). In TCC group, 12 patients (63.1%) had a distant organ metastasis with nodal metastasis, whereas in atypical group, majority of the patients with distant organ metastasis (n=5 [83.3%]) had no lymph node involvement. Moreover, in transitional cell group, not all patient  $(n=17 \lceil 73.1\%])$  had local invasion of the tumor, while all patients with distant organ metastasis in atypical group  $(n=6 \lceil 100\% \rceil)$  had abdominal or pelvic wall invasion (cT4b). Conclusion: TCC is the most common pathology findings and with Prostate is the most common site for local tumor invasion. Obturator lymph nodes is the most common nodal metastasis and liver is the most common site for distant metastasis in bladder cancer.

Keywords: Bladder cancer, local invasion, metastasis.

# **ABSTRAK**

Tujuan: Tujuan penelitian ini adalah untuk menyediakan data tentang pola invasi lokal dan metastasis, serta karakteristik penyakit kanker buli di RSUP Hasan Sadikin Bandung. Bahan & Cara: Antara Januari 2011 dan Desember 2016 terdapat 321 kasus kanker buli di rumah sakit kami. Dari semua kasus tersebut, 106 pasien diinklusikan, dengan adanya bukti invasi lokal atau metastasis jauh baik secara radiologis maupun patologis. **Hasil:** Subyek penelitian terdiri atas 106 pasien (86 laki-laki [81.7%], 20 perempuan [28.3%]); dengan rerata usia 56.78 ± 13.19 (4-76) tahun. Gambaran histopatologis terdiri atas transitional cell carcinoma (TCC) sebanyak 82 (77.3%) pasien dan gambaran atipikal sebanyak 24 (22.7%) pasien. Invasi lokal ditemukan pada 99 dari 321 (30.8%) pasien, dengan organ yang paling sering diinvasi adalah prostat pada laki-laki (n=38 [35.8%]). Metastasis kelenjar getah bening (KGB) ditemukan pada 47 pasien (44.3%), dengan metastasis KGB tersering adalah KGB obturator (n=21 [19.8%]). Metastasis jauh ditemukan pada 24 pasien (22.6%) dengan tempat metastasis jauh tersering adalah liver (n=12 [11.3%]). Pada grup dengan gambaran histopatologis TCC, 12 pasien (63.1%) memiliki metastasis jauh dengan metastasis KGB, sementara pada grup atipik, mayoritas pasien dengan metastasis jauh tidak memiliki metastasis KGB (n=5 [83.3%]). Lebih jauh, pada grup TCC tidak semua pasien (n=17[73.1%]) memiliki invasi lokal, sedangkan semua pasien dengan metastasis jauh pada grup atipik (n=6 [100%]) memiliki invasi dinding abdomen atau pelvis (cT4b). Simpulan: TCC merupakan gambaran histopatologis tersering, prostat merupakan lokasi invasi lokal tersering. KGB obturator merupakan lokasi metastasis KGB tersering dan liver merupakan tempat tersering terjadi metastasis jauh.

Kata Kunci: Invasi lokal, kanker buli, metastasis.

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# INTRODUCTION

Bladder cancer is the ninth most common cancer in the world, and the second most common urological cancer. In 2012, there were 430.000 new cases diagnosed and it counts for 3.1% of all cancer cases. Since the early 1990s, there have been major advances in the management of bladder cancer. Abdominal and pelvic cross-sectional imaging are recommended by the National Comprehensive Cancer Network (NCCN) when muscle-invasive disease is suspected before TUR. Studies vary widely on the overall sensitivity and specificity of computed tomography (CT) imaging with regard to final pathology tumor stage at the time of radical cystectomy. Studies using multi detector CT scanners have reported the best results, with sensitivities ranging from 89-91% and specificity of 92-95% for local staging.4,5

A high suspicion for extravesical disease is warranted when hydronephrosis is noted on cross-sectional imaging. The presence of hydronephrosis on staging CT is associated with an increased risk of extravesical disease (27.8% vs. 17.3%) at the time of cystectomy. The reported sensitivity and specificity of CT in detecting nodal metastasis ranges from 31-50% and 68-100%, respectively.<sup>6</sup>

Refined imaging has resulted in more accurate staging, and advances in surgical technique have been coupled with improved chemotherapeutic regimens. However, there are limited data on the metastatic and local invasive pattern of bladder cancer especially in our region.

