RESEARCH COMMUNICATION

Pre-treatment Hemoglobin Levels are Important for Bladder Carcinoma Patients with Extravesical Extension undergoing Definitive Radiotherapy

Vuslat Yurut-Caloglu[1]*, Murat Caloglu[1], Mustafa Kaplan[2], Osman Inci[2]

Abstract

Purpose: To evaluate prognostic factors affecting local control (LC), distant metastases-free survival (DMFS) and overall survival (OS) in bladder carcinoma patients undergoing extravesical extension. Patients and Methods: We retrospectively reviewed the charts of 61 consecutive patients with T3 or T4 bladder carcinoma, treated with definitive radiotherapy from 1999 through 2007. Results: Median age was 69 years and follow-up was 29 months. The LC rate was 33% at 4 years and was increased in patients with a Hb≥12 g/dl (p=0.003) or a LDH<180 U/L (p=0.021) and in those who received concurrent chemotherapy (p=0.022) on univariate analysis. DMFS was affected by anemia (Hb<12 g/dl) (p=0.039), the absence of chemotherapy (p=0.034) and the presence of newly-diagnosed disease (p=0.01). The OS rate was 19% at 4 years. Non-pure transitional cell carcinoma histological type (p=0.024), anemia (p=0.004), elevated LDH (p=0.003), and newly diagnosed disease (p=0.011) were poor prognostic factors on univariate analyses for OS. Anemia was the only negative prognostic factor for LC (p=0.03), DMFS (p=0.002) and OS (p<0.0001) on multivariate analysis. Conclusion: Pre-treatment Hb level is the most important prognostic factor in patients treated with definitive radiotherapy, so that anemia may act as a surrogate biological marker for aggressive disease.

Key Words: Anemia - bladder cancer - prognostic factor - chemotherapy/radiotherapy - Turkey

Asian Pacific J Cancer Prev, **10**, 1151-1158

Introduction

The optimal initial treatment for muscle-invasive bladder cancer has not yet been determined and is controversial. Although radical cystectomy is considered the gold standard for muscle-invasive bladder cancer, previous trials have suggested that definitive radiotherapy (RT) with surgical salvage produces a survival rate similar to that of immediate surgery (Hayter et al., 1999; Scrimger et al., 2001; Tsukamoto et al., 2004; Kotwal et al., 2008). The best candidates for radical cystectomy are those who are mostly young and otherwise healthy. Such patients often have small tumors that are confined to the bladder and are able to tolerate adjuvant systemic treatment. However, a significant proportion of the patients treated with RT are not suitable for surgery because they are elderly, have significant co-morbidity, and/or have locally advanced disease (Moonen et al., 1998; Santacaterina et al., 2002; Chahal et al., 2003). Previous studies have attempted to identify variables that have prognostic value in patients with bladder cancer undergoing RT. One such variable is the pre-treatment hemoglobin (Hb) level (Milosevic et al., 2007). It has long been recognized that oxygen plays an important role in the stabilization of genetic damage from ionizing radiation (Gray et al., 1953). The relationship between anemia and hypoxia, however, is complex and influenced by multiple variables. According to one hypothesis, low Hb levels may negatively influence intratumoral oxygen tension leading to radiation resistance. Other researchers have speculated that low Hb levels are merely a symptom of a more aggressive and intrinsically radioresistant malignancy. Therefore, the correction of Hb levels would have a little chance in altering outcomes (Hill et al., 1971; Fyles et al., 2000).

To our knowledge, previous studies have emphasized the prognostic importance of anemia in patients with T2 to T4 bladder cancer. In this study, we retrospectively analyzed data from patients treated with definitive RT for bladder carcinoma with extravesical extension (T3 to T4 tumors). Irresectable large tumors or comorbid illnesses made surgical treatment inconvenient or patients refused surgery. Our aim was to identify factors affecting local control, distant recurrence-free survival and overall survival.

Materials and Methods

Patients

We identified 61 consecutive patients with T3 or T4

*[1]Department of Radiation Oncology, [2]Department of Urology, Faculty of Medicine, Trakya University, Edirne, Turkey *For Correspondence: vuslatyurut@yahoo.com*

non-metastatic bladder cancer who were treated in our clinic between October 1999 and April 2007. All patients were initially evaluated by a team of radiation oncologists, medical oncologists, and urologists. The extent of the disease was defined using the American Joint Committee on Cancer Staging Manual, 2002 (AJCC, 6th Edition). All patients received definitive RT since they were not suitable for primary surgery by virtue of advanced diseases (54%) or comorbid illnesses (25%) or because they refused cystectomy (21%). Transurethral resection of bladder (TURB) was performed as completely and safely as possible; TURB was judged to be complete in 34 patients (56%).

