The Egyptian Journal of Hospital Medicine (January 2019) Vol. 74 (1), Page 193-207

Adjuvant Chemotherapy Treatment after Radical Cystectomy in Patients with Muscle Invasive Bladder Cancer

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ABSTRACT

Background: about 25% of patients newly diagnosed with bladder cancer have muscle-invasive bladder cancer (MIBC). Patients with MIBC have a worse prognosis than those with non-MIBC. Radical cystectomy with pelvic lymphadenectomy has been shown to be effective against MIBC. The pathologic stage of the primary tumor and regional lymph nodes status has been shown to be the most accurate predictors of disease recurrence after radical cystectomy.

Aim of the Work: to evaluate the toxicity profile related to the adjuvant chemotherapy cisplatin, gemcitabine when added to radical cystectomy as primary treatment, and to estimate disease free survival (DFS) and overall survival (OS).

Patients and Methods: during the period between December 2013 and October, 2017, a total number of 42 patients were included in this study at Clinical Oncology and Nuclear Medicine Department, Al-Hussein University Hospital with a provisional diagnosis of invasive type bladder cancer. The cutoff date for the analysis of overall survival was 31st April, 2018 corresponding to 6 months of follow-up for the last patient enrolled in the study. All patients were subjected to radical cystectomy and pelvic lymphadenectomy and received four cycles of adjuvant chemotherapy cisplatin 70mg/m^2 D1, gemcitabine 1000mg/m^2 D1,8, every three weeks.

Results: the most common grade 3 and 4 adverse events of hematological and non-hematological toxicities recorded during adjuvant chemotherapy were neutropenia (18.8%), grade 3 anemia (9.5%), grade 3 thrombocytopenia (2.3%), grade 3 nausea (28.5%), grade 3 and 4 vomiting (9.4%), grade 3 diarrhea (9.4%) while grade 3 renal toxicities observed in two patients (4.7%). As regard the survival analysis, the median disease-free survival (DFS) rate was not reached due to a relatively short follow up period and DFS was 82.9% at 1 year, 74% at 2 years, and 70.1% at 3 years. Concerning overall survival analysis, the median overall survival in our study was not reached due to a relatively short follow up period. Overall Survival rate at 1 year was 90.4%; at 2 years was 77.3% and 73.4% at 3 years.

Conclusion: for patients with bladder cancer who were not treated with neoadjuvant chemotherapy, we suggest not routinely administering chemotherapy following cystectomy. However, for patients with high-risk (T3 or higher, pathologic node involvement) urothelial carcinomas who are candidates for cisplatin -based combination chemotherapy and are willing to accept the risk for treatment-related toxicities in the absence of high level of evidence, adjuvant chemotherapy is a reasonable option. If administered, we prefer to use a cisplatin-based combination.

Keywords: Chemotherapy - Radical Cystectomy - Muscle Invasive Bladder

INTRODUCTION

Radical cystectomy is the standard treatment for patients with muscle invasive bladder cancer. Five-year survival for patients with pT3-pT4a pN0 M0 bladder cancer after radical cystectomy is 35%-40%. In pN+ patients, five year survival is no more than 10% [(1)].

Surgical approaches, including en bloc cystectomy, bilateral pelvic iliac lymph node dissection, and various forms of lower urinary tract reconstruction, have been developed to enhance survival in patients with MIBC. Improvements in medical, surgical, and anesthetic methods have reduced the morbidity and mortality associated with surgery. Radical cystectomy provides an accurate evaluation of both the primary bladder tumor and the regional lymph nodes, allowing for adjuvant treatment strategies based on clear pathologic rather than clinical staging [(2)].

Invasive bladder cancer is generally a lethal disease requiring aggressive therapy, with fewer than 15% of untreated patients surviving to 2 yr after diagnosis. The optimal goals of treatment for any invasive bladder cancer include long-term survival, prevention

Received: 06/10/2018
Accepted: 25/10/2018

of pelvic recurrence or development of metastatic bladder cancer, and an excellent quality of life [1].

Meta-analysis of nine RCTs (five previously analyzed, one updated, and three new), which included 945 patients, was performed in 2013 [3]. It showed **23%** relative decrease in the risk of death with AC compared with controls and **34%** relative decrease in the risk of recurrence. Although it was thought that this updated meta-analysis offered further evidence of OS and DFS benefits, there were some limitations and it is still controversial. First, individual patient's data (IPD) for this meta-analysis was not available. Second, the Italian [4] and Spanish trials [5] had completely opposite results.

Generally, adjuvant chemotherapy is recommended for patients with high-risk features such as T3 or T4 disease and/or lymph node involvement, who have not been treated with neoadjuvant chemotherapy. Routine use of adjuvant chemotherapy in patients with MIBC without such high-risk features is controversial due to the lack of evidence of clear benefit in this group. There are limited data on the management of patients who are not candidates for cisplatin-based adjuvant chemotherapy [6].

The primary aim of this work was to evaluate the toxicity profile related to the adjuvant chemotherapy cisplatin, gemcitabine when added to radical cystectomy as primary treatment. A secondary endpoint was to estimate disease free survival (DFS) and overall survival (OS). A tertiary objective was to describe the associations between pathologic features and lymph node density to clinical outcomes.

PATIENTS AND METHODS

This study included a total of 42 patients with a provisional diagnosis of invasive type bladder cancer attending at Clinical Oncology and Nuclear Medicine Department, Al-Hussein University Hospitals. Approval of the ethical committee and a written informed consent from all the subjects were obtained. This study was conducted between December 2013 and October, 2017.

The cutoff date for the analysis of overall survival was 31st April, 2018 corresponding to 6 months of follow-up for the last patient enrolled in the study.

Patient criteria:

- Adult ≥ 18 years of both genders.
- ECOG performance status 0-2 at the start of treatment.
- Operable patient subjected to radical cystectomy.
- Physically fit for adjuvant chemotherapy.
- Hemoglobin > 9 g/dL
- WBC ≥ 3000/ × 10^9/L; ANC > 1500/× 10^9/L
- Platelet count ≥ 100,000/× 10^9/L
- Creatinine ≤ 1.2 mg/dl
- Creatinine clearance > 50 ml/minute
- Bilirubin ≤ 1 times of upper limit of normal (ULN)
- AST, ALT < 2 times of upper limit of normal (ULN)
- Treatment begins within 3 months after surgery.

