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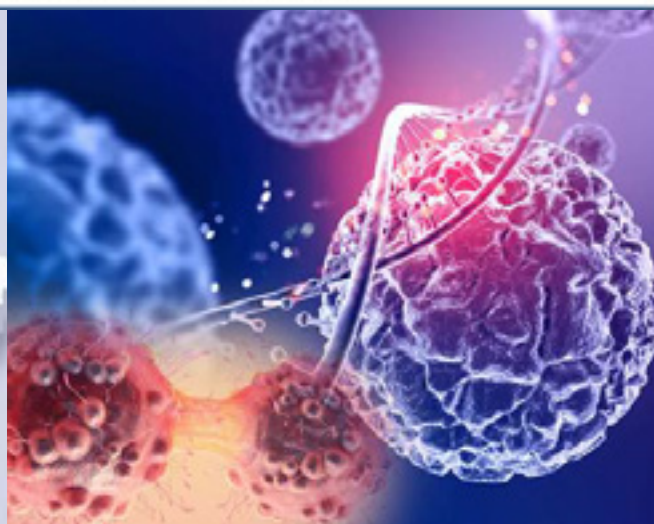


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Promoting, protecting and delivering health for all by all"



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Original Article

Neoadjuvant Chemotherapy for Muscle–invasive Bladder Cancer in a Lebanese experience: in all aspects

Nizar Ahmadieh¹, Toufic Zeidan², Josselin Abi Chebel¹, Fady Gh Haddad², Elie Nemr¹

¹Department of Urology, Faculty of Medicine, Saint Joseph University of Beirut, Beirut, Lebanon.

²Department of Hematology–Oncology, Faculty of Medicine, Saint Joseph University of Beirut, Beirut, Lebanon.

Abstract

Background: Bladder cancer (BC) is the most common malignant tumor of the urinary tract and the 11th most frequent cancer worldwide. BC is the 2nd most common cancer in Lebanon in men and women.

Materials and Methods: After searching for patients records in the pathology and oncology database, we identified those who underwent a cystectomy between 2017 and 2019 in our hospital, Hotel Dieu de France – Beirut. We selected for the study the patients who have undergone a cystectomy for MIBC. We excluded patients who initially had a pelvic tumor, or a prostate cancer invading the bladder, and patients with absent medical record from the study. We also noted the gender of the patients, if they are smokers and the number of pack years at the time of diagnosis, as well as their age, the histological type of the tumor, its stage according to the TNM classification and its grade. We also noted whether neoadjuvant chemotherapy was taken by the study's subjects.

Results: The total number of patients who met the inclusion and exclusion criteria was 38. The median age of the population was 66 (\pm 10) years and the median number of pack years at diagnosis was 60 (\pm 36). 79% of study's patients were males and 21% were females. Regarding the tumor's histological type, the urothelial

type predominated with 92% while the remaining 8% were of the squamous type.

Regarding treatment modalities, only 20% of patients in the study received neoadjuvant chemotherapy before cystectomy. 80% of patients underwent a cystectomy directly without neoadjuvant and/or adjuvant chemotherapy. No patient received adjuvant chemotherapy.

Among the 7 patients, 2 patients (29%) presented a pathological complete response (pCR; equivalent to pTONOMO). 14% had a pT3 stage post–neoadjuvant chemotherapy and 43% had a pT4 stage.

Discussion and conclusions: We can note a reluctance of urologists at our institution to prescribe neoadjuvant chemotherapy. It would therefore be interesting to extend the study to the national level with a larger number of patients, as well as to evaluate survival in patients who received neoadjuvant chemotherapy, especially in those presenting a pCR. Our study can serve as a point of change in the practice of urologists in Lebanon regarding BC.

Keywords: Bladder cancer, Lebanese, chemotherapy, neoadjuvant chemotherapy.