Complete hematological and biochemical profiles were checked before the treatment. An erythrocyte suspension was administered before RT if a patient's Hb level was < 12 g/dl, also during treatment. Patients who developed suspicious bone metastasis symptoms underwent whole body bone scintigraphy.

The follow-up evaluations included clinical examination and repeat resection 6 weeks after the end of (RT), every 3 months for the first year, biannually for 5 years, and yearly thereafter. Data were collected regarding patient demographics, disease and treatment parameters and outcomes.

Radiotherapy:

All patients were placed in the supine position during RT. A pelvic box technique was used. Individual lead blocks or multileaf collimators were used to protect normal tissues. Wedge and compensator filters were used to optimize the dose distribution. Patients were treated with Co60 instrument until the year 2000 and later with LINAC 6-18 MV photon.

Radiation was delivered at 1.8 Gy/fraction once daily, 5 days per week. 45 Gy RT was administered to the tumor and bladder including the external and internal iliac lymph nodes. The following field borders were used: the L5-S1 interspace cephalad, at least 1 cm beyond the pelvis bone laterally, and the inferior border of the obturator foramen caudally. Later, 15 to 21 Gy dose was applied to the bladder. Acute and delayed toxicities arising from RT were reported according to standard RTOG criteria.

Chemotherapy:

Patients received Cisplatin (CDDP); the dose was either 100 mg/m^2 on days 1, 22 and 43 or 40 mg/m^2 once a week. Both regimens were administered concurrently with RT when possible. Patients who were not good candidates for CDDP, due to impaired kidney function, received carboplatine. Toxicity arising from chemotherapy was reported according to World Health Organization (WHO) criteria.

Statistical Analysis:

Follow-up was estimated from the first date of RT to the date of death or the last contact date. Clinical and therapeutic factors as well as tumor characteristics were first analyzed in a univariate analysis. Summary tables (absolute and relative frequencies) were used for descriptive analysis of the categorical variables. The $\chi 2$ two-tailed test was used as appropriate to compare the categorical variables. The Fisher-exact test was used to compare the complication rates between the different treatment modalities. Factors that seemed determinant were subsequently evaluated with Kaplan–Meier survival curves and by the Log-rank test. Finally, the significant factors in the univariate analysis were tested in a multivariate analysis using the Cox regression model. A two-sided 5% significance level was applied for the comparison of the groups. P was considered statistically significant when <0.05.

Table 1. Characteristics of the Patients

Characteristic		Number (%)
Gender	Male	55 (90%)
	Female	6 (10%)
Age (years)	median	69 (range; 40-93 years)
	<70	32 (53%)
	≥70	29 (47%)
Classification of histology	pure-TCC	48 (79%)
	epidermoid	4 (6%)
	adenocarcinoma	2 (3%)
	transitional with squamous cell mixt	7 (12%)
Disease	progressive	19 (31%)
	primary	42 (69%)
Pre-RT treatment	TURB	34 (56%)
	biopsy alone	27 (44%)
Anemia	median	10.7 g/dl (range; 6.5- 15.6 g/dl)
	Hb<12 g/dl	38 (62%)
	Hb≥12 g/dl	23 (38%)
LDH	median	216 U/L (range; 35-638 U/L)
	<180 U/L	20 (33%)
	≥180 U/L	26 (43%)
	unknown	15 (25%)
ALP	median	86 U/L (range; 50-305 U/L)
	<100 U/L	28 (46%)
	≥100 U/L	19 (31%)
	unknown	14 (23%)
Tumor grade	low	17 (28%)
	high	40 (65%)
	unknown	4 (7%)
T stage	T3	19 (31%)
	T4	42 (69%)
N stage	N0	47 (77%)
	N1	5 (8%)
	N2	8 (13%)
	N3	1 (2%)
Clinical Stage	III	40 (66%)
	IV	21 (34%)
Treatment	RT alone	28 (46%)
	Concurrent CDDP	33 (54%)

Hb, hemoglobin; TCC, Transitional cell carcinoma; RT, radiotherapy; TURB, transurethral resection of the bladder; ALP, Alkaline phosphatase; LDH, Lactate dehydrogenase; CDDP, cisplatin

Results

Patients and tumor characteristics:

The median follow-up was 29 months (range; 0.5 to 51 months). The clinical and demographic characteristics of all 61 patients are listed in Table 1. Fifty-five patients (90%) were male. The median age was 69 years (range; 40 to 93 years). Histologic analysis showed that 48 patients