Disease criteria: All patients had one or more of the following risk factors:

- Histopathological proven invasive bladder carcinoma p T2, T3, T4a, N0-N3.
- Involvement of one or more pelvic lymph node.
- Histopathological grade 3.

Exclusion criteria:

- Evidence of hydronephrosis.
- Uncontrolled systemic disease.
- Pregnancy.
- Prior chemotherapy treatment.
- Concurrent drugs that have potential nephrotoxicity or ototoxicity.
- Other malignancy except adequately treated basal cell carcinoma of the skin.

METHODS

I. ***Full history and thorough physical examination*****;** including body surface area and performance status according to WHO scale.

II. ***Investigations:***

Routine laboratory studies: ***(***Not more than 4 weeks prior to study entry):

- CBC, Alkaline phosphatase, ALT, AST, bilirubin, BUN, creatinine, and calculated creatinine clearance levels
- Urine analysis and culture & sensitivity,

Radiologic evaluation: ***(***Not more than 6 weeks prior to study entry):

- Chest x-ray,
- Abdominal and pelvic CT scans or MRI
- Echocardiography.
- Isotopic bone scan should be performed only in patients who complain of (A) bone pain, or who have (B) an elevated serum calcium

level or (C) an elevated serum alkaline phosphatase level.
- IVP if indicated.

III. Protocol Design:

All patients were subjected to the following treatment protocol:

1. Radical cystectomy and pelvic lymphadenectomy.
2. Received four cycles of adjuvant chemotherapy cisplatin 70mg/m^2 D1, gemcitabine 1000mg/m^2 D1,8, every three weeks.

IV. The Chemotherapy:

The adjuvant chemotherapy

- Cisplatinum 70 mg/m^2 day 1.
- Gemcitabine 1000 mg/m^2 days 1, 8.

Administration (intravenous infusion)

Day 1 of the adjuvant chemotherapy:

Pretreatment Hydration and Medical Preparation:

- The Patient was given one and half liters of normal saline + 20 ml Eq of potassium chloride +1gm of magnesium sulphate followed by 200 ml of mannitol 20% over 20 mints.
- Dexamethasone 16 mg and ondansetron 16 mg or granisetrone 3mg in 100 ml saline given as an intravenous infusion over 15 min, 30 min before cisplatin administration.
- Apripatent (EMEND) 120 mg one hour before cisplatinum on day one, and 80 mg on day two and three.

Chemotherapy Administration:

- Cisplatin 70 mg/m^2 was given in 500 ml of normal saline over 2 hours.
- Gemcitabine 1000 mg/m^2 in 250 ml normal saline over 30 minutes.

Post treatment hydration:

- One liter of normal saline + 1gm magnesium sulphate +20 ml Eq of potassium chloride over 2 hours
- Patients were instructed to drink ample fluids with careful monitoring of diuresis (500 ml of urine output at minimum is required within the first 6 hours on day one).

Day 8 of adjuvant chemotherapy

- Dexamethasone 8 mg and ondansetron 8mg or granisetrone 3mg in 100 ml saline as an intravenous infusion over 15 min.
- Gemcitabine 1000 mg/m2 in 250 ml normal saline over 30 minute's infusion.

Dose Modifications:

I. Dose modification for Cisplatin:

Table (1): Modifications of Cisplatin according to Creatinine clearance

Creatine clearance (CRCL)	N	%	Dose Reduction
(30-44) ML/h	1	2.38	50% Dose reduction
(45-60)ML/h	8	19.05	25% Dose reduction
>60ML/h	33	78.57	Nill

Table (2): Modifications of Cisplatin for myelosuppression

Calculated dose %				
ANC(/× 10^9/L) (Absolute neutrophils count)	**Platelet count**			
	>150.000	**100-149.000**	**75-99.000**	**<75.000**
≥1.4	**100**	**100**	**100**	**75**
1.0 - < 1.4	**100**	**75**	**75**	**75**
< 1.0	**0**	**0**	**0**	**0**

II. Dose modification for Gemcitabine:

Table (3): Modifications of Gemcitabine for myelosuppresion

ANC(×10^9/L) (Absolute neutrophils count)		Platelet (×10^9/L)	Percent of full dose
≥1.0	**And**	**≥75**	**100**
0.5 to 0.99	**OR**	**50 to 74**	**50**
<0.5	**OR**	**<50**	**Hold**

III. Assessment schedule:

During adjuvant chemotherapy:

- Physical examination each visit.
- CBC, urea and creatinine before each cisplatinum administration.
- CBC before each Gemcitabine administration.
- Toxicity assessment was done each visit according to WHO toxicity.

IV. Follow up:

- CBC, kidney function and liver function tests, done every two months in the first year, three months in second year and every six months thereafter.
- Chest x-ray and CT abdomen and pelvis every six months in the first two years, and every 12 months thereafter.

RESULTS

Note on Results:

1. **For each table or graph, your data should be first presented collectively as a text and then presented in detail as tables or graphs.**

Table (4): Patient's characteristics of study group patients

Epidemiology		
Age		
Range	41-70	
Mean ±SD	59.833±7.197	
Sex	**N**	**%**
Male	36	85.71
Female	6	14.29
Occupation		
Worker	15	35.71
Farmer	21	50.00
Driver	2	4.76
Employee	1	2.38
Housewife	3	7.14
Residence		
Upper Egypt	14	33.33
Lower Egypt	11	26.19
Greater Cairo	17	40.48
Residence		
Urban	20	47.62
Rural	22	52.38
Special habit		
Non-Smoker	9	21.43
Smoker	33	78.57
F.H.		
No	42	100.00
Yes	0	0.00
Comorbidities		
Bilharzial Cystities		
Negative	29	69.00
Positive	13	31.00
HCV		
Negative	28	66.67
Positive	14	33.33
HBV		
Negative	42	100.00
Positive	0	0.00
DM		
Negative	33	78.57
Positive	9	21.43
HTN		
Negative	35	83.33
Positive	7	16.67
Performance status (ECOG)		
ECOG 0	15	35.71
ECOG 1	22	52.38
ECOG 2	5	11.90

