TÜBİTAK

Original Article

Turk J Med Sci
2012; 42 (4): 623-629
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1103-20

Effects of neoadjuvant chemotherapy on pathological parameters and survival in patients undergoing radical cystectomy for muscle-invasive bladder cancer

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Aim: To evaluate the effect of neoadjuvant chemotherapy on tumor pathology and patient survival in patients with muscle-invasive bladder cancer undergoing radical cystectomy. Neoadjuvant chemotherapy is believed to prevent micrometastasis and provide pathological downstaging.

Materials and methods: Between June 2004 and March 2009, 74 patients with muscle-invasive bladder cancer were treated with radical cystectomy. Patients fit to receive chemotherapy were administered systemic chemotherapy of methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC); gemcitabine and cisplatin (GC); or carboplatin and gemcitabine (CG). Patients in Group 1 (n = 36) did not receive any chemotherapy, while the remaining 38 patients in Group 2 did so, before radical cystectomy. Patient characteristics, pathological staging, and survival analysis were compared statistically between groups.

Results: The mean follow-up time was 16.12 ± 12.13 months. There was no significant difference between the groups regarding patient age, sex, preoperative clinical staging, lymph node invasion, comorbidity, type of urinary diversions done, postoperative early complications, progression-free survival (21.96 ± 3.5 and 23.44 ± 2.5 months; P = 0.275), and overall survival rates (25.76 ± 3.5 and 23.57 ± 2.4 months; P = 0.646). However, differences in pathological downstaging (pT3-pT4, 21.58% and 16.42% for groups 1 and 2, respectively; P < 0.001) and perioperative mortality (6 vs. 0 deaths in groups 1 and 2; respectively) were significant between groups.

Conclusion: Neoadjuvant chemotherapy may result in pathological downstaging while having no effects on progression-free or overall survival rates.

Key words: Bladder cancer, chemotherapy, cystectomy, neoadjuvant

Kas invaziv mesane kanseri için radikal sistektomi yapılan hastalarda neoadjuvan kemoterapinin patolojik parametreler ve sağkalıma etkileri

Amaç: Kas invaziv mesane tümörü için sistektomi yapılan hastalarda mikrometastazları önlediğini ve patolojik evre gerilemesini sağladığını düşünülen neoadjuvan kemoterapinin etkinliğini değerlendirmek.

Yöntem ve gereç: Haziran 2004 ve Mayıs 2009 arasında 74 kas invaziv mesane kanserli hastaya radikal sistektomi yapıldı. Hastalara sistemik MVAC, GC ve CG kemoterapisi verildi. Radikal sistektomi öncesi Grup 1 (n = 36) kemoterapi almazken, Grup 2 (n = 38) kemoterapi aldı. Gruplararası hasta özellikleri, patolojik evre ve sağkalım analizleri istatistiksel olarak karşılaştırıldı.

Received: 07.03.2011 – Accepted:29.05.2011

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Bulgular: Ortalama takip süresi 16,12 ± 12,13 aydı. Gruplar arasında hasta yaşı, cinsiyet, preoperatif klinik evre, lenf nodu invazyonu, komorbidite, üriner diversiyon tipi, postoperatif erken komplikasyonlar, hastalıksız sağkalım (21,96 ± 3,5 ve 23,44 ± 2,5 ay, P = 0,275) ve tam sağkalım oranları (25,76 ± 3,5 ve 23,57 ± 2,4 ay, P = 0,646) arasında anlamlı farklılık yoktu. Gruplar arasında patolojik evre gerilemesi (pT3-4, % 21,58 ve % 16,42 grup 1 ve 2 için sırasıyla, P < 0,001) ve perioperatif mortalite (6 ve 0 ölüm, grup 1 ve 2 için sırasıyla) anlanlı olarak farklıydı.

Sonuç: Neoadjuvan kemoterapi hastalıksız ve tam sağkalım oranlarını etkilemeden patolojik evre gerilemesini sağlayabilir.

Anahtar sözcükler: Kemoterapi, mesane kanser, neoadjuvan, sistektomi

Introduction

Bladder cancer is the second most common cancer among urogenital tumors. Despite its high recurrence rate and progression if recurrence occurs, it still has a better survival advantage over many other malignancies (1,2).

