

Original Research Article

A study on effect of neoadjuvant chemotherapy on peri operative complications and outcome in patients under-going radical cystectomy for muscle invasive bladder cancer

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ABSTRACT

Background: To compare the peri-operative complications, related to radical cystectomy and to compare peri operative outcomes between patients receiving neoadjuvant chemotherapy and those treated with radical cystectomy alone.

Methods: This was prospective observational study. The study was conducted at 'The Department of Urosurgery, R. G. Kar Medical College and Hospital, Kolkata'. Study period was between March 2016 to March 2018. Total 36 patients were included in present study. Patients after clinical diagnosis and risk factor profile analysis were divided into two groups: (1) radical cystectomy alone (n=24) (2) patients received neoadjuvant chemotherapy (gemcitabine and cisplatin regime) followed by radical cystectomy (n=12). Different parameters were compared.

Results: Total 36 patients were underwent radical cystectomy. In group 1, 96% (n=23) were having T2 stage while 4% (n=1) were having T3stage. In group 2 25% (n=3) patients were having T2stage while 75% (n=9) were having T3 stage as per CECT staging. There were no significant difference noted in perioperative complications in both groups except perioperative adhesions (group 2, 47% vs group 1, 8.3%). There was significant time delay in radical cystectomy in group 2 (patients received neoadjuvant chemotherapy).

Conclusions: We found there were no significant increase in perioperative morbidity and mortality with Neoadjuvant Chemotherapy. Most of the complications were comparable to previous studies.

Keywords: Bladder cancer, Complications, Neoadjuvant chemotherapy, Radical cystectomy

INTRODUCTION

Bladder cancer is fourth most common cancer in US with 6% incidence.¹ Incidence of bladder cancer increases with increasing age. Bladder cancer is most commonly occurs beyond 70th year of life.² But scenario is changing, bladder cancer is occurring in younger people too. Radical cystectomy (RC) is the standard treatment of localised muscle invasive bladder cancer.³ Nearly 50% of patients with muscle-invasive bladder cancer treated with cystectomy alone will progress to metastatic disease.^{4,5}

Clearly, surgery alone is not sufficient therapy in a large number of patients with invasive bladder cancer. Systemic therapy with cisplatin-based chemotherapy has been shown to provide good response rates in multiple bladder cancer studies since the mid-1980s.^{3,6} There are several arguments for cisplatin-based chemotherapy in the neoadjuvant (NAC) setting for patients with muscle-invasive bladder cancer. Chemotherapy is often better tolerated before surgery, micro metastatic disease will be taken care in a more timely fashion, potential to downstage bulky and advanced tumors and finally allows

the clinician to assess the response to therapy.^{7,8} Limitations of NAC are patients with comorbidities, renal insufficiency, patient's or surgeon preference, lack of access to medical oncologist, delay in definitive local therapy for patients who do not respond to chemotherapy and associated disease progression along with systemic toxicities including neutropenia, anemia, hair loss, neurotoxicity ototoxicity etc.⁹⁻¹¹

By using the 21-day schedule GC could be given for 4 cycles in 12 weeks, with higher dose intensity than the standard 28-day schedule. This well-tolerated regimen is worthy of more extended use and evaluation in the neoadjuvant setting.¹¹ Study population of our country is different from European and American population in terms of nutrition, average built, anemia, availability of health services. That is why it needs to be studied that Neoadjuvant chemotherapy could benefit our population or not.

METHODS

Urological patients after clinical diagnosis and risk factor profile analysis were divided into two groups:

- RC alone: Radical cystectomy alone
- RC+NAC: Patients receiving neoadjuvant chemotherapy (gemcitabine and cisplatin regime) followed by radical cystectomy.

Patients with stage T2-T4a/N0-N1/M0 were included. While patients with T4b and metastatic disease or unfit for surgery were excluded. Different patients variables like age, sex, region, weight, height, body surface area, baseline renal function and GFR, tumor stage (clinical), Intraoperative finding, operative duration, blood loss, transfusion requirement, postoperative ileus, infections, leakage, cardio-respiratory complications, neurological effects were studied.

