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Surgery Versus Perioperative Chemotherapy In Non Metastatic Muscle Invasive Bladder Carcinoma

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Absract:

According to treatment guidelines of urinary bladder carcinoma, using Neoadjuvent chemotherapy followed by radical cystectomy is the standard treatment which improve overall survival and progression free survival. This study is conducted to compare effect of (1) neoagjuvent chemotherapy followed by radical cystectomy with (2) radical cystectomy followed by adjuvant chemotherapy, (3) Radical cystectomy only on OS and PFS. **Patients and methods:** This a retrospective study of all patients with urinary bladder cancer attended out patients at oncology , Beni seuf university hospital at period of 2013 to 2017 with follow up for 5 year. **Results:** In our study mean progression free survival was 24.6 months, longest time was among the patients underwent radical cystectomy followed by adjuvant chemotherapy with 27.8 months then neoadjuvant arm with 20.8 months then radical cystectomy only with 18.1 months with statistically significant difference between the three arms regarding the time spent till the occurrence of relapse (P-value<0.001). Mean over all survival was 27.1 months, the longest survival was among the patients underwent(1) radical cystectomy then adjuvant chemotherapy 28.1 months follow by patients who received(2) neoadjuvant with 23.1 months then(3) radical cystectomy with

20.7 months, there was a statistically significant difference between the three arms regarding the survival (P-value=0.003). **Conclusion:** Radical cystectomy followed by adjuvant treatment has the longest OS with 28.1 months and longest PFS with 27.8 months with statistical significant p value for OS 0.003* and for PFS <0.001** .

Keywords: Neoadjuvant, adjuvant, Radical cystectomy, PFS, OS.

1. Introduction

In united states , in 2019 about 80.470 new cases were diagnostic with bladder cancer (61.700 men and 18.770 women) , mortality was about 17.670 (12.870 men and 4.800women) during this same time (siegel RL,et al, 2019). In united states, bladder carcinoma is 6th most common cancer and rarely diagnosed in persons < 40 years of age. At diagnosis, the median age is 73 years (cancer status fact, 2019).

At the time of diagnosis, about 75–80% of bladder cancers are superficial, while the rest 15–20% present as muscle infiltrative tumors. About 50% of patients with metastatic disease and historical the median overall survival was about 3–6 months without systemic treatment. The addition of cisplatin based therapy improved survival to between 12 and 15 months (1). Even with improvement in surgical techniques, the rate of local and distent relapse remains high. After radical cystectomy the five-year OS rates range from 36 to 48% for pT3-T4 and/or pN0/pN+ disease, most probably due to the presence of micro metastasis at the time of diagnosis (2).

Before or after surgery treatment, can decrease the danger of both local and remote recurrence and increase OS. The most common presenting symptom is painless haematuria, seen in >80% of patients. Others may also present with irritative symptoms such as dysuria, frequency or urgency. Symptoms of metastases such as bone or loin pain which are rare.(3)

Risk factors include : male gender, smoking, bilharzias, occupational workers exposed to arylamines in the contrast, paint, latex, fabric, and leather

industries, recurrent infection, genetic as{ fibroblast growth receptor3 (FGFR-3) and tumor protein p53 (TP53) } and prior pelvic radiation.(4)

Bladder carcinoma is arised from cells lining bladder, the most common pathological type is transitional cell carcinoma followed by squamous cell carcinoma, and other rare types are adenocarcinoma, lymphoma and sarcoma.

Choices of treatment are, for stage Transuretheral excision and intra vesicle injection of BCG, mytomicen or chemotherapy, radical cystectomy followed by adjuvant chemotherapy and radiotherapy is the standard treatment for invasive bladder cancer not metastatic. For locally advanced neadjuvent chemotherapy used as down staging before surgery.

Many studies and meta-analyses have been shown, with more consistent results in favor of neoadjuvent chemotherapy, which is recommended for the treatment of MIBC (level 1 evidence). The problems in accrual and methodological problems of the trials explain that there was no strong evidence for adjuvant therapy arises mainly from that have been conducted in this setting. However, adjuvant chemotherapy is an important choice for patients who have not received neoadjuvent chemotherapy with muscle invasive bladder carcinoma (pT3-T4 and/orpN0 /pN+ disease).

Limited studies, mostly retrospective, have compared the two treatment strategies of NC and AC, so data on the ideal sequence of treatment remains controversial. The aim of this analysis is to compare the efficacy of NC, AC and surgery alone in MIBC.