# **OBJECTIVE**

To provide database about local invasion and metastasis pattern, as well as the disease characteristics of bladder cancer in our hospital.

#### MATERIAL & METHODS

Between January 2011 and December 2016 there were 321 cases of bladder cancer recorded in our hospital. We reviewed the medical records of 106 patients with pathologically proven muscle-invasive bladder cancer consecutively registered at our institution. 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 histopathology 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 and was classified according to European Association of Urology. Nodal status at presentation also was noted. 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. Retrospective review of all available CT scans. Thorax Xray, head CT scans was performed to determine the sites, number, and imaging features of the metastatic lesions and the presence of local recurrence. For patients who underwent cystectomy, the pathology 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 CT findings in the pelvis.

The histopathology subtypes of bladder cancer included transitional cell carcinoma (TCC), squamous cell carcinoma, adenocarcinoma, and other types. Due to small numbers of other histopathology types, we group them as atypical histology type.

# **RESULTS**

The study group consist of 106 patients (86 men [81.7%], 20 women [28.3%]); with mean age of  $56.78 \pm 13.19$  (4-76) years old. Histopathology findings of transitional cell carcinoma (TCC) consist of 82 (77.3%) patients and the atypical histology features group of 24 (22.7%) patients. Local invasion was found in 99 patients of 321 (30.8%). Lymph node metastasis were found in 47 patients (44.3%). Distant metastasis was found in 24 patients (22.6%).

Local invasion pattern was collected either radiologically (abdominal pelvic CT scan with contrast) or pathologically (cystectomy specimens) T3 and T4 (extravesical extension). In total, 99 patients with local invasion was documented. The most common extravesical extension was prostate (35.8%), followed by pelvic wall and abdominal wall (29.2%, 24.5%) and the least common extravesical extension was the peritoneum (2.8%). The sites and frequency of local invasion lesions are shown in Table 1 and Figure 1.

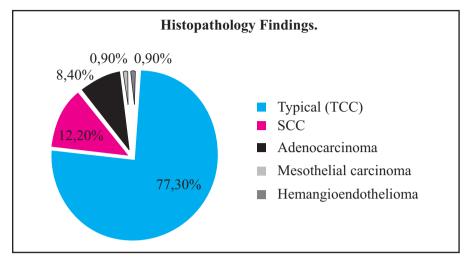


Figure 1. Histopathology Findings.

Table 1. Local invasion pattern of bladder cancer.

Local Invasion Pattern	Overall (n=99)	TCC (n=75)	Atypical (n=24)
Prostate	35.8%	40.2%	20.8%
Pelvic wall	29.2%	28%	33%
Abdominal wall	24.5%	18.2%	45.8%
Large bowel	22.6%	17%	42%
Women internal genitalia	9.4%	7.3%	16.6%
Ileum	6.6%	4.8%	12.5%
Ureter	5.6%	7.3%	
Urethra	4.7%	3.6%	
Seminal vesicle	4.7%	6%	
Peritoneum	2.8%	1.2%	8.3%

**Table 2.** Lymph node metastasis pattern.

Lymph Nodes	Overall (n=47)	TCC (n=34)	Atypical (n=14)
Obturator External iliac	19.8% 15%	21.9% 13.4%	12.5% 20.8%
Hypogastric	13.2%	10.9%	20.8%
Presacral	3.7%	2.4%	8.3%
Para aortic Common iliac	6.6% 6.3%	4.8% 8.8%	12.5%

Table 3. Distant metastasis pattern.

Metastasis site	Overall (n=27)	Typical (n=21)	Atypical (n=6)
Liver	12.2%	10.7%	16.6%
Bone	6.6%	5.9%	8.3%
Lung	5.6%	7.1%	
Brain	0.94%	1.2%	

Lymph node metastasis data were collected either radiologically (abdominal pelvic CT scan with contrast) or pathologically (confirmed positive lymph node pathology). In total, 47 patients (44.3%) with lymph node metastasis were documented.

Twenty-nine (61.7%) of 47 patients had multiple lymph node site metastasis. The most common lymph node metastasis were pelvic regional lymph nodes (46.2%) with obturator lymph node was the most common metastasis site. Other lymph node metastasis site were para aortic lymph node, and common iliac lymph nodes. The sites and frequency of lymph node metastasis lesions are shown in Table 2 and Figure 2.

Distant metastasis data were collected radiologically (Thorax X-ray, abdominal CT scan or ultrasound, head CT scan, and bone scan).