Table 2. Prognostic Factors for 2 Years Local Control

Factor	Category	Control rate (%)	Log-rank test	Cox regression
Anemia	Hb<12 g/dl	22	<0.0001	0.009
	Hb≥12 g/dl	87		
LDH	<180 U/L	58	0.005	NS
	≥180 U/L	41		
Concurrent CDDP	Yes	69	<0.0001	NS
	No	22		
Completely TURB	Yes	37	0.013	NS
	No	27		

Hb, hemoglobin; LDH, Lactate dehydrogenase; CDDP, cisplatin; NS, non-significant; TURB, Transurethral resection of bladder

Table 3. Prognostic Factors for 2 Year Distant Metastasis Free Survival

Factor	Category	DMFS rate (%)	Log-rank test	Cox regression
Anemia	Hb<12 g/dl	19	0.004	0.002
	Hb≥12 g/dl	66		
Concurrent CDDP	Yes	69	0.034	NS
	No	22		
Disease	Progressive	73	0.01	NS
	Primary	46		

Hb, hemoglobin; CDDP, cisplatin; NS, non-significant

Table 4. Prognostic Factors for Overall Survival

Factor	Category	OS rate (%)	Log-rank test	Cox regression
Anemia	Hb<12 g/dl	19	0.004	<0.0001
	Hb≥12 g/dl	66		
Histological type	Pure TCC	43	0.024	NS
	Others	9		
LDH	<180 U/L	55	0.003	NS
	≥180 U/L	25		
Disease	Progressive	43	0.011	NS
	Primary	12		

Hb, hemoglobin; TCC, transitional cell carcinoma; NS, non-significant

(79%) had transitional cell carcinoma. The remaining 13 patients (21%) has less common bladder tumors: squamous cell carcinoma (4 patients), adenocarcinoma (2 patients) and transitional with squamous cell mixed type carcinoma (7 patients). 65% of the patients had high-grade tumors. The diagnosis of 19 (31%) patients with muscle-invasive carcinoma was made on follow-up of superficial in situ or T1 carcinoma. Nineteen patients (31%) had T3 disease and 42 patients (69%) had T4 disease. Positive nodal disease was detected in 14 patients (23%). Forty patients (66%) had stage III disease and 21 (34%) had non-metastatic stage IV disease. Before RT, the median Hb value was 10.7 g/dl (6.5-15.6 g/dl), the median alkaline phosphatase (ALP) was 86 U/L (range; 50-305 U/L) and the median lactate dehydrogenase (LDH) was 216 U/L (range; 35-638 U/L).

Thirty-eight (62%) patients had a Hb level of <12 g/dl before the treatment. There was a significant correlation between pre-treatment anemia and non-pure transitional cell carcinoma histologic type (p=0.01), WHO performance status (p<0.0001), and LDH level (p=0.005).

Treatment details:

Chemotherapy concomitant with RT was applied to the 33 (54%) of the patients. The median RT dose was 62 Gy (range; 9 to 68 Gy). Fifty-six patients (92%) completed their planned treatment. RT duration of <50 days was a significantly important prognostic factor for local control in the patients who completed their planned definitive treatment (log-rank; p=0.021). The 2-year local control rate was 58% in patients with a RT duration of <50 days versus 33% in the patients with a RT duration ≥50 days. Three patients refused to complete treatment due to acute toxic effects. Two patients died of acute cardiovascular complication during concurrent chemoradiotherapy.

Treatment was generally well tolerated. Acute side effects related to RT were seen in 31 (50.8%) patients. There was no Grade IV acute toxicity. The most common treatment-related acute side effect was urinary toxicity (n=31): 19 patients (31.1%) had pure urinary toxicity, 4 patients (6.6%) had pure bowel toxicity and 8 patients (13.1%) had combined bowel and urinary toxicity. Grade 3 acute urinary toxicity was recorded in 9 patients (14.7%) and 4 patients (6.6%) experienced grade 3 acute bowel toxicity. Moreover, 4 patients (6.6%) experienced grade 3 or 4 late urinary toxicity. One (1.6%) of the 61 patients developed grade 4 late bowel toxicity without tumor progression.

Data for prognostic factors are summarized in Tables 2-4.