Chemotherapy is the first line of treatment For stage IV (metastatic). Symptomatic treatment for metastatic site including palliative Rth to bone or brain. Regular follow up including regular CT and cystoscopy every three months in 1st year increase to be every six months in 2nd year then annually.

2. Patients and methods:

This study was retrospective study and ethics approval was obtained from local ethics committee of FM-BSU REC, at the department of clinical oncology, Beni suef university hospital, Beni suef, Egypt. 122 patients with urinary bladder cancer were identified in the period between January 2013 and December 2017 with follow up for 5 year.

Patient inclusion criteria for the current analysis included a diagnosis of MIBC of any histology treated with neoadjuvent chemotherapy followed by radical cystectomy, or the contrary, with surgery first, followed by adjuvant chemotherapy or Radical cystectomy only. Patients treated with adjuvant radiotherapy or a combination of radiation and chemotherapy were excluded, as well as those treated with both NC and AC.

Data collected from the patient's files including

1-Full history taking including:

- Age, sex, residence, special habit (mainly smoking).

- Family history, similar condition in the family.

- Past history especially history of bilharziasis, Rth to pelvis.

-Any comorbidity (mainly DM conditions).

- Time of the first presentation.

- Presenting symptoms.

- Tumor site and size.

- Tumor grade.

- Lines of treatment include surgery (excision, debulking, excisional biopsy and radical cystectomy), chemotherapy(type, aim and duration).

- Onset of first relapse and treatment received for relapse.

- Date of last follow up and dead or alive status.

- Estimation of follow up periods (including DFS, OS).

2- Clinical examination:

- The examination included general examination as well as examination of all systems which was documented in files .

3- Investigations:

Ct imaging (chest, abdomen and pelvis)

Laboratory investigation (routine labs)

Biopsy (according to site)

Imaging for assessment after treatment (ct)

Metastatic work up (bone scan)

The end points of view are (1) Overall survival (OS) is defined as the time from pathological diagnosis to death from any cause, (2) Progression-free survival is defined as the time from pathological diagnosis to occurring of progression or relapse, and (3) mortality rate.

Statistical analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS V20 for windows). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics:

Mean, Standard deviation (± SD), Minimum and maximum values (range) for numerical data, Frequency and percentage of non-numerical data. Analytical statistics: Chi-Square test was used to assess the relationship between the prognostic factors and different intervals to chemotherapy initiation. P-value: Statistical significance was defined as P <0.05. Kaplan-Meier method was used to construct the Disease free survival and overall survival curves of their relationship with the different time intervals and the collected prognostic and predictive factors and compared via log-rank tests.

3. Results:

A total 122 patients who were non metastatic bladder carcinoma visit outpatient clinics at oncology department were enrolled in the current study. The patients were divided into three arms, **(A)** arm 1 (radical cystectomy no. 43), **(B)** arm 2 (Neoadjuvent chemotherapy then surgery (no.32) and **(C)** arm 3 (surgery followed by adjuvant chemotherapy (no.47).

Table 1: Baseline demographic characteristics and risk factors of the three arms of the study:

Characteristics		Arms			P-value
		Surgery only (N=43)	neo-adjuvant (N=32)	surgery then adjuvant therapy (N=47)	
Sex	Males	36 (83.7%)	27 (84.4%)	39 (83.0%)	0.986

	Females	**7 (16.3%)**	**5 (15.6%)**	**8 (17.0%)**	
Age	**40 < years**	**2 (4.7%)**	**0 (0.0%)**	**2 (4.3%)**	**0.058**
	40-60 years	**15 (34.9%)**	**9 (28.1%)**	**26 (55.3%)**	
	60 > years	**26 (60.5%)**	**23 (71.9%)**	**19 (40.4%)**	
Smoking	**No**	**14(32.6%)**	**16 (50.0%)**	**13 (27.7%)**	**0.112**
	Yes	**29 (67.4%)**	**16 (50.0%)**	**34 (72.3%)**	
Bilharziasis	**No**	**21(48.8%)**	**15 (46.9%)**	**22 (46.8%)**	**0.987**
	Yes	**22 (51.2%)**	**17 (53.1%)**	**25 (53.2%)**	

Table 1: The current study showed no statistically significant difference between the arms of the study regarding their age, sex, smoking and bilharziasis (P-value>0.05).