Table (5): Histopathologically assessment of the eligible 42 patients

Pathological criteria:			
	N		**%**
T2a	2		4.76
T2b	6		14.29
T3a	11		26.19
T3b	9		21.43
T4a	11		26.19
T4b	3		7.14
Histopathology			
TCC	35		83.33
SCC	7		16.67
Squamous differentiation			
No	32		76.19
Yes	10		23.81
Grade			
Grade II	13		30.95
Grade III	29		69.05
Bilharzial cystitis			
No	29		69.05
Yes	13		30.95
Lymph node Total			
Range	1	-	29
Mean ±SD	11.048	±	7.116
Lymph node Status			
No	31		73.81
Yes	11		26.19
Extra nodal spread	**N**		**%**
No	41		97.62
Yes	1		2.38
Lymphovascular invasion			
No	35		83.33
Yes	7		16.67
Pathological Stages			
Stage 2	8		19.05
Stage 3	22		52.38
Stage 4a	12		28.57

Table (6): Relatives of dose intensities

Relative dose intensities %			
Range	55	-	100
Mean ±SD	91.517	±	10.942

Table (7): Hematological toxicity

Hematological toxicity:		
	N	**%**
HB		
Grade 0	4	9.52
Grade I	25	59.52
Grade II	9	21.43
Grade III	4	9.52
WBC		
Grade 0	10	23.81
Grade I	16	38.10
Grade II	8	19.05
Grade III	7	16.67
Grade IV	1	2.38
PLT		
Grade 0	33	78.57
Grade I	6	14.29
Grade II	2	4.76
Grade III	1	2.38

Table (8): Gastrointestinal toxicity

GIT TOXICITY:		
ANOREXIA & WEIGHT LOSS		
Grade 0	2	4.76
Grade I	28	66.67
Grade II	11	26.19
Grade III	1	2.38
NAUSEA		
Grade 0	3	7.14
Grade I	12	28.57
Grade II	15	35.71
Grade III	12	28.57
VOMITING		
Grade 0	6	14.29
Grade I	19	45.24
Grade II	13	30.95
Grade III	2	4.76
Grade IV	2	4.76
DIARRHOEA		
Grade 0	10	23.81
Grade I	25	59.52
Grade II	3	7.14
Grade III	4	9.52
MUCOSITIS		
Grade 0	34	80.95
Grade I	6	14.29
Grade II	2	4.76

Table (9): Renal Toxicities

RENAL TOXICITY:		
	N	**%**
S. Cr.		
Grade 0	29	69.05
Grade I	9	21.43
Grade II	2	4.76
Grade III	2	4.76
PROT.		
Grade 0	31	73.81
Grade I	10	23.81
Grade II	1	2.38
HAEMAT.		
Grade 0	33	78.57
Grade I	8	19.05
Grade II	1	2.38

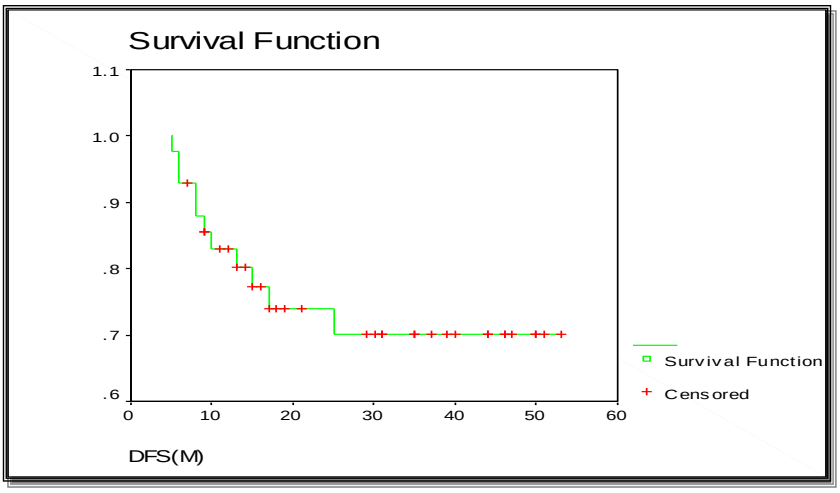

Fig. (1): Curve for disease free survival.

Table (10): Relation between DFS and different factors of the studied group

		DFS (M)				T-Test or ANOVA	
		N	**Mean**	**±**	**SD**	**T or F**	**P-value**
Occupation	Worker	15	17.867	±	13.384	2.172	0.091
	Farmer	21	26.714	±	14.585		
	Driver	2	42.000	±	7.071		
	Employment	1	17.000	±	0.000		
	Housewife	3	37.000	±	25.159		
Residence 1	Upper Egypt	14	22.643	±	15.998	0.385	0.683
	Lower Egypt	11	23.545	±	14.264		
	Greater Cairo	17	27.353	±	16.621		
Residence 2	Urban	20	23.600	±	16.753	-0.465	0.644
	Rural	22	25.864	±	14.782		
Special Habit	Non-Smoker	9	29.333	±	19.455	0.986	0.330
	Smoker	33	23.545	±	14.481		
Bilharzial Cystities	Negative	29	24.172	±	15.229	-0.377	0.708
	Positive	13	26.154	±	16.945		
Surgical Types	Non-Orthotopic	20	21.750	±	13.879	-1.209	0.234
	Orthotopic (illeal pouch)	22	27.545	±	16.852		
Performance Status (ECOG)	ECOG 0	15	27.333	±	15.523	0.370	0.693
	ECOG 1	22	23.909	±	15.418		
	ECOG 2	5	21.000	±	18.868		
Squamous Differentiation	No	32	26.750	±	15.610	1.481	0.146
	Yes	10	18.500	±	14.539		
Grade	Grade II	13	27.385	±	15.634	0.719	0.477
	Grade III	29	23.621	±	15.715		
Lymphovascular Invasion	No	35	25.229	±	15.488	0.407	0.686
	Yes	7	22.571	±	17.213		

T -Independent samples t-test.
F-One-way ANOVA tests.