Radical cystectomy together with lymph node dissection is the golden standard for treatment of local muscle-invasive bladder cancer. Neoadjuvant chemotherapy is preferred in patients with cT2-cT4 tumors since it adds a 5% survival advantage by treating micrometastasis at the time of diagnosis (2-11).

In this study, we present our results from patients who underwent radical cystectomy together with lymph node dissection for muscle-invasive bladder cancer and we look at the effects of neoadjuvant chemotherapy.

Methods and materials

This study included 74 patients who underwent radical cystectomy for muscle-invasive bladder cancer between June 2004 and March 2009. Patients were evaluated using medical history, physical examinations, and the results of complete blood counts, serum biochemistry, urinalysis, electrocardiography, chest X-rays, computerized tomography of the thorax and the abdomen, and total body bone scans.

The mean patient age was 62 years (range: 28-80). Of our 74 patients, there were 4 women. Clinical staging done using cystoscopy, bimanual examination under anesthesia, computerized tomography of the abdomen, and pathological evaluation of the specimen removed by transurethral resectioning of the bladder tumor revealed that 72 of our patients were at stage cT2 and 4 were at stage cT4a.

All patients were evaluated for chemotherapy by the medical oncology staff at our hospital. Group 1 consisted of 36 patients who were not fit to receive chemotherapy and underwent radical cystectomy and lymph node dissection. The remaining 38 patients (group 2) were given 1 of the following 3 chemotherapy protocols: MVAC (methotrexate at 30 mg/m^2, vinblastine at 3 mg/m^2, Adriamycin at 30 mg/m^2, and cisplatin at 70 mg/m^2), GC (gemcitabine at 100 mg/m^2 and cisplatin 70 mg/m^2), or CG (carboplatin at 400 mg/m^2 and gemcitabine at 100 mg/m^2), depending on the medical status of the patient as determined by medical oncology staff. All patients in group 2 were intended to receive 3 courses of chemotherapy, but only 15 completed the full cycle; the majority of patients in this group (n = 21) were able to receive only 2 courses. Out of the 74 patients, 41 had accompanying comorbidities including diabetes (14 cases), coronary artery disease (7 cases), chronic obstructive pulmonary disease (6 cases), and others (14 cases). There was no statistically significant difference regarding comorbid situations between groups.

In addition to the bladder, the ovaries and uterus were also removed in female patients. An extended lymphadenectomy was performed, which involved removing lymphatic tissue between the distal 5-cm aortic segment above its bifurcation cranially, genitofemoral nerves on each side laterally, internal iliacs posteriorly, and Cooper's ligament distally, including lymphatics around the common, external, and internal iliacs as well as the presacral area. For urinary diversion, a Studer pouch, Ghoneim pouch, and ileal loop were done on 54, 7, and 3 patients, respectively.

Patients were followed for a median of 16.12 ± 12.13 months postoperatively. Perioperative and postoperative complications and mortality rates were recorded during the follow-up. Mortality within the first 30 days of surgery was considered to be perioperative mortality.

The data were analyzed using SPSS 13.0. Fisher's exact test, Student's t-test, Cochran's Q test, and McNemar's test were used when necessary in comparing patient and tumor characteristics including age, sex, comorbidities, chemotherapy regimens, clinical and pathological stagings, lymph node involvements, urinary diversion, perioperative mortality, and postoperative complications. A Kaplan-Meier analysis was performed when comparing progression-free and overall survival rates.

Results

There were 36 and 38 patients with mean ages of 61.61 and 63.63 years in groups 1 and 2, respectively. There were no statistically significantly differences between the groups (Table 1).

Table 1. Demographic characteristics.