Neoadjuvant chemotherapy doses and schedule: All the group 2 patients had received three cycles of NAC with GC regime (gemcitabine and cisplatin). 21 days cycles were given. Studies shows by using the 21-day schedule GC could be given for 4 cycles in 12weeks, with higher dose intensity than the standard 28-day schedule.¹¹ Before giving NAC total leukocyte counts, absolute neutrophil counts, creatinine, creatinine clearance, liver function tests and echocardiography were checked. Cardiologist fitness was taken. Inj filgrastim was given as per mentioned schedule:

D1: inj. Gemcitabine 1000mg/m²
Inj. Cisplatin 70mg/m²
D4, D5: inj Filgrastim (G-CSF) 1 vial/sc
D8, inj Gemcitabine 1000mg/m²
D10, D11: inj Filgrastim (G-CSF) 1 vial/sc.

The collected data was entered in MS excel and statistical analysis was done by SPSS 16 using appropriate

statistical tests (t test and chi square tests and correlation coefficient analysis, agreement analysis). P <0.05 was considered as statistically significant between the groups.

RESULTS

Patient characteristics

In present study, 36 patients were analysed between March 16 and March 18. Baseline characteristic and outcome are listed in Table 1.

Patients were divided into two groups. The first group (group 1 termed as RC) comprised of patients (n=24) who have undergone direct radical cystectomy. The second group (group 2 termed as RC+NAC) included patients (n=12) who have undergone neoadjuvant chemotherapy followed by radical cystectomy. Mean age in group1 was 55.17±6.58 year while in group 2 mean age was 54.25±8.16. No statistically significant difference was noted (P=0.71). Other parameters like height, weight, BMI, BSA, creatinine, creatinine clearance and comorbidities were also compared and there was no significant difference noted in both groups as mentioned in Table 1.

Staging: In group 1 (RC), as per CECT abdomen, 23 (out of 24 patients) were having T2 stage. Only one patient was having T3 disease with bilateral hydronephrosis, raised creatinine and intractable haematuria. Bilateral PCN was done but patient did not improve. Hence direct radical cystectomy without neoadjuvant chemotherapy was planned for this patient. In group 2 (RC+NAC), 3 (25%) patients out of twelve were having T2 stage and nine patients (75%) were having T3 stage.

All group 2 patients received 3 cycles of neoadjuvant chemotherapy (G C regime). Toxicity were noted as showed in Table 2. Except for mild nausea, occasional vomiting (50%) and mild alopecia (75%) none of our patient had developed severe haematological, cardiac or any other side effects.

There was significant (P=.00) delay in surgery in group 2 patients (mean 109.92days) compared to group 1 patients (mean 34.21days). In between group 1 and group 2 no statistically significant difference was seen in mean operative duration.

However, formation of orthotopic neobladder was taking more time than ileal conduit in both groups. Only one patient sustained inadvertent rectal injury during surgery while dissecting between rectum and bladder. On table rectal injury repair with proximal diverting colostomy was done. There was significant difference in proportion of peri vesicle adhesion between both groups (41.7% in group 2 compared to 8.3% only in group 1) (P=0.05). Bleeding amount was comparatively less in patient underwent direct radical cystectomy than patients who

underwent neoadjuvant chemotherapy with radical cystectomy. But this difference was statistically non significant (P=0.13). There was linear relationship

between operative duration and bleeding amount. As operative duration increases, bleeding amount also increases (Figure 1).

Table 1: Summary of base line parameters and outcome in both groups.