Table (11): Relation between DFS and different factors of the studied group

DFS		**N**	**1 Y**	**2 Y**	**3 Y**	**Median (95% CI)**	**P-value**
Age	**<60 Years**	17	0.765	0.701	0.701	NA	0.776
	≥60 Years	25	0.875	0.757	0.673	NA	
Histopathology	**TCC**	35	0.824	0.710	0.659	NA	0.375
	SCC	7	0.857	0.857	0.857	NA	
pathological T-Stages	**T2a**	2	NA	NA	NA	NA	0.002*
	T2b	6	0.833	0.833	0.833	NA	
	T3a	11	0.900	0.800	0.800	NA	
	T3b	9	0.889	0.762	0.571	NA	
	T4a	11	0.818	0.818	0.818	NA	
	T4b	3	0.333	0.333	0.333	8(3.2-12.8)	
Pathological TN Stages	**Stage 2**	8	0.875	0.875	0.875	NA	<0.001*
	Stage 3	22	0.947	0.947	0.947	NA	
	Stage 4a	12	0.583	0.292	0.146	13(4.04-21.96)	
Lymph node status	**No**	31	0.898	0.898	0.898	NA	<0.001*
	Yes	11	0.636	0.318	0.159	15(6.35-23.65)	

NA: not applicable, **CI**: confidence interval, **PS**: performance status.

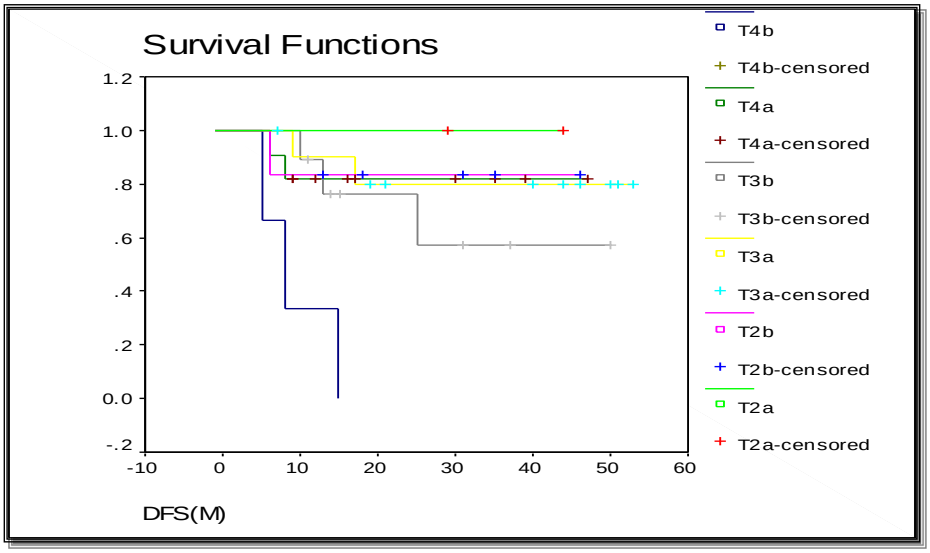

Fig. (2): Effect of pathological T-stage on DFS.

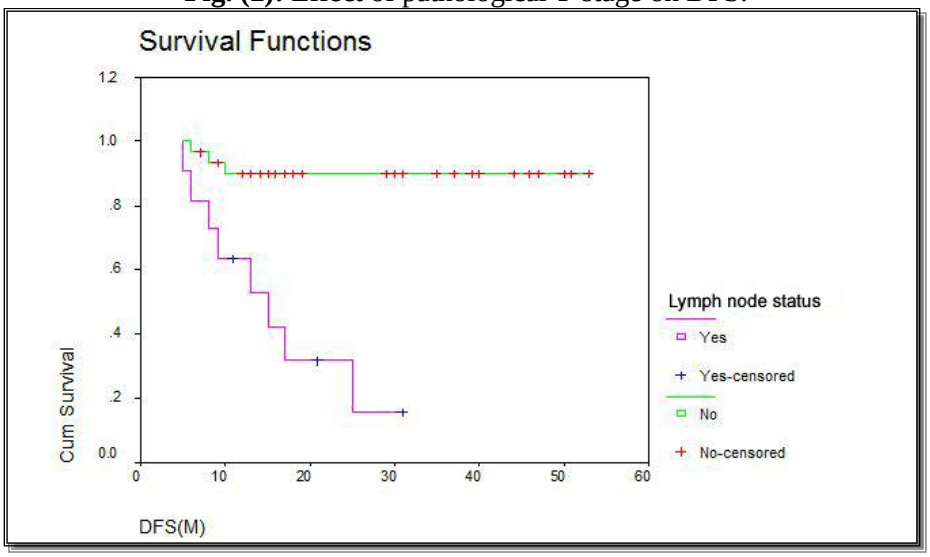

Fig. (3): Effect of positive lymph nodes on DFS**.**

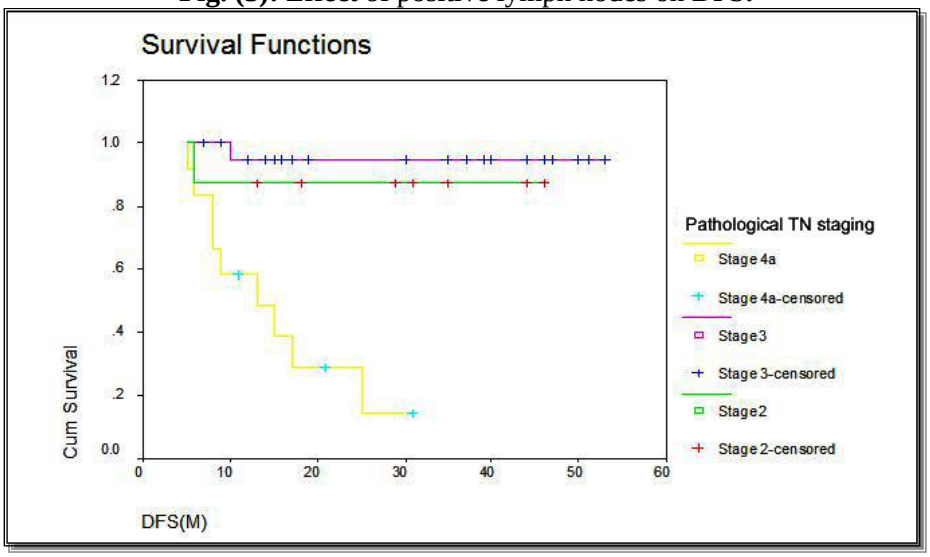

Fig. (4): Effect of pathological stages on DFS.