	Group 1		Group 2	
	(n)	(%)	(n)	(%)
Number of patients	36	48.6	38	51.4
Age	61.61		63.63	
Sex (male/female)	34/2	94.4/5.6	36/2	94.7/5.3
Preoperative pathologic stage				
T2b	34	47.2	38	52.8
T4a	2	100	0	0
Postoperative pathologic stage				
T0	2	5.6	12	31.6
Tis	0	0	1	2.6
T1	1	2.8	0	0
T2a	1	2.8	1	2.6
T2b	9	25	8	21.1
T3a	9	25	9	23.7
T3b	2	5.6	0	0
T4a	12	33.2	7	18.4
Lymph node stage				
N0	18	50	26	68.4
N1	10	27.8	9	23.7
N2	8	22.2	3	7.9
Neoadjuvant chemotherapy				
MVAC	0	0	4	5.4
GC	0	0	11	14.9
CG	0	0	23	31.1
Urinary diversion methods				
Ileal loop	8	22.2	2	5.3
Studer pouch	23	63.9	31	81.6
Ghoneim pouch	2	5.6	5	13.1
Ureterocutaneostomy	3	8.3	0	0

Clinical evaluation revealed that there were 2 patients with cT4a disease in group 1. The remaining 34 patients in group 1 and all 38 patients in group 2 were in stage cT2.

As per pathological evaluation, stage distribution was as follows: 14 pT0, 1 pTa, 1 pTis, 1 pT1, 2 pT2a, 17 pT2b, 18 pT3a, and 1 pT3b. While 44 patients had no lymphatic metastasis, there was pN1 in 19 and pN2 in 11 patients. While advanced-stage tumors were more common in group 1 (12/36, 33.2%, and 7/38, 18.4% for pT4a disease in groups 1 and 2, respectively; P = 0.038, chi-square), pT0 tumors were much more frequent in group 2 (2/36, 5.6%, and 12/38, 31.2% in groups 1 and 2, respectively; P = 0.038, chi-square). Of the remaining cases, there were 1 pT1 (2.8%), 1 pT2a (2.8%), 9 pT2b (25%), 9 pT3a (25%), and 2 pT3b (5.6%) patients in group 1, and 1 pTis (2.6%), 1 pT2a (2.6%), 8 pT2b (21.1%), and 9 pT3a (23.7%) patients in group 2 (Table 1).

A statistically significant discordance between clinical and pathological stagings was evident in both groups when compared separately with the Cochran Q and McNemar tests (P < 0.001) (Tables 2 and 3).

Out of 74 patients, lymph node metastasis was diagnosed in 30 (40.5%). Lymph node invasion was much more common in group 1 (18/36 patients, 50%) than in group 2 (12/38 patients, 31.58%) (P = 0.155, Fisher's exact test). Of patients with lymph node involvement, there were 10 (27.8%) and 8 patients (22.2%) with pN1 and pN2 in group 1, and 9 (23.7%) and 3 (7.9%) pN1 and pN2 patients in group 2 (Table 1), which was not statistically significant (P = 0.155, Fisher's exact test).

The postoperative complication rate related to surgery was 28%. Among 21 patients, 1 case of pulmonary embolism, 7 of sepsis, 2 of acute renal failure, 4 of wound dehiscence, and 7 of electrolyte imbalance were seen. There were no statistically significant differences between the groups regarding postoperative complications (P = 0.02, Fisher's exact test) (Table 4).

The perioperative mortality rate was 8.1% (6/74). All of the 6 patients who died were in group 1, while no deaths were seen in group 2 (P < 0.001, Fisher's exact test) (Table 5).

Table 2. Comparison of group 1 preoperative and postoperative pathologic stages (Cochran's Q test).

		Group 1: Postoperative pathologic stage				
		T0 (n, %)	**Ta-Tis-T1 (n, %)**	**T2 (n, %)**	**T3-T4 (n, %)**	**P**
Preoperative pathologic stage	**T2b**	2, 6%	1, 3%	10, 27%	21, 58%	<0.001
	T4a	0, 0	0, 0	0, 0	2, 6%	

Table 3. Comparison of group 2 preoperative and postoperative pathologic stages (Cochran's Q test).

		Group 2: Postoperative pathologic stage				
		T0 (n, %)	**Ta-Tis-T1 (n, %)**	**T2 (n, %)**	**T3-T4 (n, %)**	**P**
Preoperative pathologic stage	**T2b**	12, 32%	1, 3%	9, 24%	16, 42%	<0.001
	T4a	0, 0	0, 0	0, 0	0, 0	

Table 4. Early postoperative complications.