Local control:

The local control rates at 2 years and 4 years were 44% and 33%, respectively. The Kaplan-Meier survival curve for local control is shown in Figure1. Local recurrence was detected in the bladder of 23 patients (38%). Twenty-two patients had muscle-invasive recurrence. Only one patient had superficial recurrence that was treated with TURB and Bacille Calmette-Guérin (BCG). Three patients were treated with salvage cystectomy, and the other patients with chemotherapy or

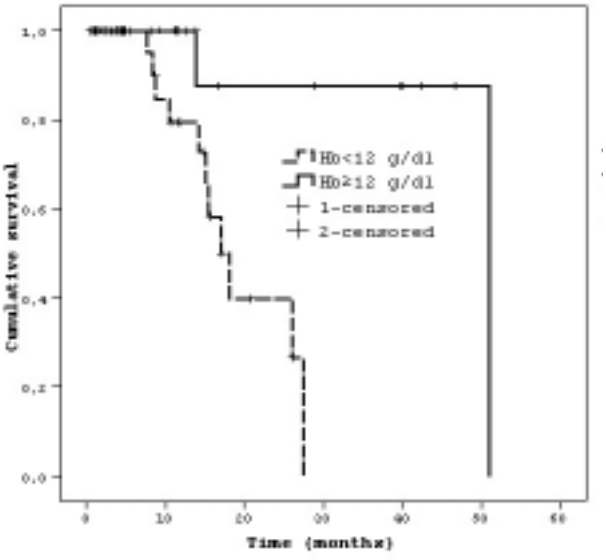

Figure 1. Kaplan-Meier Survival Curves Showing the Difference in Local Control between Anemic and Non-anemic Patients

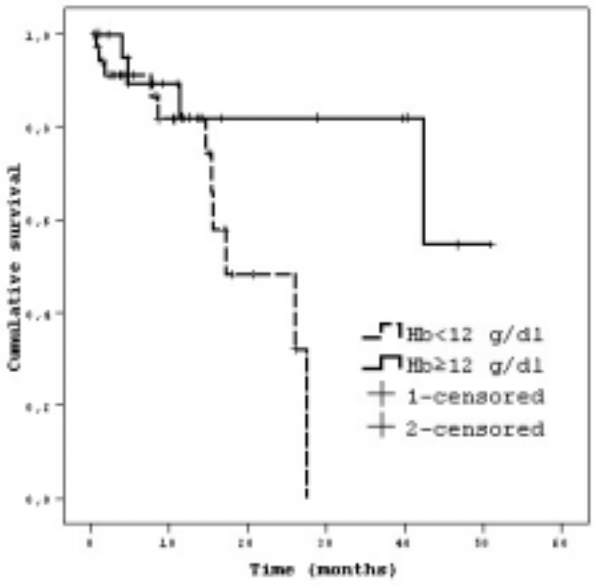

Figure 2. Kaplan-Meier Survival Curves Showing the Difference in Distant Metastasis-free Survival between Anemic and Non-anemic Patients

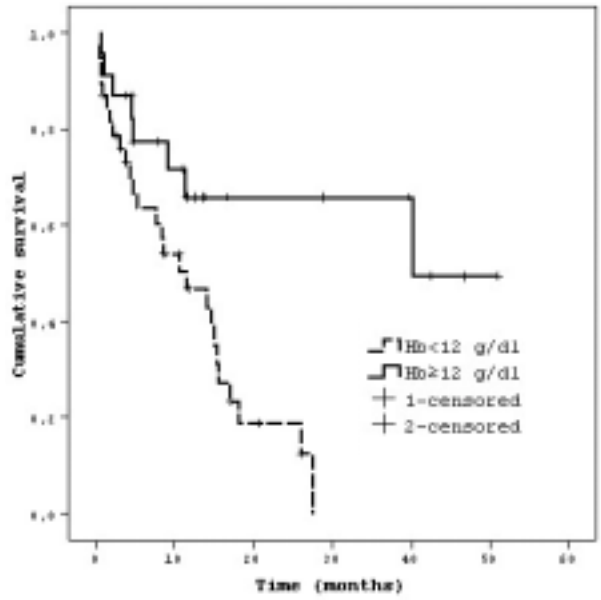

Figure 3. Kaplan-Meier Survival Curves Showing the Difference in Overall Survival between Anemic and Non-anemic Patients

chemoradiotherapy or the best supportive care owing to poor general health, locally advanced disease, distant metastases or refusal of surgery. Local control at 2 years was found to be similar between T3 and T4 disease (61% for patients with T3 disease versus 54% for T4 disease; log-rank; p=0.42). However, these rates were 40% in patients with a Hb level <12 g/dl versus 65% with a Hb level of ≥12 g/dl. Univariate analysis showed that the local control rate was significantly increased in the patients with a Hb level of ≥12 g/dl (log-rank; p=0.003) and those with an LDH of <180 U/L (log-rank; p=0.021), in those who underwent complete TURB (log-ranks test; p=0.013) and in those who received concurrent chemotherapy (log-rank ; p=0.022). All of these parameters dropped out of the Cox regression model. The only prognostic factor related to local control was the Hb level (p=0.009).