	Group 1 (RC)	Group 2 (RC + NAC)	P value
No of patients	24	12	
Mean age	55.17	54.25	0.71
Sex			
Male (%)	21 (87.5%)	9 (75%)	0.638
Female (%)	3 (12.5%)	3 (25%)	
Mean Wt (Kg)	61.96	57.17	0.10
Mean Height (CM)	164.46	161.17	0.19
BMI (Mean)	22.79	21.92	0.18
BSA (Mean)	1.687	1.60	0.11
T Staging as Per CECT			
T2	23	3	0.00
T3	1	9	
Histopathology	TCC all	TCC all	
Time lag b/w TURBT and radical cystectomy (days)	34.21	109.92	0.00
Associated comorbidities (%)	7 (29%)	3 (25%)	0.956
H/o previous surgery (%)	2 (.08%)	2(16%)	0.75
Mean creatinine	1.137	0.957	0.13
Mean Cr clearance	68	69.68	0.78
Kernofsky performance score	>80%	>80%	
Pre-op Hb (Mean)	12.48	11.9	0.16
Operative duration (Mean, min)			
IC	308.75	339.5	0.096
ONB	414.17	415	.983
Procedure			
Ileal conduit (%)	12 (50%)	10 (84%)	0.19
Orthotopic Neobladder (%)	12 (50%)	2 (16%)	
On table complication	1 (4%)	0	0.91
Peri-bladder adhesion	2 (8.3)	5 (41.7%)	0.05
Mean unit of transfusion (mean, unit)	1.83	2.16	0.07
Blood loss in surgery (cc)	1040.13	1201	0.13
Over all complications (%)	14 (58.3%)	6 (50%)	0.89
Skin infection (%)	8 (33.3)	4 (33.3)	1.0
Wound dehiscence (%)	1 (4%)	1 (8%)	0.87
Paralytic ileus (%)	3 (12.5%)	1 (8%)	0.93
Gastrointestinal (%)	3 (12.5%)	0	0.53
Respiratory infection (%)	3 (12.5%)	2 (8%)	0.94
Neurological (%)	0	1 (8%)	0.49
Cardiological (%)	0	0	
Reoperation rate (%)	4 (16.6%)	2 (16.6%)	1.00
Readmission rate	1 (4%)	0	0.91
Mortality (%)	2 (8%)	1 (8%)	1.00
Length of hospital stay	20.27 (days)	20.36 (days)	0.98
Lymphnode positivity	5 (20.83%)	6 (50%)	0.20
Adjuvant chemotherapy	6 (25%)	8 (66.6%)	0.05
ICU stay (mean, days)	0.62	0.58	0.89

Table 2: Toxicity of neoadjuvant chemotherapy.

Type of toxicity	% of patients (n)	Grade of toxicity
Neutropenia	0	-
Alopecia	75% (9)	Grade 1
Nausea and vomiting	50% (6)	Grade 1
Fever	0	-
Cardiac complication	0	-
Other complications	0	-

Table 3: Clavien dindo grading of complications in both groups.

Grading	Group 1, RC	Group 2, RC+NAC
0	10	6
1	5	2
2	3	1
3A	1	1
3B	3	1
4	0	0
5	2	1

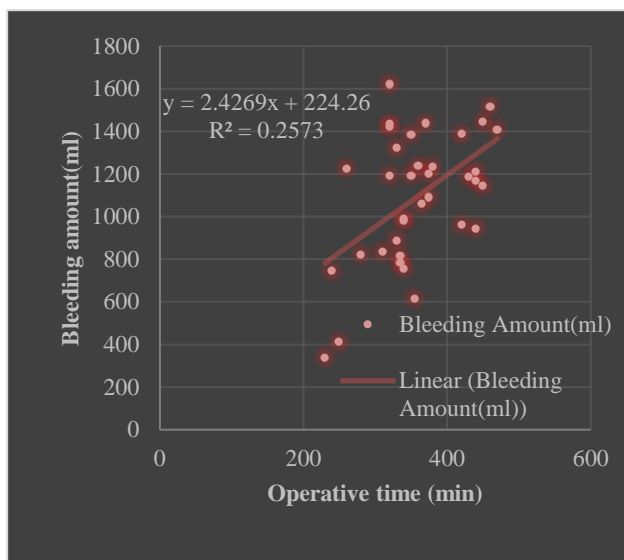


Figure 1: Linear relationship between operative duration and bleeding amount.