Corresponding Author:

ORCID ID <https://orcid.org/0000-0002-0225-3373> Nizar Ahmadieh, MD, MRCS
Saint Joseph University, Beirut – Lebanon Heidelberg University, Germany
Emergency Department, Doncaster and Bassetlaw NHS Teaching Hospitals Doncaster/South Yorkshire/England,
United Kingdom DN2 5BH +447417465565 Email: nizar.ahmadieh@gmail.com
Nizar.elahmadie@nhs.net

Introduction

Bladder cancer (BC) is the eleventh most common cancer globally for both sexes and the fourteenth in terms of mortality, with 550,000 new cases diagnosed each year and 200,000 deaths per year.⁽¹⁾

In order of frequency, it is first among cancers of the urinary tract.

In Lebanon, it is the 2nd most common cancer in men.⁽²⁾ According to the Globocan database in 2018, Lebanon has the highest incidence of BC globally for both sexes combined, and for the women population, and second only to Greece for the men population.⁽¹⁾

Men typically have an incidence and death rate almost two to four times greater than women. The World Health Organization (WHO) estimated in 2014 in the “World Cancer Report” that 72% of new cases are diagnosed in developed countries.⁽³⁾

As a result of different responsible risk factors, the worldwide distribution of each tumor histological type is varied. The urothelial type is most common in developed countries. The latter is mainly caused by exposure to tobacco and occupational exposure to some chemical carcinogens. In addition, there is a higher prevalence of the squamous cell type in the Middle East and in West Africa; this is due to chronic inflammations and infections with *Schistosoma haematobium*.^(3–5)

In most cases, it is a Non–Muscle Invasive Bladder Cancer (NMIBC) with a survival rate of about 96% at 5 years, or a Muscle Invasive Bladder Cancer (MIBC) reducing the survival rate to 70% at 5 years or even to 5.5% at 5 years in the event of metastasis, despite treatment.^(6–7)

The therapeutic management of bladder tumors is multidisciplinary, ranging from instillations of Calmette–Guerin bacillus (BCG) to surgery, including neoadjuvant, adjuvant or palliative chemotherapy and/or radiotherapy. Several advances have been made about neoadjuvant chemotherapy treatment, especially for MIBC, which has been shown to be effective in improving the survival of the invasive stages of this cancer, gradually integrating international recommendations since 2008.^(8–10)

In 2008, radical cystectomy was still considered the ‘gold standard’ treatment for MIBC. Survival with radical cystectomy alone was around 50% at 5 years.⁽¹¹⁾

To improve this figure, neoadjuvant chemotherapy was studied. After several randomized studies, three meta–analyses were done. The most recent, from the Cochrane Database review in 2005, included 3005 patients in 11 randomized controlled trials comparing neoadjuvant chemotherapy with local treatment versus local treatment

alone. A 14% decrease in mortality was noted in the first group, equivalent to a 5% improvement in absolute survival at 5 years. (45% to 50%; HR 0.86, 95% CI 0.77–0.95, P = 0.003), in addition to an increase in disease–free survival of 9% at 5 years.⁽¹²⁾

In the first meta–analysis, dating from 2003, a 13% reduction in the risk of mortality was equivalent to a 5% improvement in absolute 5–year survival (50% vs. 45%).⁽¹³⁾ The second, dating from 2004, similarly showed a 5% improvement in absolute 5–year survival (55% vs. 50%).⁽¹⁴⁾

This has only been observed with multidrug therapy containing cisplatin.⁽¹¹⁾

Thanks to the results of these studies, several recommendations published from 2008 are in favor of neoadjuvant chemotherapy.

In addition, when it was published in 2011, the “BA06 30894 trial”, an international randomized phase III clinical trial, showed a reduction in mortality of 16% as well as an improvement in absolute survival from 6% to 10 years (36% vs 30%).⁽¹⁵⁾ It should be noted that this study was carried out on 946 patients, recruited between 1989 and 1995, divided into two groups: patients with single surgical treatment and others who received 3 cycles of neoadjuvant chemotherapy based on cisplatin, methotrexate, and vincristine (CMV).⁽¹¹⁾

Moreover, several new meta–analyses have been published on this subject.