Table 2: Tumor characteristics among the three arms of the study

		Arm			**P-value**
		Surgery only	**neo-adjuvant**	**surgery then adjuvant therapy**	
tumor	**< 3 cm**	**4 (9.3%)**	**3 (9.4%)**	**7 (14.9%)**	**0.011***

size	**3-5 cm**	**23 (53.5%)**	**5 (15.6%)**	**18 (38.3%)**	
	> 5 cm	**16 (37.2%)**	**24 (75.0%)**	**22 (46.8%)**	
Pathology	**TCC**	**26 (60.5%)**	**25 (78.1%)**	**24 (51.1%)**	**0.155**
	adenocarcinoma	**0 (0.0%)**	**1 (3.1%)**	**2 (4.3%)**	
	Squamous cell carcinoma	**8 (18.6%)**	**1 (3.1%)**	**11 (23.4%)**	
	Mixed	**9 (20.9%)**	**5 (15.6%)**	**10 (21.3%)**	
Grade	**G1**	**1 (2.3%)**	**1 (3.1%)**	**1 (2.1%)**	**0.398**
	G2	**19 (44.2%)**	**7 (21.9%)**	**17 (36.2%)**	
	G3	**23 (53.5%)**	**24 (75.0%)**	**29 (61.7%)**	
T	**T1**	**7 (16.3%)**	**0 (0.0%)**	**1 (2.1%)**	**<0.001****
	T2	**13 (30.2%)**	**7 (21.9%)**	**2 (4.3%)**	
	T3	**18 (41.9%)**	**15 (46.9%)**	**35 (74.5%)**	
	T4	**5 (11.6%)**	**10 (31.3%)**	**9 (19.1%)**	
N	**N0**	**36 (83.7%)**	**10 (31.3%)**	**28 (59.6%)**	**0.001****
	N1	**4 (9.3%)**	**12 (37.5%)**	**9 (19.1%)**	
	N2	**2 (4.7%)**	**9 (28.1%)**	**10 (21.3%)**	
	N3	**1 (2.3%)**	**1 (3.1%)**	**0 (0.0%)**	

Table 2: There was no statistically significant difference between the arms of the study regarding tumor size, pathological type and grade (P-value>0.05). However surgery was done more

frequent in T1**(16.3%),** T2**(30.2%)** and T3 **(74.5%)** was more associated with adjuvant arm, N0 **(83.7%)** was associated with surgery.

Table 3: Response to treatment after the 1st line of treatment:

		Arm			P-value
		Surgery only	neo-adjuvant	surgery then adjuvant therapy	
Response after 1st line	CR	42 (97.7%)	13 (40.6%)	43 (91.5%)	<0.001**
	PR	0 (0.0%)	13 (40.6%	1 (2.1%)	
	PD	1(2.3%)	6 (18.8%)	3(6.4%)	

Table 3: There was a statistically significant difference between the arms of the study regarding the response to 1st line of treatment as the complete remission was achieved more in surgery only (97.7%) and surgery then adjuvant (91.5%), however the partial and complete remission were more equal in the neo-adjuvant arm (40.6%) (P-value<0.001)

Table 4: Incidence of relapse among the main three arms of treatment

		Arm			P-value
		Surgery only	neo-adjuvant	surgery then adjuvant therapy	
Relapse	No	26 (60.5%)	24 (75.0%)	39 (83.0%)	0.053
	Yes	17 (39.5%)	8 (25.0%)	8 (17.0%)	

Table 4: There was no statistically significant difference between occurring of relapse and 3 arms of study.

Table 5: The mortality rate in the main three arms of treatment

		Arms			P value
		Surgery only	Neo-adjuvent	adjuvent	
Mortality	Alive	37 (86.0%)	29 (90.6%)	41 (87.2%)	0.830
	Died	6 (14.0%)	3 (9.4%)	6 (12.8%)	

Table 5: There was no statistically significant difference between the arms of the study regarding the mortality rate (P-value=0.830)

Table, figure 6: the overall survival of the three arms of management of the studied cases

Arm	Overall survival				P-value (log-rank)
	Mean	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound	
Surgery only	20.750	.461	19.846	21.654	0.003*
neo-adjuvant	23.139	1.547	20.107	26.170	
surgery then adjuvant therapy	28.177	.703	26.798	29.555	
Overall	27.151	.651	25.874	28.427	