			Group 1		Group 2	
			n	%	n	%
Early postoperative complications		(-)	24	66.00	29	76.00
	(+)	Pulmonary thromboembolism	0	0.00	1	2.70
		Urosepsis	5	14.00	2	5.30
		Acute renal failure	1	3.00	1	2.70
		Evisceration	2	6.00	2	5.30
		Electrolyte imbalance	4	11.00	3	8.00
		Other	0	0.00	0	0.00
Total			36.00	100.00	38.00	100.00

Table 5. Perioperative mortality.

		Group 1		Group 2		Total	
		n	%	n	%	n	%
Perioperative	Died	6	100	0	0	6	100
	Lived	30	44.1	38	55.9	68	100
Total		36	48.6	38	51.4	74	100

With a mean follow-up time of 16.12 ± 12.13 months, 50 patients died of disease (28 and 22 in groups 1 and 2, respectively), and disease recurrence was evidenced in 30 patients (18 in group 1 and 12 in group 2). Of these, 19 were distant metastasis (11 in group 1 and 8 in group 2). Overall survival rates (25.76 ± 3.5 and 23.57 ± 2.4 months for groups 1 and 2, respectively; P = 0.646) and progression-free survival rates (21.96 ± 3.5 and 23.44 ± 2.5 months for groups 1 and 2, respectively; P = 0.275) were similar between the groups as compared with the Kaplan-Meyer test (Figures 1 and 2).

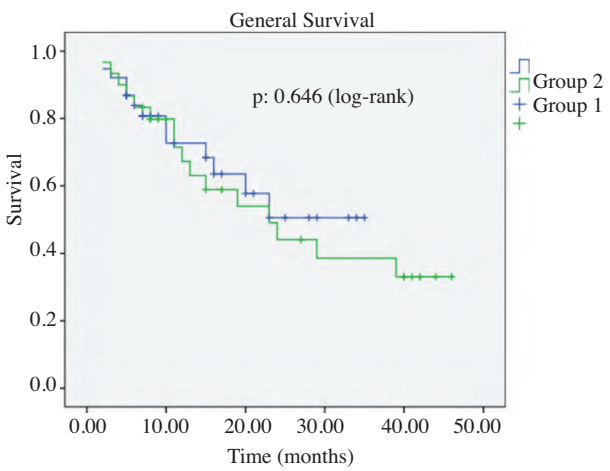

Figure 1. General survival

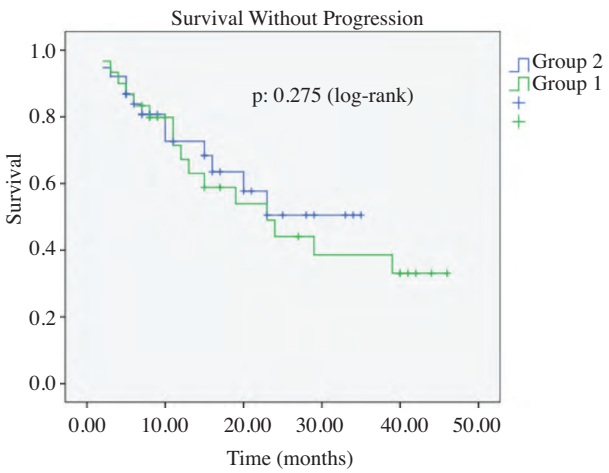

Figure 2. Progression-free survival.

Discussion

It is well known that clinical staging by means of radiological evaluation is not appropriate most of the time and does not reflect the true pathological stage of patients with muscle-invasive bladder cancer (2,7,11). We have evidenced the same situation in the present study. When we look at patients in group 1 only, in order to not compromise the staging with the effect of neoadjuvant chemotherapy, only 29.41% (10/34) of the patients in cT2 were accurately clinically staged. In fact, 61.76% (21/34) and 8.82% (3/34) of cT2 patients were, respectively, overstaged and understaged postoperatively.

Despite the fact that only 15 of 74 (20.27%) patients received the intended full 3 courses of chemotherapy, its administration before surgery did not seem to increase postoperative complication rates.

Neoadjuvant chemotherapy has been shown to provide an additional 5% survival advantage over surgical treatment alone, probably due to stage reduction of the primary tumor and earlier treatment of micrometastasis (2,3,5-7,9-11).