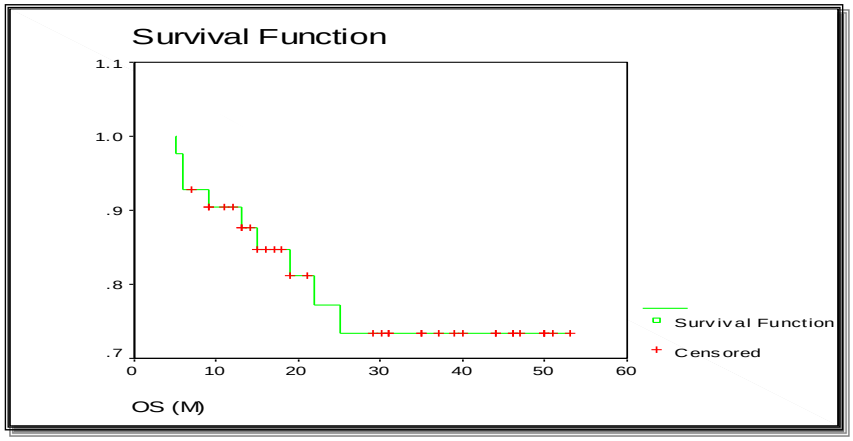

Fig. (5): Overall survival curve.

Table (12): Relation between OS and different factors of the studied group

		OS (M)				T-Test or ANOVA	
		N	Mean	±	SD	T or F	P-value
Occupation	Worker	15	18.200	±	13.181	4.909	0.343
	Farmer	21	27.381	±	14.059		
	Driver	2	42.000	±	7.071		
	Employment	1	17.000	±	0.000		
	Housewife	3	51.000	±	1.732		
Residence 1	Upper Egypt	14	23.286	±	15.628	0.795	0.459
	Lower Egypt	11	24.364	±	13.735		
	Greater Cairo	17	29.882	±	16.605		
Residence 2	Urban	20	23.850	±	16.544	-0.950	0.348
	Rural	22	28.409	±	14.543		
Special Habit	Non-Smoker	9	34.667	±	18.042	1.897	0.065
	Smoker	33	23.939	±	14.188		
Bilharzial Cystities	Negative	29	25.931	±	15.418	-0.189	0.851
	Positive	13	26.923	±	16.317		
Performance Status (ECOG)	ECOG 0	15	28.133	±	14.784	0.386	0.682
	ECOG 1	22	26.136	±	15.713		
	ECOG 2	5	21.000	±	18.868		
Pathology (Sq. Diff)	No	32	27.344	±	15.120	0.823	0.415
	Yes	10	22.700	±	17.023		
Grade	Grade II	13	28.000	±	15.149	0.488	0.628
	Grade III	29	25.448	±	15.865		
Lymphovascular invasion	No	35	25.743	±	15.130	-0.458	0.649
	Yes	7	28.714	±	18.373		

T -Independent samples t-test.
F-One-way ANOVA tests.

Table (13): Relation between OS and different factors of the studied group

OS		N	1 Y	2 Y	3 Y	Median (95% CI)	P-value
Age	<60 Years	17	0.824	0.755	0.755	NA	0.976
	>60 Years	25	0.960	0.770	0.684	NA	
Histopathology	TCC	35	0.914	0.746	0.696	NA	0.494
	SCC	7	0.857	0.857	0.857	NA	
pathological T-Stages	T2a	2	NA	NA	NA	NA	0.219
	T2b	6	0.833	0.833	0.833	NA	
	T3a	11	0.867	0.857	0.857	NA	
	T3b	9	0.710	0.700	0.525	NA	
	T4a	11	0.818	0.818	0.818	NA	
	T4b	3	0.667	0.333	0.333	15(0-31)	
Pathological TN Stages	Stage 2	8	0.875	0.875	0.875	NA	0.001*
	Stage 3	22	0.954	0.944	0.944	NA	
	Stage 4a	12	0.750	0.402	0.268	22(12.62-31.38)	
Lymph node status	No	31	0.968	0.931	0.931	NA	<0.001*
	Yes	11	0.727	0.323	0.162	19(10.94-27.06)	

NA: not applicable, **CI**: confidence interval, **PS**: performance status.

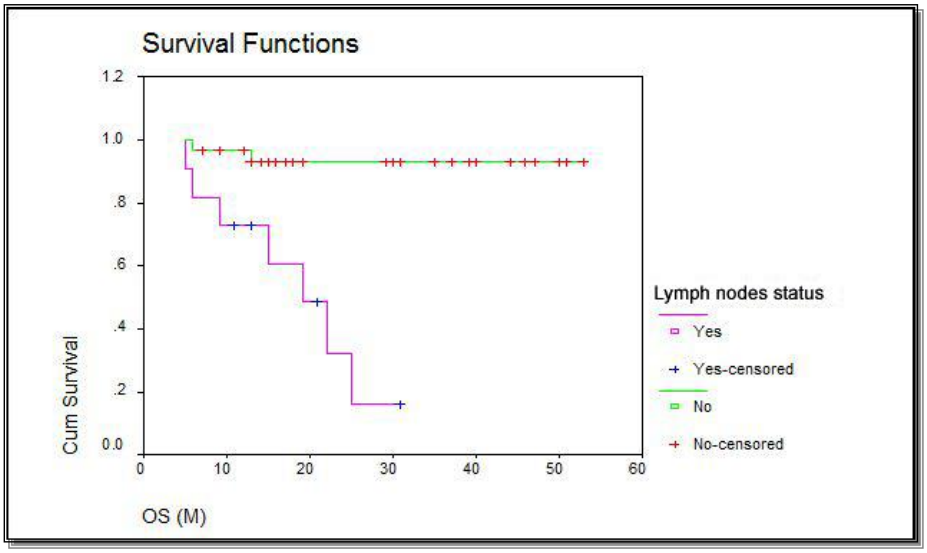

Fig. (6): Effect of positive lymph nodes on DFS.