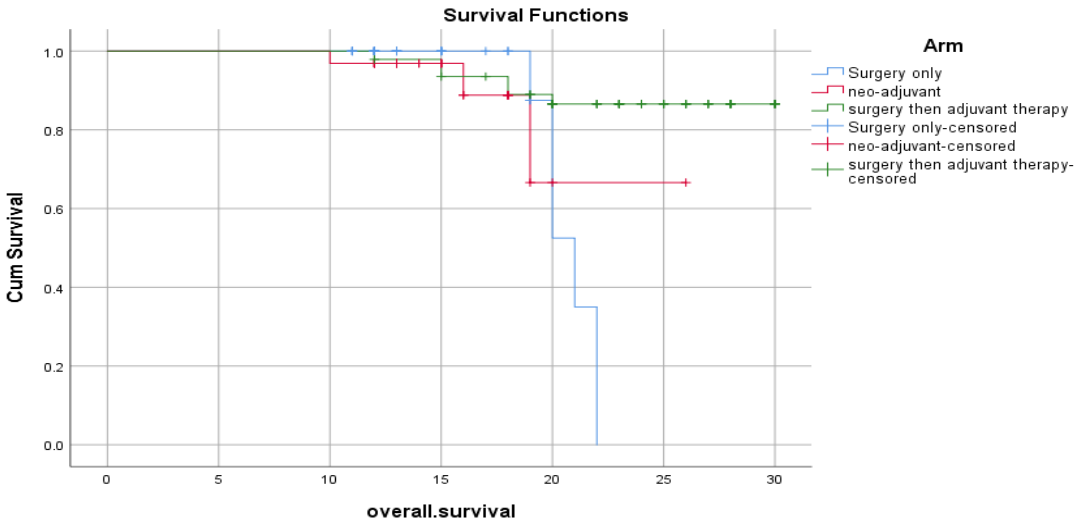

Table 6, figure 1: There was a statistically significant difference between the three arms regarding the survival time spent till the occurrence of death as the longest overall survival time was among the patients underwent surgery then adjuvant therapy (28.17±0.703) months followed by the neoadjuvant arm (23.1±1.5) months then the patients underwent surgery only (20.7±0.461) months (P-value=0.003).

Table 7: two years and three years survival in each arm of the study:

Arms	2 years survival	3 years survival
Surgery only	**37/43(86%)**	**0/37 (0%)**
neo-adjuvant	**29/32(90.6%)**	**1/29(3.4%)**
surgery then adjuvant therapy	**41/47(87.2%)**	**19/41(46.3%)**
P-value	**0.432**	**<0.001***

Table 7: There was no statistically significant difference between the three arms regarding the 2 year survival however the 3 years survival was statistically higher in the surgery then adjuvant arm than the other 2 arms.

Table 8: the progression free survival of the three arms of management of the studied cases

Arms	PFS after 1st line				P-value (log-rank)
	Mean	Std. Error	95% Confidence Interval		
			Lower Bound	Upper Bound	
Surgery only (43)	18.164	.735	16.724	19.605	<0.001**
neo-adjuvant (32)	20.862	1.413	18.093	23.632	
surgery then adjuvant therapy (47)	27.863	.693	26.504	29.221	
Overall	24.660	.738	23.213	26.107	

Table 8: There was a statistically significant difference between the three arms regarding the progression free survival as the longest time to relapse was among the patients underwent surgery then adjuvant therapy (27.8±0.693) months followed by the neoadjuvant arm (20.8±1.4) months then the patients underwent surgery only (18.1±0.735) months (P-value<0.001)

4. Discussion:

Muscle infiltrative bladder carcinoma is a very aggressive disease, with a high rate of early metastatic spreading, and a low 5-year OS rate. in addition to radical cystectomy perioperative cisplatin-based chemotherapy improves results in high risk MIBC, increased disease control with improved survival, maybe due to eradication of micro metastatic disease. At this time, at least two randomized trials and multiple meta-analyses support neoadjuvent chemotherapy, which has shown an improvement in OS for cisplatin based combinations chemotherapy.

The optimal use of perioperative chemotherapy one of the most remarkable issues in the treatment of MIBC. Data support the role of NC for

stage II – IIIA lesions (5)**.** In a SWOG randomized trial of 307 patients with MIBC, radical cystectomy alone versus 3 cycles of neoadjuvant methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) followed by radical cystectomy were compared. Neoadjuvant chemotherapy improved median survival to be 77 months vs. 46 months and decrease rate of residual disease 15% vs. 38% with no evidence of increasing in treatment related morbidity or mortality (6),(7). In a meta-analysis of 11 trials involving 3005 patients, cisplatin-based companied neoadjuvant chemotherapy was related to improve 5 year OS by 5% and DFS by 9%.(8)

The NCCN guidelines recommend neaadjuvant chemotherapy followed by radical cystectomy for patients with stage II-IIIA bladder carcinoma. Based on high level data, useing neoadjuvant chemotherapy followed by radical cystectomy is a category 1 recommendation.