Distant recurrence-free survival:

The estimated distant recurrence-free survival was 30.8±3.7 months (95% CI; 23.4 months to 38.1 months). Distant recurrence was detected in 15 patients (25%), 5 with pure bone recurrence, 5 with pure lung recurrence, 2 with pure liver recurrence and 3 with multiple metastases. The distant recurrence-free survival was significantly affected by a Hb level of <12 g/dl (log-rank; p=0.039), the absence of concurrent of chemotherapy (log-rank; p=0.034) and the presence of newly-diagnosed disease (log-rank; p=0.01). In addition, there was a positive trend in favor of better recurrence-free survival in patients with an LDH of <180 U/L compared with those with an LDH of ≥180 U/L (log-rank; p=0.057). When the variables were tested in the Cox regression model, the only prognostic variable was the Hb level (p=0.002).

Overall survival:

Overall survival rates at 2 years and 4 years were 33% and 19%, respectively. The Kaplan-Meier survival curve for overall survival is shown in Figure 2. Thirty-five patients (57%) had died at the time of this analysis. Overall survival was 11.9±1.6 months in patients with a Hb level of <12 g/dl and 33.6±4.8 months in the patients with a Hb level of ≥12 g/dl. There was no significant difference in overall survival between the patients with T3 and T4 disease (95% CI; 23±5.6 months for patients with T3 versus 18.4±3 months for T4 disease, log-rank; p=0.45). Overall survival was significantly lower in the patients with newly diagnosed muscle-invasive bladder carcinoma than in those with progressive disease (2-year survival of 11% versus 42%, log-rank; p=0.011). The significant important poor prognostic factors on the log-rank test for overall survival were non-pure transitional cell carcinoma histologic type (p=0.024), a Hb level of <12 g/dl (p=0.004), LDH>180 U/L (log-rank; p=0.003), and newly diagnosed disease (p=0.011). Concurrent chemotherapy did not significantly affect overall survival (p=0.096). For overall survival, the only significantly negative prognostic factor on multivariate analysis was a Hb level of <12 g/dl (p<0.0001).

Discussion

Radical cystectomy is regarded as the mainstay of treatment for muscle-invasive bladder carcinoma. Radiotherapy is usually reserved for those patients who are medically unfit, have advanced tumor for surgery or have refused cystectomy. The purpose of this study was to determine the prognostic factors affecting local control, distant metastases-free survival and overall survival in bladder carcinoma patients with extravesical extension who were treated with definitive RT. We found that patients who had locally advanced T3 to T4 tumors with either fatty or adjacent organ involvement and/or positive lymph nodes had a poor prognosis. Moreover, our study showed that the most important prognostic factor for these patients was their pre-treatment Hb level.

The population of this study is typical of a clinical practice in that patients treated with definitive RT tend to

have medical comorbidities, advanced disease and a poorer performance status. Definitive external-beam RT leads to local control of muscle-invasive bladder cancer in approximately 30% to 50% of patients. Nevertheless, distant metastases develop in >50% of patients, and the long-term overall survival rate ranges from 25% to 30% (Milosevic, Gospodarowicz et al. 2007). Our results were different than previous reports in that our local control and overall survival rates were lower (our 4-year local control was 33% and the overall survival was 19%). This discrepancy might be explained by our small sample and the unfavorable selection criteria.

Salvage cystectomy is an important part of the integrated management plan for progressive or recurrent disease after RT (Milosevic et al., 2007). However, our patients had tumors that were more advanced or they had comorbid illnesses at the initial evaluation, excluding the possibility of effective salvage cystectomy after RT failure.

How an institution defines anemia is important in patients who are treated with RT. According to the WHO and the National Cancer Institute, anemia is defined as a Hb level< 12 g/dl (Bron et al., 2001). Although the blood Hb values that might lead to hypoxia in tumors have not been clearly described, patients with a Hb value of 12–14 g/dl are considered to have an optimal oxygen pressure (Vaupel et al., 1991). Therefore, we defined anemia as Hb<12 g/dl in our clinical practice. The presence of anemia can be used to predict reduced local control after RT as well as higher rates of distant metastases and death from bladder cancer. Both Quilty and Duncan (1986) and Gospodarowicz et al (1991) reported that a pre-treatment Hb level <12 g/dl was a poor prognostic indicator for tumor response, local control and overall survival in patients with muscle-invasive bladder cancer. This may be explained by anemia-induced tumor hypoxia, which leads to genetic instability and the emergence of more aggressive metastatic phenotypes. Furthermore, patients who are anemic at diagnosis may be more likely to have advanced disease (Joynson et al., 2006).