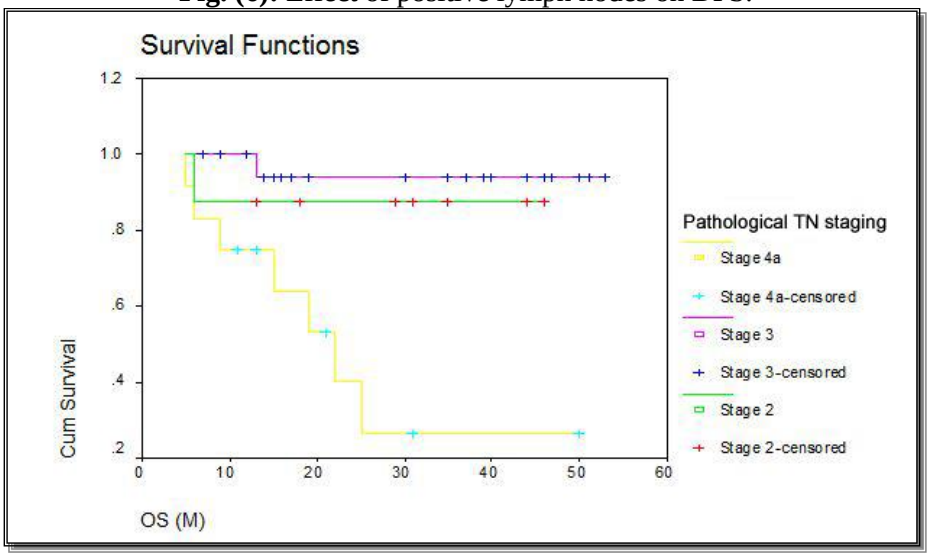

Fig. (7): Effect of pathological stages on DFS.

DISCUSSION

For patients with muscle invasive bladder cancer, cystectomy alone is associated with a 50 to 65 percent overall survival rates, which may be as high as 80 percent in patients who have pT2 disease. However, patients with locally advanced disease are at risk for worse outcomes. The five-year survival rate in patients with invasion beyond the bladder muscle is approximately 40 percent, while the survival for patients with lymph node involvement does not exceed 10 percent [7].

Given the benefit of chemotherapy in the neoadjuvant setting and the poor prognosis of patients following surgical resection, adjuvant chemotherapy is often used in patients with high-risk bladder cancer. Although this rationale provides the justification for the use of adjuvant chemotherapy, the available data from randomized trials provide little conclusive evidence that adjuvant therapy improves survival outcomes. In addition, approximately 30 percent of patients experience complications following radical cystectomy that preclude them from receiving adjuvant chemotherapy [8].

Clinical trials are the cornerstone of evidence development in oncology, yet they are not without limitations. Clinical trials have a relatively high rate of incomplete enrollment; often not providing definitive answers to critical questions. This phenomenon more apparent in the setting of adjuvant chemotherapy for bladder cancer, with all three contemporary clinical trials addressing this question terminating prematurely because of poor accrual [9].

A series of randomized clinical trials over the past 30 years have explored the efficacy of adjuvant chemotherapy in locally advanced

bladder cancer. Early trials were instrumental in demonstrating feasibility but used suboptimal chemotherapy regimens, were underpowered, and/or suffered from methodological flaws, thus yielding conflicting results. Three trials ***Cognetti et al. [4]; Paz-Ares et al. [5] and Sternberg et al. [10]*** sought to evaluate contemporary chemotherapy regimens in the adjuvant setting in patients with locally advanced bladder cancer post cystectomy. Unfortunately, all three trials closed early because of *poor accrual*, collectively enrolling less than 40% of their target **[9].**

The resulting evidence gap has fueled controversy regarding the role of adjuvant chemotherapy. Clinical practice guidelines offer mixed guidance, with the National Comprehensive Cancer Network guidelines supporting adjuvant chemotherapy as a category 2B recommendation (i.e., based on lower-level evidence) and the European Association of Urology guidelines stating that "neither randomized trials nor a meta-analysis has provided sufficient data to support the routine use of chemotherapy **[9].**

In this study of adjuvant chemotherapy treatment by cisplatin/gemzar, after radical cystectomy in patients with muscle invasive bladder cancer, were designed to show the efficacy of adjuvant chemotherapy treatment regarding survival in comparison to its toxicity. The tested regimen was found effective with manageable acute toxicity when appropriate supportive care was employed.

In our study the mean age was 59.8 (±7.1) years. 36 patients (85.7%) were males and 6 patients (14.2%) were females, 33 patients (78.5%) were smokers and 9 patients (21.4%) non-smoker.

The performance status (PS) of patients ranged from 0-II WHO. Fifteen patients (35.7%) were presented with performance status (PS) 0 WHO, twenty two (52.3) presented with (PS) I WHO, while 5 patients (11.9%) with (PS) II.

The whole study group showed transitional cell carcinoma in 35 patients (83.3) and only 10 patients (23.8%) of that patient had squamous differentiation, while squamous cell carcinoma in 7 patients (16.6%), grade II in 13 patients (30.9%), and grade III was found in 29 patients (69%).

Fourteen patients (33.2%) presented with T4 staging, while T3 staging was found in 20 patients (47.5%), and only 8 patients (18.9%) had T2 staging. Regional lymph node involvement was observed in 11 patients (26.1%), only one patient had extra nodal spread (2.3), and 7 patients had lymphovascular invasion (16.6).Total number of lymph nodes excision ranging from one to twenty nine with mean 11 lymph node excision.

Eight patients (19%) presented with stage two, 22 patients (52.3%) were stage III and 12 patients (28.5%) were stage IVA disease.

An intergroup, open-label, randomized, phase 3 trial (EORTC 30994): Recruited patients from hospitals across Europe and Canada. No age limits were applied, but patients had to have a good performances status (WHO 0 or 1), adequate hematological function (white blood cell count $\geq 3{\cdot}5 \times 10^9$ cells per L and platelet count $\geq 120 \times 10^9$ cells per L), adequate renal function (glomerular filtration rate ≥60 mL/min), and normal auditory and cardiac function. Patients with previous systemic chemotherapy or radiation to the bladder and patients regarded as unfit for cisplatin- containing combination chemotherapy or with grade 2 or worse peripheral neuropathy were ineligible. Eligible patients had histologically proven urothelial carcinoma of the bladder, pT3–pT4 disease or node positive (pN1–3) M0 disease after radical cystectomy and bilateral lymphadenectomy, with no evidence of any microscopic residual disease.

An Italian, multicenter, randomized phase III trial: Eligible patients were required to have an Eastern Cooperative Oncology Group performance status (PS) of two or less, age ≤ 75 years, adequate bone marrow reserve and a good renal (creatinine level ≤ 1.25 umol/l, measured creatinine clearance > 60 ml/min) and liver function. A radical cystectomy with no residual disease and a minimum of 10 lymph nodes dissection was required. Randomization was required within 10 weeks after surgery. Neither prior neoadjuvant chemotherapy nor radiotherapy was allowed. One hundred and ninety-four patients with histologically proven transitional cell carcinoma of the bladder pT2 G3 (N0–2), pT3–4 (N0–2) any G or pN1–2, any Tumor (T), any G were considered eligible.