Our results confirm tumor downstaging and an increased number of pT0 tumors in resected cystectomy specimens in patients who receive neoadjuvant chemotherapy. In the published literature, the incidence of tumor downstaging is reported to be about 32.5% (2,3,5-7,9-11). In the present study, tumor downstaging was prominent in patients who received neoadjuvant chemotherapy (Tables 2-5). In group 1, 33.2% of patients (12/36) were found to harbor a tumor of clinical stage of pT3-pT4. However, in group 2, the incidence of pT3-pT4 tumors was 18.4% (7/38), which was statistically significantly different (P = 0.038, Tables 2-5). On the other hand, 5.6% (2/36) and 31.2% (12/38) of patients in groups 1 and 2, respectively, were found to have pT0 tumors (P = 0.038, Tables 2-5), both supporting the findings of previous studies.

Neoadjuvant chemotherapy is believed to reduce the incidence of lymph node metastasis (6,7,9-11). Our results showed a decrease in the incidence of lymph node involvement in patients who received chemotherapy up front, but it did not reach a statistically significant level: 50% (18/36) and 31.58% (12/38) in groups 1 and 2, respectively (P = 0.155). The burden of lymphatic involvement in the neoadjuvant chemotherapy group was also less, but again not statistically significant compared to the surgery-alone group; the incidence of pN1 and pN2 stages were, respectively, 27.8% and 23.7% in group 1, and 22.2% and 7.9% in group 2 (P = 0.155).

Perioperative mortality rates related to radical cystectomy were reported to be around 5% in the recent literature (2,7,12,13). We lost 6 patients within the first 30 days of surgery among the 74 patients who underwent radical cystectomy, which makes our perioperative mortality rate 8.1%. Interestingly, all 6 patients were in group 1, while no patients in group 2 died within the first month of surgery. It is assumed so far that those patients who can tolerate chemotherapy also do better with surgery, or vice versa. Administering chemotherapy up front may be an inadvertent preselection of patients. On the other hand, patients with better performance in daily activities were given up-front chemotherapy, so this may be another method of preselection. Another explanation could be the effect of certain cytokines produced by tumor cells, which might render patients more fragile to surgery if not suppressed by the administration of neoadjuvant chemotherapy, which alters cellular metabolism and the production of cytokines.

Neoadjuvant chemotherapy has been shown to increase overall survival rates by approximately 5% (2,7). Overall survival rates were 32.33% and 52.2% with a mean follow-up of 16.12 ± 12.13 months. Even though there was a trend of better survival with neoadjuvant chemotherapy, the log-rank test did not show a statistically significant difference (P = 0.646), and the same holds true for disease-free survival rates. In group 1, 18 patients had disease recurrence (50%), while 12 patients in group 2 had recurrence. There was no statistically significant difference in disease-free survival rates between the groups (21.96 ± 3.5 and 23.44 ± 2.5 months for groups 1 and 2, respectively; P = 0.275). Since only 20.27% of our patients received the full dose of chemotherapy, only a partial effect might have been seen in this study. The relatively shorter follow-up periods and smaller groups in our study may also not reflect the true effect of neoadjuvant chemotherapy on overall and progression-free survival rates in patients with muscle-invasive bladder cancer.

Our results showed that clinical staging by means of radiologic evaluation is not appropriate and does not generally reflect the true pathological stage in patients with muscle-invasive bladder cancer. The results also showed a clear benefit of chemotherapy on pathological tumor downstaging and an increase in pT0 tumor rates in patients with muscle-invasive bladder cancer when administered in a neoadjuvant setting. However, decreases in lymph node involvement and tumor burden in the involved lymph nodes did not reach statistically significant levels.

Our results fell short of showing a statistically significant benefit in overall and progression-free survival attributable to neoadjuvant chemotherapy, most probably due to the relatively shorter follow-up, smaller number of patients in each group, and incomplete administration of the chemotherapy protocol in the great majority of patients assigned to receive it. Looking at perioperative mortality rates, patients who survived chemotherapy seemed to tolerate surgery better, either due to preselection of patients or a hypothetical advantage of neoadjuvant chemotherapy in suppressing production of cytokines, which might render patients more fragile to surgery.

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