In 2013, a meta–analysis also showed a 21% decrease in mortality with a significant increase in absolute survival in patients who received neoadjuvant chemotherapy. Regarding the regimens studied, a decrease in mortality of 28% was noted in the group treated with CMV, 25% for methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), but no variation in mortality was noted in patients on cisplatin, cisplatin–methotrexate, or cisplatin–docetaxel.⁽¹⁶⁾

Another meta–analysis published in 2014, comprising of 886 patients, and evaluating 13 clinical trials, showed that patients who present a pathological complete response (pCR, stage TONOMO) after neoadjuvant chemotherapy, have a greater overall survival with a lower risk of recurrence.⁽¹⁷⁾

A new meta–analysis in 2015 comprising 3285 patients encompassing 15 randomized clinical trials, confirmed the increase in absolute survival in patients who received cisplatin–based chemotherapy (‘Hazard ratio’ [HR], 0.87; 95% ‘confidence interval’ [CI], 0.79–0.96), with a greater increase in the group having received the MVAC diet compared to the Gemcitabine–Cisplatin regime (GC) (HR, 1.26; 95% CI, 1.01–1.57); but after excluding the group that received carboplatin, the difference remained greater with MVAC compared to GC (HR, 1.31; 95% CI, 0.99–1.74), with no significant difference between the two regimens for the

complete pathological response.⁽¹⁸⁾

Materials and methods

After getting Institutional Review Boards' (IRB) approval from the Saint Joseph's University (Beirut) Research Ethics Committee and following accepted ethical standards, we performed a retrospective observational study at our hospital, the Hotel Dieu de France – Beirut, searched for patients' records in the pathology and oncology database, and identified those who had a cystectomy between 2017 and 2019.

We selected for the study the patients who have undergone a cystectomy for MIBC. We also noted the gender of the patients, if they are smokers and the number of pack years at the time of diagnosis, as well as their age, their Body Mass Indexes (BMI), the histological type of the tumor, its stage according to the TNM classification and its grade. We also noted whether neoadjuvant chemotherapy was taken by the study subjects.

The inclusion criteria were patients who underwent a cystectomy for MIBC between 2016 and 2019 (44 patients)

The exclusion criteria were patients who initially had a pelvic tumor (uterine, ovarian, a prostatic invading the bladder etc.), (4 patients) or had an incomplete medical record (2 patients).

The inclusion and exclusion criteria are illustrated below. (Table 1)

Exclusion criteria		Inclusion criteria
C Y S T E C T O M Y	Pelvic tumor (uterine, ovarian, prostate cancer invading the bladder, etc.): 4	Cystectomy for MIBC:44
Absent/incomplete medical file: 2		

Table I. Table detailing the study's inclusion and exclusion criteria.

Results

Population

The total number of patients who underwent cystectomy for MIBC from 2017 to 2019 was 44, of whom 38 were meeting the exclusion criteria. 2 patients were excluded from the study as their medical records were missing or insufficient, and 4 were excluded as the primary tumor was not of vesical origin (i.e. prostatic, uterine or ovarian).

38 patients, meeting both the inclusion and exclusion criteria, were thus retained in the study.

The median age of this population was 66 (\pm 10) years and the median number of pack years at diagnosis was 60 (\pm 36).

79% of patients in the study (30/38) were males and 21% (8/38) were females. The median BMI of the study population was 25.3.

Regarding the ECOG performance status in the studied population, it was 0 in 37% of cases, 1 in 34% (13 cases), 2 in 24% (9 cases), 3 in 3% (1 case), and 4 in 3% (1 case). (fig. 2)

Histological and anatomopathological characteristics

The patients were then classified according to their stage according to the TNM classification after cystectomy. (fig. 3) It should be noted that all the patients who received neoadjuvant chemotherapy had a pT2 stage on Transurethral resection of bladder tumor (TURB) before taking chemotherapy and cystectomy. Two patients presented with a pT0 stage (equivalent to a pCR) to chemotherapy, which will be illustrated in the remainder of the study. 8 patients had received a BCG treatment before cystectomy was done, and 0 received mitomycin.