In our study forty two patients subjected to radical cystectomy either orthotopic type 22 patients (52.3%) and non orthotopic type 20 patients (47.6%), the most common complication after surgery was urinary tract infection (UTI) in all patients, while the second most common was urinary

incontinence. these patients followed by adjuvant combination chemotherapy treatment, patients were received four cycles of cisplatin 70mg/m^2 day one every three weeks and gemcitabine 1gm/m^2 day one and day eight. Thirty Patients (71.4%) were received adjuvant treatment less than two months from surgery, while 12 patients (28.5%) received treatment more than two months.

In phase 3 trial (EORTC 30994), Within 90 days of cystectomy, patients were centrally randomly assigned (1:1) by minimization to either immediate adjuvant chemotherapy (four cycles of gemcitabine plus cisplatin, or high-dose methotrexate, vinblastine, doxorubicin, and cisplatin [high-dose MVAC], or MVAC) or six cycles of deferred chemotherapy at relapse, with stratification for institution, pT category, and lymph node status according to the number of nodes dissected. Overall survival was the primary endpoint; all analyses were by intention to treat. The trial was closed after recruitment of 284 of the planned 660 patients [(10)].

An Italian, multicenter, randomized phase III trial: Patients were randomly allocated to control (92 patients) or to four courses of AC (102 patients). These latter patients were further randomly assigned to receive gemcitabine 1000 mg/m2 days 1, 8 and 15 and cisplatin 70 mg/m2 day 2 or gemcitabine as above plus cisplatin 70 mg/m2 day 15, every 28 days [(4)].

Spanish Oncology Genitourinary Group (SOGUG) 99/01 study: Eligibility criteria included: (1) resected high-risk muscle invasive bladder carcinoma (pT3-4 and/or pN+), (2) ECOG PS 0-1, (3) adequate renal function (CrCl > 50 ml/min), (4) ≤ 8 weeks post-cystectomy, (5) no relevant co-morbidities, and (6) signed informed consent. Eligible patients were assigned to observation or 4 courses of PGC (paclitaxel 80 mg/m^2 d1 and 8, gemcitabine 1000 mg/m^2 d1 and 8 and cisplatin 70 mg/m^2 d1) q21 days. The primary objective was overall survival (OS) [(5)].

In this study adverse events were an important factor studied in this study as the addition of adjuvant CTH to radical cystectomy could affect the survival without causing significant toxicity. Eighty five percent of all patients completed the planned four cycles.

The most common grade 3 and 4 adverse events of hematological and non-hematological toxicities recorded during adjuvant chemotherapy were neutropenia (18.8%), grade 3 anemia (9.5%), grade 3 thrombocytopenia (2.3%), grade 3 nausea (28.5%), grade 3 and 4 vomiting (9.4%), grade 3 diarrhea (9.4%) while grade 3 renal toxicities observed in two patients (4.7%).

Fatigue and bony aches were also common symptoms in patients receiving adjuvant treatment. Fatigue occurred mostly in all patients. These symptoms are graded, grade 3 and 4 had occurred in (20%) of patients, and the fact that they were life threatening, they are still an important factor affecting patients' compliance to treatment and quality of life. In multiple instances, they were the cause of treatment delay, reduction and treatment cessation.

In phase 3 trial (EORTC 30994), the toxicity adjuvant treatment had a considerably higher rate, Grade 3–4 myelosuppression was reported in 33 (26%) of 128 patients who received treatment in the immediate chemotherapy group versus 24 (35%) of 68 patients who received treatment in the deferred chemotherapy group, neutropenia occurred in 49 (38%) versus 36 (53%) patients, respectively, and thrombocytopenia in 36 (28%) versus 26 (38%). Two patients died due to toxicity, one in each group.

However, the toxicity was less compared to the Italian, randomized phase III trial, 62% of patients received the planned four cycles, mainly due to treatment-related toxic effects. In the B2 arm, 67% required dose adjustment and 39% patients required an early stop treatment. In the B15 arm, a dose reduction and an early stop treatment was required for 72% and 26% patients, respectively. All the WHO hematologic and non-hematologic toxic effects observed in B2 and B15 arms. A statistically significant higher incidence of grade 3/4 thrombocytopenia was observed in B2 arm as compared with B15 arm (25.6% versus 4.3%, P = 0.006). On the contrary, patients in B15 arm experienced more grade 3/4 leukopenia (15.2% versus 9.3%) and neutropenia (34.8% versus 21%), not reaching statistical significance. The incidence of grade 3 and 4 nausea and vomiting was higher in B2 arm (9.4% versus 2.2%, P = 0.31). No drug toxicity-related death was observed in either arm**.**

In (SOGUG) 99/01 study, 76% of patients completed all 4 courses of therapy in the PGC arm. the toxicity during adjuvant treatment had a considerably higher rate of

grade 3-4 toxicities were neutropenia 41%, febrile neutropenia 8%, thrombocytopenia 14%, anemia 5%, fatigue 14%, alopecia 10%, vomiting 8%, renal 5%. There was one toxic death (sepsis).

As regard the survival analysis, the median disease free survival rate was not reached due to a relatively short follow up period and DFS was 82.9% at 1 year, 74% at 2 years, and 70.1% at 3 years, These results are comparable to immediate treatment group in phase 3 trial (EORTC 30994) by ***Sternberg et al.*** [10], it was 78%, 59%, 50% respectively, Median disease-free survival was 37 months (95% CI 1·84–7·77) in the immediate treatment group compared with 11 months (0·63–1·49) in the deferred treatment group (HR 0·54, 95% CI 0·40–0·73; p<0·0001;), 5-year disease -free survival was 47·6% (95% CI 38·8–55·9) in the immediate treatment group and 31·8% (24·2–39·6) in the deferred treatment group.

This superiority in our results at two and three years of DFS, probably due to the consistent percentage of node-negative patients included, inclusion of early pathological stages (pT2N0) and bladder cancer pathology of squamous cell carcinoma while they were not included in (EORTC 30994) trial.