In our study, the multivariate analyses showed that the pre-treatment Hb level was the only independent prognostic factor for local control, distant recurrence-free survival and overall survival. The local control rates in anemic patients were significantly lower than those seen in patients with a normal pre-treatment Hb level. However, the patients who had anemia either before or during RT received blood transfusions, and the Hb levels in our patients were within the normal range during RT. Therefore, it is unlikely that either anemia-related tumor hypoxia or hypoxia-related radioresistance can explain why the local tumor control rate in the patients with anemia was poor. Moreover, previously published data suggest that anemia has a prognostic role in the treatment of malignancy, apart from its role in radiosensitivity (Joynson et al., 2006). Additionally, the surgical series in which anemia has been reported to have a negative prognostic role, also support this finding. Thrasher et al (1994) reported that a pre-cystectomy Hb level below 12 g/dl was a predictor of poor cancer-specific survival. In addition, in the presented study, the high incidence of anemia and distant metastases suggested that anemia is an indicator of metastasis. The presence of anemia should be considered a micrometastatic disease, which can not be seen with current imaging techniques.

Radiotherapy has been combined with chemotherapy to treat bladder cancer in many studies with the aim of enhancing local tumor control, reducing metastasis development, and improving patient survival. Cisplatin is the most active single agent in the treatment of patients with muscle-invasive bladder cancer (Coppin et al. 1996; Scrimger et al., 2001; Milosevic et al., 2007). Univariate analysis showed that concurrent chemoradiotherapy significantly increased local control and distant recurrence-free survival rates. Although an association was found between chemotherapy and overall survival, it was not a statistically significant one (p=0.096).

Gross complete TURB before RT is related to improved local control, although this finding has not been reported consistently (George et al., 2004; Milosevic et al., 2007). Our results showed that gross complete TURB was a statistically significant parameter for local control. However, distant recurrence-free survival or overall survival was not affected by TURB before definitive RT.

Advanced T category, large tumor size and the presence of extravesical disease all have been associated with local disease recurrence. Several studies have reported overall treatment results of T4 disease were poorer than that of T3 disease(Duncan and Quilty, 1986; George et al., 2004; Chung et al., 2007). All treatment results were better in the patients with T3 tumors than in those with T4 tumors in our study but the differences were not statistically significant. This result may be related to underestimation of the extent of the T3 disease, since our patients were staged according to clinical staging rather than pathological staging.

Most of the complications caused by definitive RT were associated with the bladder and bowel. Approximately 50% of patients had dysuria and urinary frequency during treatment, and 15% of patients reported acute toxic effects of the bowel (Henningsohn et al., 2002). Our study showed that acute urinary toxicity developed in 44.2% of the patients, and 19.7% of the patients experienced acute bowel toxicity. Late morbidity is important issue related to RT. Chahal et al (2003) reported that 5.2% of their patients had severe late bladder and 6.6% of their patients suffered significant complications. In this study, 6.6% of the patients experienced severe late bladder toxicity symptoms. Moreover, 1.6% of them developed severe late bowel toxicity without tumor progression. In our study, two patients died of treatment-related toxicities, which is similar to previous reports (Chahal et al., 2003). However, due to the retrospective nature of our database, we cannot exclude the possibility of interreporting of the treatment toxicity in some patients.

More than 90% of all malignant bladder tumors are transitional cell carcinoma. Squamous cell carcinomas and adenocarcnomas accounted for 5% and 2% of all malignant bladder tumors, respectively (Mostofi, 1988). Each has, for example, a different propensity for metastasis and local recurrence. One common observation to all subtypes is that variant histology usually imparts a poorer prognosis than pure-transitional cell carcinoma (Black et

al., 2008). Our study supports this hypothesis - we found that the non-pure transitional cell carcinoma histologic subtype significantly decreased the overall survival in the univariate analysis. Moreover, there was a significant correlation between non-pure transitional cell carcinoma histologic subtypes and anemia. This relation may explain why the non-pure histologic subtypes have the potential to become more aggressive.

A large number of publications have emphasized the importance of overall treatment time, implying that tumor proliferation during RT (Withers et al. 1988; Saunders et al. 1996). Maciejewski and Majewski (1991) found that protraction of the overall treatment time from 40 to 55 days led to a decrease in local control rates from 50% to about 5%. Our study showed a significant influence of overall treatment time in the patients who completed their planned treatment on local tumor control in the univariate analyses.