In total, 27 patients (25.5%) of 106 patients with distant metastasis were documented. Twentyone of 82 patients with transitional cell pathology findings (25.6%) experienced distant metastasis, while 6 of 24 patients with atypical pathology findings (25%) experienced distant metastasis. Overall, the most common metastasis site was the liver (12.2%), as in transitional cell group (10.7%) and also in atypical group (16.6%). The next most common metastasis site was the bone, either overall (6.6%), transitional cell group (5.9%) or atypical group (8.3%). Lung metastasis was found only in transitional cell group (7.1%) as in brain metastasis (1.2%) (Table 3, Figure 3).

Hydronephrosis was found either from ultrasound or abdominal-pelvic CT scan with contrast of the bladder cancer patients. From 106

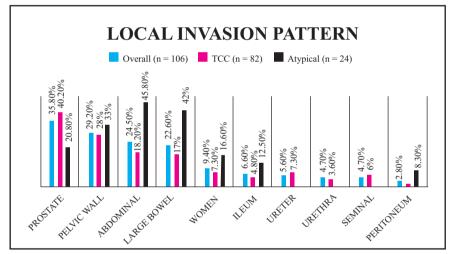


Figure 1. Local invasion pattern.

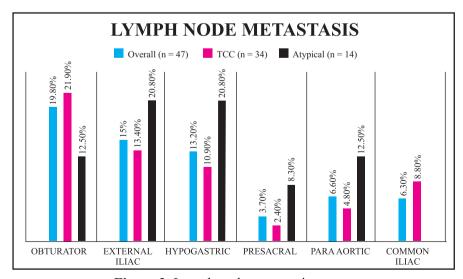


Figure 2. Lymph node metastasis pattern.

Table 4. Hydronephrosis pattern.

Hydronephrosis	Overall	TCC	Atypical
Unilateral	21.60%	19.50%	29.10%
Bilateral	69.80%	69.50%	70.83%
No hydronephrosis	8.40%	10.90%	0%

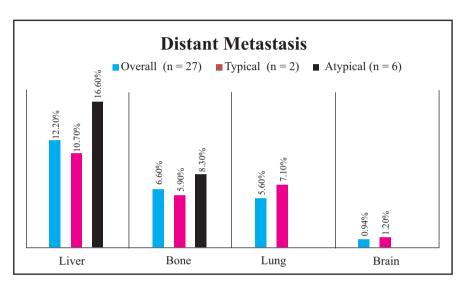


Figure 3. Distant metastasis pattern.

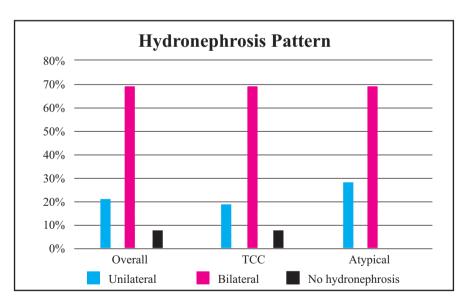


Figure 4. Hydronephrosis pattern of bladder cancer patients

patients, 97 patients (91.5%) had hydronephrosis either unilateral (23 patients, 21.6%) or bilateral (74 patients, 69.8%) and 9 patients without hydronephrosis (8.4%). The same pattern was encountered in transitional cell group (bilateral

69.5%, unilateral 19.5%, no hydronephrosis 10.9%). In atypical group, 70.83% experienced bilateral hydronephrosis, 29.10% with unilateral hydronephrosis and no patient found without hydronephrosis.

# **DISCUSSION**

Metastatic status is an essential determinant of prognosis of patients with muscle-invasive bladder cancer treated by cystectomy, and preoperative metastases detection is crucial for treatment selection in these patients. The current gold standard of preoperative staging were transurethral resection of bladder tumor (TURBT) followed by computed tomography (CT) imaging. They provides excellent staging specificity, but often understages the disease, leading to pathology upstaging and adverse outcomes in patients undergoing radical cystectomy. The accuracy of CT in determining extravesical tumour extension varies from 55-92% and increases with more advanced disease. 9

In our study, both pathological and clinical staging were used to determine tumor advancement. For those who unfit or denied to underwent radical cystectomy, clinical staging using abdomen and pelvic CT scan were used. For patients who underwent radical cystectomy and pelvic lymph node dissection, pathological staging were used, and we combine the data to evaluate the local invasion and metastasis pattern.