Particularly, the MRC BA06/EORTC 30894 trial, proved a 10-year benefit of 6% for NC, and the SWOG study by Grossmann et al, proven a direction toward better OS in favor of NC with M-VAC (5, 6). Also, in 2005, a meta-analysis of 11 trials of NC including 3,005 patients showed a decrease in the risk of death of 14% (HR = 0.86, 95% CI 0.77–0.95, *P*: 0.003), with a survival benefit of 5% at 5 years (from 45 to 50%) (9).

The role of adjuvant chemotherapy is more controversial because that given data derived mainly from studies with varying results due to methodological problems and insufficient patient numbers due to early ending and poor staffing. No single study, taken individually, has showed a statistically significant survival benefit in favor of adjuvant chemotherapy with the exception of the Spanish study (Spanish Oncology Genitourinary Group-SOGUG). It showed a possible benefit in OS for AC with cisplatin, paclitaxel, gemcitabine (median OS 26 months; 5-year OS, 31%; $P < 0.0009$), DFS (*P*: < 0.0001), TTP (*P*: < 0.0001), and CSS (*P*: < 0.0002). This study was closed prematurely due to poor staffing, and the results were presented at an ASCO meeting but have never been fully published (10).

The EORTC did the largest adjuvant chemotherapy study to date (trial 30994). This study was also tied up by difficulties in recording. The study compared immediate AC with four cycles of chemotherapy vs. observation and six cycles of chemotherapy at the time of recurrence. GC, M-VAC or HD-VAC was allowed. This study did not express a benefit in OS (adjusted HR 0.78, 95% CI.0.56–1.08; $P = 0.13$), but did reveal a highly significant

improvement in PFS, with 5 year PFS of 47.6 vs. 31.8% for those given immediate adjuvant chemotherapy (HR: 0.54, 95% CI: 0.40–0.73, $P < 0.0001$). There was, however, a benefit in OS for the subgroup of patients with negative lymph nodes (pN0) (11) and a non-significant 22.2% reduction in the risk of mortality with immediate adjuvant chemotherapy in the ITT population.

Meta-analyses have been bringing out to explain the role of AC. The analysis published in 2014 without the EORTC study data, showed a decrease in the risk of mortality with AC of 23% (HR 0.77, 95% CI 0.59–0.99; *P*: 0.049) (12). A furthermore update of this meta-analysis, inconsistent with the EORTC 30994 study, give a survival benefit with immediate adjuvant treatment (HR 0.77, 95% CI 0.65–0.91; $P = 0.002$) (12,13).

New two trails were published in September 2017 and January 2019 demonstrated role of adjuvant chemotherapy for muscle invasive bladder carcinoma.

In the network meta-analysis, the gemcitabine/cisplatin/paclitaxel (GCP) combination was the only adjuvant chemotherapy regimen associated with significant increase in both the PFS (HR, 0.38; 95% CrI, 0.25–0.58) and OS (HR, 0.38; 95% CrI 0.22–0.65).

Adjuvant chemotherapy following radical cystectomy for MIBC may share in improving PFS and OS. Particularly, the GCP combination may be the ideal adjuvant chemotherapy regimen for improving postoperative survival outcomes.(14).

Four randomized controlled trails with a total of 490 patients were selected for the analysis. These four trials included patients with locally advanced MIBC. Pooled HRs for PFS and OS across the studies were 0.48 (95% confidence interval [CI], 0.39–0.60; p<0.00001) and 0.63 (95% CI, 0.48–0.83; p=0.0009), respectively. Absolute increases in PFS and OS for locally advanced muscle invasive bladder carcinoma were 17% and 10%, respectively (i.e., equivalent to numbers needed to treat of 5.9 and 10).(15)

Therefore, at present cisplatin-based combination adjuvant chemotherapy is a appreciated option for patients with bladder cancer pT3-pT4, pN0/pN+, M0 who have not received neoadjuvent treatment.