Overall complication rate in group 1 was 58.3% (n=14) while in group 2 was 50 % (n=6). Difference was insignificant (p 0.89). In both groups wound infection rate were similar (33.3%). Wound dehiscence was noted 8.3% in group 2 patients while in group this was 4%, but difference was not significant. In comparison to group 1 (RC alone), group 2 (RC+NAC) patients had less over all complication rate (58% vs 50), less paralytic ileus (12.5% vs 8.3%), less GIT complications (12.5% vs 0%), less respiratory complication (12.5% vs 8.3%) and less readmission rate (4% vs 0%) respectively although statistically not significant. (P value >0.5). One patient (0% vs 8.3%) in group 2 developed monoparesis of lower limb which resolved slowly within few days. Reoperation rate (16.6% vs 16.6%), mortality (8.3% vs 8.3%) and length of stay (20.27days vs 20.36 days) were almost similar in group 1 and group 2 respectively. All the complication was graded according to clavien dindo classification as mentioned in Table 3 but, no significant difference was found in both groups (P=.85). In present study, CECT sensitivity for lymph node was 40% with specificity of 100%, which was comparable to previous studies. Picchio M et al, had done a study in 2006 and showed sensitivity and specificity of CT in detecting nodal metastasis ranges from 31% to 50% and 68% to 100%, respectively in bladder cancer.³⁰

DISCUSSION

The present study was prospective observational study done on small scale, while most of previous studies were retrospective study based on recorded dataset. In few studies recorded the included data does not have information on surgical technique (open vs laparoscopic), and does not include whether a PLND or removal of adjacent organs was performed. Chemotherapeutic regimen or number of cycles completed is unknown, which could certainly affect outcomes.¹³

All the basic parameters like height, weight, age, sex, BMI, BSA, creatinine, creatinine clearance, associated comorbidities and preoperative Hb were comparable and akin in both groups. All the patients were having Kernofskys performance score more than 80 and all patients were having histology of transitional cell carcinoma with muscle invasion. In present study mean age was 54.86 year. In group 1 mean age was 55.17 while in group 2 mean age was 54.25year. In study done by Gandaglia et al, mean age at diagnosis was 73year, while in study done by Johnson et al, mean age in RC group was 70 year, while in RC+NAC group mean age was 65 year.^{14,13} In our study muscle invasive bladder cancer was diagnosed at younger age, approximate 10 year earlier than other studies.^{13,14} This may be because present study was done in government institution situated in Kolkata, West Bengal, India. West Bengal is one of high tobacco consuming state in India. Approximately 39% of persons are smoker while 23.2% are tobacco chewer in this region. Other factors may be associated with this younger age presentation and need further epidemiological study.¹⁵

Although Radical cystectomy is standard of treatment, adding neoadjuvant chemotherapy increases overall survival rate approximately 5%.¹⁶ In the face of limited previous data, we aimed at reassessing the effect of NAC on perioperative morbidity and mortality. In previous studies neoadjuvant chemotherapy was underutilised while in ours 33% patients had received NAC, which is more than two times of previous studies.^{13,14} In study done by Gandaglia et al, 11% and in study by Johnson et al 8.9% patients received NAC.

In present study, mean creatinine level was comparable to one previous study while creatinine clearance was less than that creatinine clearance in that study.¹³ Probable reason for this difference may be most of previous studies were done in European and American countries.^{13,14} Their patient's height, weight, BMI and other parameters are different from our population and more than 50% of their population is overweight. Creatinine clearance is also affected by weight, race of the population.¹⁷ Delay of surgery (radical cystectomy) after TURBT in group 1 was 34.21 days while in group 2 this was 109.92. In present study, delay of surgery in RC group was very short comparative to previous study.⁷ In present study, toxicity of GC regime was minimal. No patient we have found with haematological complications as seen in previous studies.¹¹ Reason for this may be addition of G-CSF in neoadjuvant chemotherapy in our protocol.

In previous studies T staging of both groups were comparable. While in present study T staging of both group were significantly different with only 1 patient (4%) with T3 stage in group 1 while in group 2, 9 patients (75%) were T3 stage and rest were T2 stage (P value 0.00). Reason for this discrepancy may be that traditionally neoadjuvant chemotherapy was given in \geq T3 stage while in T2 stage it was optional to give neoadjuvant chemotherapy. In current NCCN guidelines also clinicians recommends to strongly considering neoadjuvant cisplatin based chemotherapy for cT2N0M0 patients and recommends neoadjuvant cisplatin based chemotherapy for cT3-T4aN0M0 patients.¹⁸ That is why, more patients with T3 stage were selected in Neoadjuvant group.