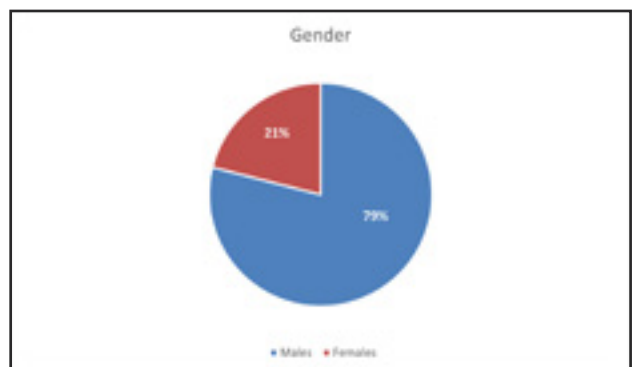


Fig. 1. Pie chart detailing the gender repartition of patients.

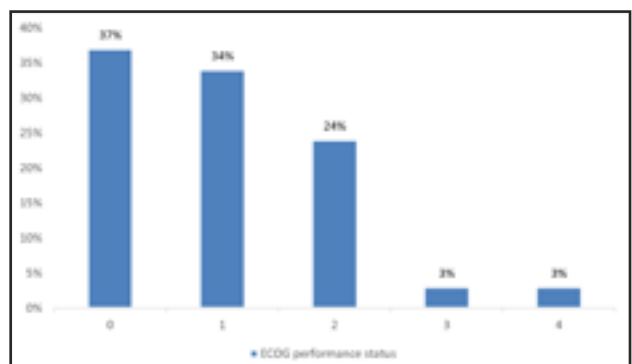


Fig. 2. Bar chart detailing the ECOG performance status in the studied population.

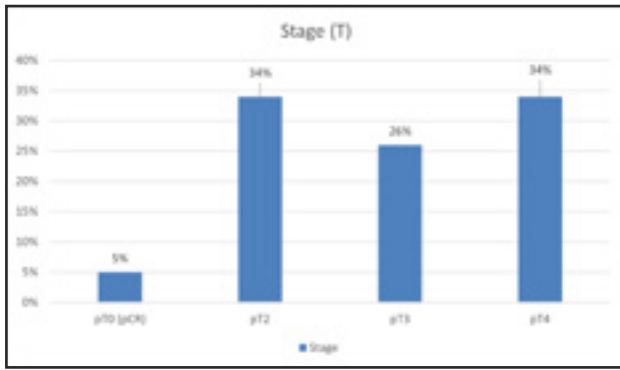


Fig. 3. Bar chart detailing the repartition of subjects according to the tumor's stage, after cystectomy.

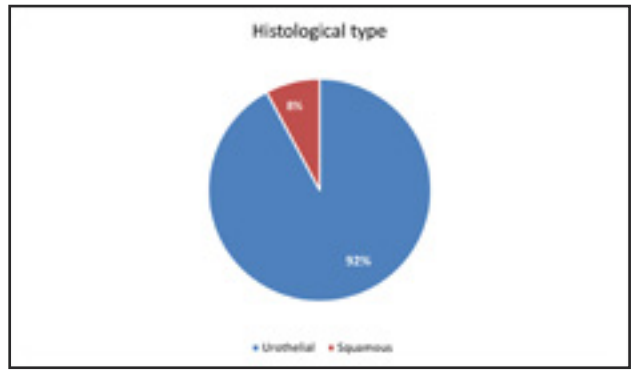


Fig. 7. Pie chart showing the percentage of histological types.