Our results were also better than the results by ***Cognetti et al.*** [4], DFS of (AC) arms was 68% at 1 year, 50% at 2 years, and 44.2% at 3 years, the trial failed to confirm any survival advantage associated with adding adjuvant treatment, The control and AC arms were almost comparable relative to disease-free survival: 42.3%, arm A and 37.2%, arm B (P = 0.70, HR 1.08; 95% CI 0.73– 1.59).

In the subgroup analysis according to nodal status, the 5-year disease-free survival of the node-negative patients was 59.5% in the control arm and 57.6% in the AC arm (P = 0.97). In node- positive patients, 5-year disease-free survival was 19.4% in the control group and 18.9% in the AC group (P = 0.80).

Concerning overall survival analysis, the median overall survival in our study was not reached due to a relatively short follow up period. Overall Survival rate at 1 year was 90.4%; at 2 years was 77.3% and 73.4% at 3 years. Comparably, In (EORTC 30994) trial, the immediate treatment arm had a median OS of 80.5 months (95% CI 3·85–not reached), OS was 88% at 1 year, 75.4% at 2 years, and 64.1% at 3 years, our results seems to be equal to the EORTC 30994trial. The 5-year overall survival was 53·6% (95% CI 44·5–61·8) in the immediate treatment group and 47·7% (39·1–55·8) in the deferred treatment group with no significant difference between two groups.

Sternberg et al. [10], The duration of survival after progression was longer in the deferred treatment group than in the immediate treatment group (HR 1·45, 95% CI 1·02–2·07; p=0·037). In particular, patients with local or locoregional progression in the deferred group had a median survival of 2·31 years (95% CI 0·94–5·14) after starting treatment versus 1·11 years (95% CI 0·51–1·49) after starting treatment in those with local or locoregional progression in the immediate treatment group.

Cognetti et al. [4], the trial failed to confirm any survival advantage associated with adding adjuvant treatment, The 5-year OS of the whole series was 48.5% (standard error 4.2%), with no significant difference between the two arms (P = 0.24): 53.7% in the control group and 43.4% in the AC arm. Our results was better than the results by ***Cognetti et al.*** [4], OS of (AC) group was 65% at 2 years, and 54% at 3 years comparable to 77.3 at two year and 73.4 at three year.

In the subgroup analysis according to nodal status, In patients with lymph node-negative disease, 5-year OS rates were 73.2% in the control arm and 64.5% in the AC arm (P = 0.65), in contrast to results of EORTC trial which showed survival benefit, 5-year overall survival was 79·5%(95% CI 63·0–89·2) in the immediate treatment group and 59·0% (42·6–72·2) in the deferred treatment group (HR 0·37, 95% CI 0·16–0·83; p=0·012).

Whereas in patients with lymph node involvement, OS rates were 27.6% and 25.8% in the control and AC groups, respectively (P = 0.71). However, the results are similar to EORTC trial, with no addition of survival benefit between both arms in lymph node involvement, 5-year overall survival was 42·7% (32.3–52.8) in the immediate treatment group and 42·9% (32·9–52·6) in the deferred treatment group (HR 0·94, 0·65–1·34; p=0·72).

Paz-Ares et al. [5] reported a trial (Spanish Oncology GU Group 99/01) evaluating adjuvant paclitaxel, gemcitabine, and cisplatin (PGC) that showed a progression-free survival benefit at five years compared to control (P < 0.0001) after four cycles of adjuvant PGC in patients with high-risk MIBC (pT3–T4 and/or pN+). Results also showed a prolonged five-year overall survival in the PCG

arm (60%) compared to (53.6%) of immediate treatment group in (EORTC) trial. However, this study was terminated early due to poor recruitment (140 enrolled out of an expected 340)

In fact, ***Yelfimov et al.*** [(11)] investigated 675 patients who underwent RC for pT2–4N0–3. A total of 80 patients (12%) received AC and were compared with the non-AC group. In this study, when controlling for age, sex, stage, and performance status in multivariate analysis, AC was associated with a 29% decrease in the risk of bladder cancer death.

Meta-analysis of nine RCTs (five previously analyzed, one updated, and three new), which included 945patients, was performed in 2013 [(3)]. It showed **23%** relative decrease in the risk of death with AC compared with controls and **34%** relative decrease in the risk of recurrence. Although it was thought that this updated meta-analysis offered further evidence of OS and DFS benefits, there were some limitations and it is still controversial. *First*, individual patient's data (IPD) for this meta-analysis was not available. *Second*, the most recent Italian [(4)] and Spanish trials [(5)] had completely opposite results.

Those different results may be attributable to the different regimens used and because of patient selection bias. The Italian trial enrolled 194 patients and reported a non-significant OS HR of 1.29 (95%CI, 0.84–1.99) and a non-significant DFS HR of 1.08 (95% CI, 0.73–1.59), although mortality hazards were significantly correlated with pT stage (stage pT3 or higher) and lymph node status in a multivariate analysis. In contrast, the Spanish trial, enrolled 142 patients and demonstrated statistically significant benefits of OS and DFS, with HR of 0.38 (95% CI, 0.22–0.65) and HR of 0.38 (95% CI, 0.25–0.058), respectively [(3)].

Overall survival benefit for adjuvant chemotherapy over the deferred chemotherapy group (HR 0.77, 95% CI 0.65–0·91; p=0.002). In particular, when restricting to the Italian, Spanish, and EORTC studies that mostly used gemcitabine plus cisplatin, severe heterogeneity was noted between the study results (heterogeneity p=0·002) and a borderline significant benefit of immediate gemcitabine plus cisplatin chemotherapy was noted (HR for overall survival 0·79, 95% CI 0·62–1·00; p=0.05) [(3)].

CONCLUSION

- Despite potentially curative-intent radical cystectomy, approximately one-half of patients with deep muscle-invasive bladder cancer involving the muscularis propria (T2), perivesical tissue (T3), or pelvic structures (T4, including prostatic stroma, seminal vesicles, uterus, vagina, pelvic side wall or abdominal wall) develop metastatic disease within two years and most will succumb to their disease.
- For patients with bladder cancer who were not treated with neoadjuvant chemotherapy, we suggest not routinely administering chemotherapy following cystectomy (Grade 2C). However, for patients with high-risk (T3 or higher, pathologic node involvement) urothelial carcinomas who are candidates for cisplatin -based combination chemotherapy and are willing to accept the risk for treatment-related toxicities in the absence of high level of evidence, adjuvant chemotherapy is a reasonable option. If administered, we prefer to use a cisplatin-based combination.

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