Overall complication rate in group 1 (RC) was 58.3% and in group 2 (RC+NAC) was 50%. In study done by Gandaglia et al, overall complication rate in RC alone was 72.7% while in RC+NAC was 71.9%.²¹ In study done by Johnson et al, overall complication rate in RC group was 51.8% while in NAC + RC group this was 55.1%.¹³ In present study, complication rate was comparable to Johnson et al, study while lesser than the Gandaglia et al study. In present study most common complication was wound infection. In this study, in both groups this was 33.3% while in study of Gandaglia et al, wound infection rate for RC alone was 4% while in RC+NAC group was 4.1%.¹⁴ In study of Johnson et al, wound infection rate in RC was 12.9% and in RC+NAC was 9%.¹³ So in our study wound infection rate was too higher than previous studies. In spite of taking all aseptic precautions cause for the increased infection rate cannot be explained. In our study, wound dehiscence rate in group 1 was 4 % while in group 2 was 8%. In study done by Johnson et al, wound dehiscence rate in RC alone was 3% while in RC+NAC was 0%. So, in present study wound dehiscence rate was comparable. In our study, gastrointestinal complication in group 1 was 12.5% which was comparable to previous studies (Gandaglia et al). While in group 2 this was 0%. This was much lesser than the previous studies.¹⁹ In our study, respiratory

infection rate was 12.5% in group 1 and 8 % in group 2 which was comparable to one study and much lesser than other study.^{13,14} In our study mean length of stay in group 1 was 20.27 days while in group 2 this was 20.36 days which was higher than previous studies.^{8,20} The reason for this observation might be that most of patients come from remote an area that's why the patient is discharged usually after complete recovery. This might also be the possible reason for our less admission rate than previous studies.^{13,14} Perioperative bleeding in present study in group 1 was 1040cc and in group 2 was 1201cc which lesser than previous study.^{8,28} Some studies have not mentioned the bleeding amount.^{13,14} In present study, mean units of transfusion in group 1 was 1.83 and in group 2 was 2.16. This was in accordance with previous studies.⁷ The operative duration also depends over choice of urinary diversion in addition to peri-vesicle adhesion and surgeon's skill.

In present study, we have further divided groups in to sub groups i.e. those who have undergone ileal conduit and other in which patients have undergone orthotopic neobladder diversion. In present study, group 1 patients who have undergone ileal conduit were having less operative duration than the patients of group 2 (308 vs 339 min) but this was insignificant statistically (P=0.096). While in orthotopic neobladder operative duration was comparable (414 vs 415min). The subdivision into groups on the basis of type of diversion was not observed in any previous study. One study had mentioned operative duration which is comparatively more than the present study.⁷ Many studies had not mentioned operative duration.^{13,14,20}

In present study, mortality rate was 8.3% in both groups which was comparable to previous studies.^{13,14} In present study CECT sensitivity for lymph node was 40% with specificity of 100%, which was comparable to previous studies. Picchio M et al had done a study in 2006 and showed sensitivity and specificity of CT in detecting nodal metastasis ranges from 31% to 50% and 68% to 100%, respectively in bladder cancer.²¹

CONCLUSION

In our population bladder cancer occur at younger age probably because of tobacco use suggesting tobacco cessation programs are needed in our country. Further epidemiological study will clarify other factors associated with younger age presentation. Although addition of neoadjuvant chemotherapy significantly delays Surgery, but this also improves overall survival. We found there were no significant increase in perioperative morbidity and mortality with neoadjuvant chemotherapy. Addition of G-CSF (filgrastim) makes GC regime (gemcitabine and cisplatin) less toxic and can be used without increase in morbidity related to chemotherapy. Possible limitations of this study were small number of patients and it is very difficult to find significant relationship from data.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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