Nearly 30% of superficial bladder urothelial tumors already have progressed or will have progressed to muscle-invasive tumors during their follow-up (Stein et al,. 2001). However, only a few studies have evaluated the difference in prognosis between these progressive and primary muscle-invasive tumors (May et al., 2004; Turkolmez et al., 2007). Schrier et al (2004) were the first to demonstrate a statistically significant decreased survival for patients with progressive tumors . However, Vaidya et al (2001) reported a 2-year survival rate of 49% for those with primary invasive tumors and 79% for those with progression from less than T2 at presentation. Our study revealed that overall survival and distant metastases-free survival were significantly lower in the newly diagnosed patients than in those with progressive disease. This could be related to patients with superficial disease have been kept under close follow-up with cytologic analysis, urinalysis, and cystoscopy. Additionally, because of clinician and patient awareness and extra care regarding tumor symptoms and signs, these patients would be more likely to be diagnosed and treated earlier than patients with primary muscle-invasive tumors. Thus, it is expected that patients with progressive tumors would have better prognosis and survival rates than those with primary muscle-invasive tumors (Turkolmez et al., 2007).

Lactate dehydrogenase is found in blood and other body tissues, and it affects cellular energy production. High blood levels may be a sign of tissue damage and some types of cancer. Sengelov et al (1999) reported that elevated LDH levels were predictive of disseminated disease . Our study showed that elevated serum LDH levels significantly affected local control rates as well as overall survival rates in the univariate analysis. Moreover, there was an adverse relation between elevated LDH levels and distant recurrence-free survival, but the difference was not statistically significant. This finding might be explained by the fact that data related to LDH was missing from 15 patients. In addition, there was a significant relationship between LDH levels and Hb levels. Consequently, because of serum LDH might have a prognostic value; those with high levels should be considered at high-risk of relapse and might be treated with a more aggressive regimen.

In conclusion, this study suggests that a patient's pre-treatment Hb level is the most important prognostic factor for local control, distant metastases-free survival and overall survival in those treated with definitive RT. Furthermore, these outcomes can not be solely explained by radiosensitivity since all of the patients with a Hb level<12 g/dl received erythrocyte suspension before and during RT. Our study states that anemia may act as a surrogate biological marker for aggressive disease and the correction of anemia does not improve treatment results. The limitations of this study are intrinsic to its retrospective design and its small patient cohort, although our results may provide some helpful information for daily practice.

Acknowledgments

The authors wish to thank Mrs. Amy Slugg Moore for her valuable assistance in English writing.

References

Black PC, Brown GA, Dinney CP (2009). The impact of variant histology on the outcome of bladder cancer treated with curative intent. *Urol Oncol*, **27**, 3-7.

Bron D, Meuleman N, Mascaux C (2001). Biological basis of anemia. *Semin Oncol*, **28 (2 Suppl 8)**, 1-6.

Chahal R, Sundaram SK, Iddenden R, et al (2003). A study of the morbidity, mortality and long-term survival following radical cystectomy and radical radiotherapy in the treatment of invasive bladder cancer in Yorkshire. *Eur Urol*, **43**, 246-57.

Chung PW, Bristow RG, Milosevic MF, et al (2007). Long-term outcome of radiation-based conservation therapy for invasive bladder cancer. *Urol Oncol*, **25**, 303-9.

Coppin CM, Gospodarowicz MK, James K, et al (1996). Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*, **14**, 2901-7.

Duncan W, Quilty PM (1986). The results of a series of 963 patients with transitional cell carcinoma of the urinary bladder primarily treated by radical megavoltage X-ray therapy. *Radiother Oncol*, **7**, 299-310.

Fyles AW, Milosevic M, Pintilie M, Syed A, Hill RP (2000). Anemia, hypoxia and transfusion in patients with cervix cancer: a review. *Radiother Oncol*, **57**, 13-9.

George L, Bladou F, Bardou VJ, et al (2004). Clinical outcome in patients with locally advanced bladder carcinoma treated with conservative multimodality therapy. *Urology*, **64**, 488-93.

Gospodarowicz MK, Rider WD, Keen CW, et al (1991). Bladder cancer: long-term follow-up results of patients treated with radical radiation. *Clin Oncol (R Coll Radiol)*, **3**, 155-61.

Gray LH, Conger AD, Ebert M, Hornsey S, Scott OC (1953). The concentration of oxygen dissolved in tissues at the time of irradiation as a factor in radiotherapy. *Br J Radiol*, **26**, 638-48.

Hayter CR, Paszat LF, Groome PA, et al (1999). A population-based study of the use and outcome of radical radiotherapy for invasive bladder cancer. *Int J Radiat Oncol Biol Phys*, **45**, 1239-45.

Henningsohn L, Wijkstrom H, Dickman PW, Bergmark K, Steineck G (2002). Distressful symptoms after radical radiotherapy for urinary bladder cancer. *Radiother Oncol*

62, 215-25.