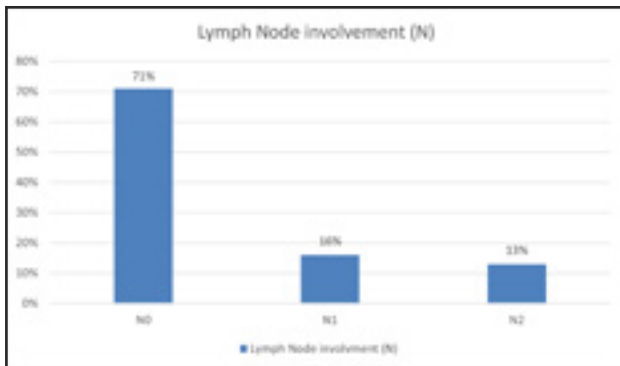


Fig. 4. Bar chart detailing the repartition of subjects according to lymph node involvement of the tumor, after cystectomy.

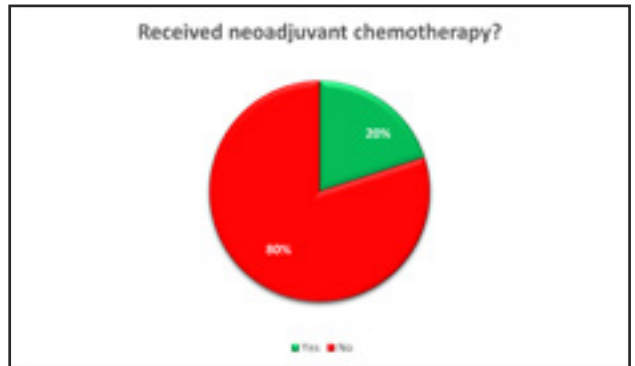


Fig. 8. Pie chart detailing the percentage of patients receiving neoadjuvant chemotherapy.

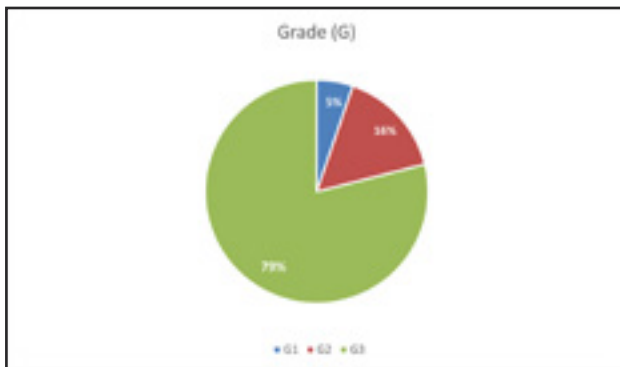


Fig. 5. Pie chart detailing the repartition of patients according to the tumor's grade.

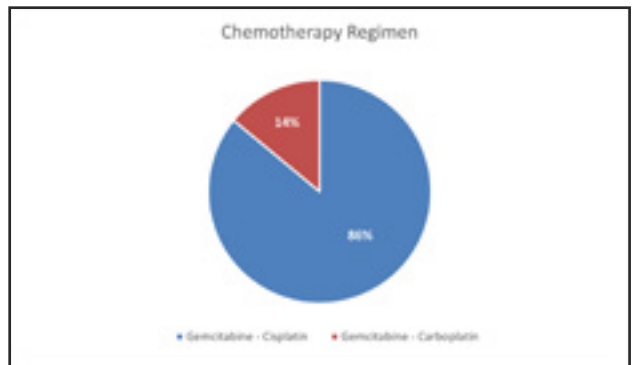


Fig.9. Pie chart illustrating the number of patients receiving each neoadjuvant chemotherapy regimen.

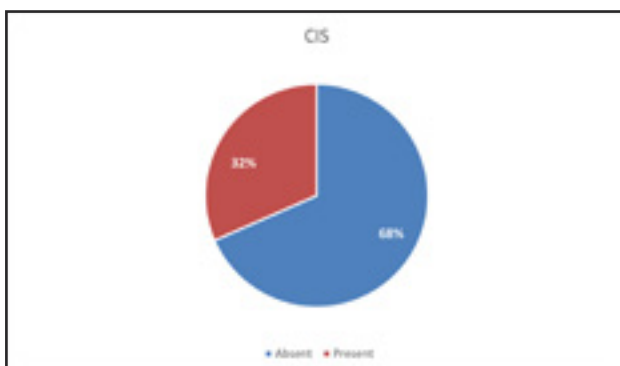


Fig.6. Pie chart showing the percentage of CIS.