In this study, the most common extravesical extension was prostate (35.8%), followed by pelvic wall and abdominal wall (29.2%, 24.5%). Stage pT4 bladder cancer is defined by tumor invasion into an adjacent organ, including the uterus, vagina, prostate, pelvic wall or abdominal wall. According to Bierley et al, pT4a includes invasion of prostate, uterus or vagina, and pT4b indicates pelvic or abdominal wall invasion.<sup>10</sup> The significance of identifying prostatic involvement is the survival rate. Esrig et al, studied 143 bladder cancers with prostatic involvement, dividing them into two groups. 11 Group I penetrated the full thickness of bladder wall to involve the prostate, and group II involved the prostate by extension from the prostatic urethra. Five-year overall survival rates were 21 and 55% for group I and group II patients, respectively. Among group II patients, the presence of prostatic stromal invasion was associated with a worse prognosis than for patients in whom urothelial cancer was confined to the urethral mucosa only. In T4b patients, complete resection of the tumour is unlikely, and local recurrence is most likely to happen within first year.<sup>12</sup> Direct perivesical tumor extension involving the seminal vesicles was associated with poor prognosis similar to that of pT4b bladder cancer.

Overall survival for these patients was only 10%, similar to pT4b cancer (7%).<sup>13</sup> Seminal vesicle involvement by direct perivesical tumor extension is a poor prognostic indicator.<sup>14</sup>

In our study, regional pelvic lymph node involvement remains the primary nodal metastasis, regardless of the tumor local stage and histopathology pattern. Assessment of LN metastases based solely on size is limited by the inability of both CT and MRI to identify metastases in normal-sized or minimally enlarged nodes. The sensitivity for detection of LN metastases is low (48-87%).<sup>15</sup> Specificity is also low because nodal enlargement may be due to benign disease. Overall, CT and MRI show similar results in the detection of LN metastases in a variety of primary pelvic tumours.<sup>15</sup> Pelvic nodes >8 mm and abdominal nodes >10 mm in maximum short-axis diameter, detected by CT or MRI, should be regarded as pathologically enlarged.<sup>16</sup> Recent studies have emphasized the importance of lymph node density for nodal staging. Lymph node density is defined by the ratio of positive lymph nodes to the total number of lymph nodes sampled.<sup>17</sup> In an analysis of 248 patients with positive nodal metastasis, Kassouf et al, found that lymph node density was an independent predictor of cancer survival. The 5-year cancer-specific survival for patients with lymph node density 420% was 15%, compared with 55% 5-year cancer-specific survival among patients with lymph node density 20%. 18

In this study, 27 patients of 106 subjects (25.5%) came with distant metastasis, with the most common metastasis site was the liver, bone, and lung. This number is higher than previous study that found 10-15% patient came with metastatic disease.19 But compared to previous study by Wallmeroth et al, this number is way lower. They found metastases in 68% of 367 patients having muscle-invasive bladder cancer.<sup>20</sup> The pattern of the metastasis of primary site is almost the same as the study, that stated regional lymph nodes, lung, liver and bones were the most frequent sites of metastases in patients with muscle-invasive urinary bladder cancer.20 This result is similar with the results of several previous studies which all found the highest rate of metastasis at these four locations. 21,22 Also in study by Wallmeroth et al, they found that almost all organs were involved by metastases in some patients, and the metastases were found in at least one of the four most frequently involved organs in 95% of patients with metastatic disease.<sup>20</sup> In our study, we are unable to found other metastasis site,

because we did not perform autopsy on our deceased patients like the previous study, and solely depends on radiology finding of suggestive distant metastasis.

#### **CONCLUSION**

In summary, the results of this study show that prostate is the most common organ invaded in transitional cell carcinoma, while the atypical histology types tends to invade the body wall. Obturator lymph nodes was the most common site for nodal metastasis. However, it tends to multiple in nature and invade the regional pelvic lymph nodes. Liver, lung and bones are the most frequent sites of bladder cancer metastases. The evaluation of local invasion, nodal invasion and distant metastasis is important to evaluate, because it affect the prognosis of the patients. Also we should kept in mind that staging CT of the abdomen and pelvis in patients with invasive bladder carcinoma has limited accuracy, mainly because of its inability to detect microscopic or small volume extravesical tumor extension and lymph nodes. Thus, CT tends to under stage advanced disease.

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