Hill RP, Bush RS, Yeung P (1971). The effect of anaemia on the fraction of hypoxic cells in an experimental tumour. *Br J Radiol*, **44**, 299-304.

Joynson CP, Sundar S, Symonds P (2006). Anaemia is associated with poor overall survival but not with inferior local control in patients with muscle invasive bladder carcinoma treated by radical external beam radiotherapy. A retrospective study. *Clin Oncol (R Coll Radiol)*, **18**, 728-34.

Kotwal S, Choudhury A, Johnston C, et al (2008). Similar treatment outcomes for radical cystectomy and radical radiotherapy in invasive bladder cancer treated at a United Kingdom specialist treatment center. *Int J Radiat Oncol Biol Phys*, **70**, 456-63.

Maciejewski B, Majewski S (1991). Dose fractionation and tumour repopulation in radiotherapy for bladder cancer. *Radiother Oncol*, **21**, 163-70.

May M, Helke C, Nitzke T, Vogler H, Hoschke B (2004). Survival rates after radical cystectomy according to tumor stage of bladder carcinoma at first presentation. *Urol Int*, **72**, 103-11.

Milosevic M, Gospodarowicz M, Zietman A, et al (2007). Radiotherapy for bladder cancer. *Urology*, **69 (1 Suppl)**, 80-92.

Moonen L, von de Voet H, de Nijs R, et al (1998). Muscle-invasive bladder cancer treated with external beam radiotherapy: pretreatment prognostic factors and the predictive value of cystoscopic re-evaluation during treatment. *Radiother Oncol*, **49**, 149-55.

Mostofi FK, Sesterhenn IA (1988). Pathology of tumors of the urinary tract. Diagnosis and Management of Genitourinary Cancer. Skinner DG and Lieskovsky G. Philadelphia, Pa, WB Saunders: 83-117.

Quilty PM, Duncan W (1986). The influence of hemoglobin level on the regression and long term local control of transitional cell carcinoma of the bladder following photon irradiation. *Int J Radiat Oncol Biol Phys*, **12**, 1735-42.

Santacaterina A, Settineri N, De Renzis C, et al (2002). Muscle-invasive bladder cancer in elderly-unfit patients with concomitant illness: can a curative radiation therapy be delivered? *Tumori*, **88**, 390-4.

Saunders MI, Dische S, Barrett A, et al (1996). Randomised multicentre trials of CHART vs conventional radiotherapy in head and neck and non-small-cell lung cancer: an interim report. CHART Steering Committee. *Br J Cancer*, **73**, 1455-62.

Schrier BP, Hollander MP, van Rhijn BW, Kiemeney LA, Witjes JA (2004). Prognosis of muscle-invasive bladder cancer: difference between primary and progressive tumours and implications for therapy. *Eur Urol*, **45**, 292-6.

Scrimger RA, Murtha AD, Parliament MB, et al (2001). Muscle-invasive transitional cell carcinoma of the urinary bladder: a population-based study of patterns of care and prognostic factors. *Int J Radiat Oncol Biol Phys*, **51**, 23-30.

Sengelov L, von der Maase H, Kamby C, et al (1999). Assessment of patients with metastatic transitional cell carcinoma of the urinary tract. *J Urol*, **162**, 343-6.

Stein JP, Lieskovsky G, Cote R, et al (2001). Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1,054 patients. *J Clin Oncol*, **19**, 666-75.

Thrasher JB, Frazier HA, Robertson JE, Dodge RK, Paulson DF (1994). Clinical variables which serve as predictors of cancer-specific survival among patients treated with radical cystectomy for transitional cell carcinoma of the bladder and prostate. *Cancer*, **73**, 1708-15.

Tsukamoto T, Kitamura H, Takahashi A, Masumori N (2004). Treatment of invasive bladder cancer: lessons from the past and perspective for the future. *Jpn J Clin Oncol*, **34**, 295-306.

Turkolmez K, Tokgoz H, Resorlu B, Kose K, Beduk Y (2007). Muscle-invasive bladder cancer: predictive factors and prognostic difference between primary and progressive tumors. *Urology*, **70**, 477-81.

Vaidya A, Soloway MS, Hawke C, Tiguert R, Civantos F (2001). De novo muscle invasive bladder cancer: is there a change in trend? *J Urol*, **165**, 47-50.

Vaupel P, Schlenger K, Knoop C, Hockel M (1991). Oxygenation of human tumors: evaluation of tissue oxygen distribution in breast cancers by computerized O_2 tension measurements. *Cancer Res*, **51**, 3316-22.

Withers HR, Taylor JM, Maciejewski M (1988). The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol*, **27**, 131-46.