Until now, only one study compared NC with AC in a prospective method. This study was released in 2001 at the MD Anderson Cancer Center. In this trial, 140 patients were randomized to receive neoadjuvent treatment with two cycles of M-VAC followed by surgery and three additional M-VAC cycles, or immediate surgery followed by five AC cycles. At a median follow-up of 6.8 years, no statistically significant differences were observed in OS and DSS between the two treatment groups (16).

In a retrospective study at Columbia University, OS and DSS were analyzed in 146 patients who received perioperative therapy between 1988 and 2009 (73 neoadjuvant and 73 adjuvant). In this report, no statistically significant difference between the two treatments was observed.(17).

Another retrospective study in 42 patients, compared the combination of cisplatin and gemcitabine in the NC and AC setting without giving any difference in recurrence free survival (*P*: 0.124) (18).

The ASCO meeting in 2016 showed the results of a retrospective study from the National Cancer Database. This study, built on a series of more than 1,600 patients treated with NC and 800 with AC, compared NC to AC and to surgery alone, in terms of OS. Multivariate analysis showed higher OS (*P*: 0.008) for the patients treated with NC (19). These results are not definite due to the retrospective nature of the work, but may recommend more caution in analysis of the results of meta-analysis and large retrospective studies in favor of the role of AC (20).

All of these results confirmed that the sequence of treatments surrounding cystectomy is not important as the perioperative therapy itself.

As far as we know, our study demonstrated the effect of those different arms of treatment of non-metastatic bladder carcinoma arm 1 (radical cystectomy), arm 2 (Neoadjuvent chemotherapy then surgery) and arm 3 (surgery followed by adjuvant chemotherapy) on OS, PFS, relapse and mortality.

Our study show that over all survival was 27.1 months, the longest survival was among the patients underwent radical cystectomy then adjuvant treatment 28.1 months follow by patients who received neoadjuvant with 23.1

months then radical cystectomy with 20.7 months, there was a statistically significant difference between the three arms regarding the survival (P-value=0.003).

In our study progression free survival was 24.6 months, longest time was among the patients underwent surgery radical cystectomy then adjuvant therapy with 27.8 months followed neoadjuvant arm with 20.8 months then radical cystectomy with 18.1 months with statistically significant difference between the three arms regarding the time spent till the occurrence of relapse (P-value<0.001).

The 2 years OS was 86%, and the 3 years OS is 0% for radical cystectomy, 90.6% in 2 years and 3.4% in 3 years survival in neoadjuvant and 87.2% in 2 years and 46.3% in 3 years survival in adjuvant. The 5 year OS was not reached at the end of the follow-up, In a retrospective study analyzing survival of patients with bladder cancer Rezaianzadeh et al found that 1, 3, 5, and 10 years overall survival were 89%, 71%, 57%, and 24% respectively.(21) This difference can be attributed to that our patients presented with more advanced stages and also most of them lost follow up resulting in lack of survival data in our study.

Comparison trail between neoadjuvant and adjuvant gemcitabine plus cisplatin chemotherapy for muscle-invasive bladder cancer published in Nov 2012 showed no statistically significant difference in RFS between neoadjuvant and adjuvant GC chemotherapy for muscle-invasive bladder cancer. We expect to validate these findings in a prospective randomized trial.(22)

Another one published in Nov 2018 showed a statistically significant difference in DFS in favor of NC (HR: 0.78, 95% CI: 0.63–0.96, *P* = 0.02), without any significant advantage in CSS (HR: 1.06, 95% CI: 0.79–1.43, *P* = 0.70) and OS (HR: 1.08; 95 % CI 0.83–1.39, *P* = 0.57).(23).

Although there was no statistically significant difference between the arms of the study regarding tumor size, pathological type and grade, it notes that 75% of patients received NC was > 5 cm with G3. 68.7% in NC was nodal positive. This may explain that PFS and OS were higher in AC arm than NC which is different from other studies comparing NC and AC which showed that neoadjuvent was better or no statistically difference as mentioned above.

It has many limitations that derive mainly from the retrospective nature of the study, a potential bias in the

distribution of patient characteristics and the type of statistical analysis, which does not allow definitive conclusions. A major limitation in this comparison is that NC is administered based on clinical staging whereas AC is given based on pathologic staging, making the comparison even more difficult. There is always the potential for heterogeneity in outcomes and understaging based on clinical staging. Another problem is the lack of data concerning performance status in all patients, and the heterogeneity of chemotherapy treatments, often without cisplatin (more than 70% of patients treated without cisplatin in each group). Moreover, subsequent therapies for metastatic disease, that may have affected OS and CSS results, were not available for all patients.

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