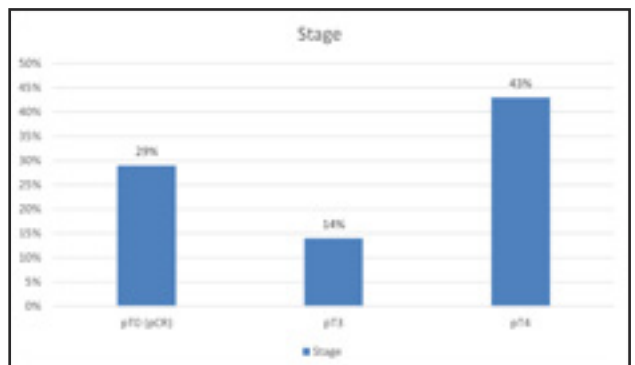


Fig. 10. Bar chart detailing the tumor's stage after cystectomy, in patients who have received neoadjuvant chemotherapy.

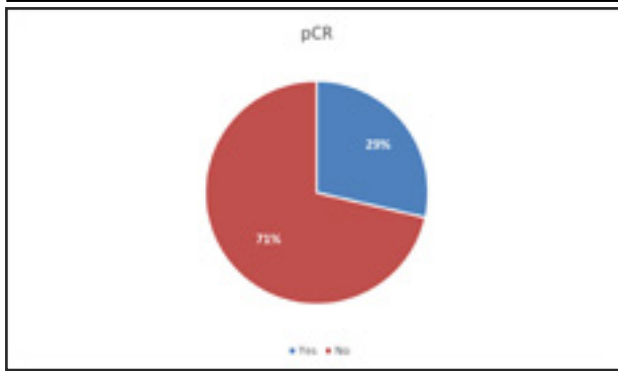


Fig. 11. Pie chart detailing the percentage of pCR in patients receiving neoadjuvant chemotherapy.

71% of patients had no lymph node involvement (N0), 16% of patients had an N1 node and 13% had an N2 stage. (fig. 4)

Likewise, 5% of patients (2/38) had grade G1, 16% (6/38) had grade G2 and 79% (30/38) had grade G3. (fig. 5)

In addition, only 32% of patients had a carcinoma in situ (CIS) at the time of diagnosis. (fig. 6)

Regarding the tumor histological type, the urothelial type predominated in 92% of the study's patients (35/38) against the remaining 8% who presented a squamous type (3/38). Of the 35 urothelial type cases, 8 (22.8%) were papillary, 6 (17%) had a squamous differentiation, 2 (5.7%) had a glandular differentiation, and 1 (2.8%) had a microcystic differentiation. (fig. 7)

Regarding treatment modalities, only 20% of patients in the study (7/38) received neoadjuvant chemotherapy before cystectomy. 80% of patients (31/38) underwent a cystectomy directly without neoadjuvant and/or adjuvant chemotherapy. (fig. 8) It should be noted that, one patient had an ECOG performance status of 4, and another patient presented with a Mantle Cell Lymphoma requiring adequate chemotherapy, one year before the diagnosis of his BC. No patient received adjuvant chemotherapy.

In addition, among the patients who received neoadjuvant chemotherapy, 14% of them had renal failure and were therefore treated with the Gemcitabine – Carboplatin regimen. The other 86% were treated with the Gemcitabine – Cisplatin regimen. (fig. 9) Moreover, of the patients who were on the Gemcitabine – Cisplatin regimen, 83% of them had 4 cycles, and 17% had 3 cycles. The single patient who received Gemcitabine – Carboplatin regimen had 4 cycles.

It was also interesting to study the response of patients who received chemotherapy. 29% of patients having received neoadjuvant chemotherapy, had a pathological complete response (pCR) (equivalent to pTONOMO) after it. 14% had a pT3 stage post–neoadjuvant chemotherapy and

43% had a pT4 stage. (fig. 9–10) It should be noted that all the patients who received neoadjuvant chemotherapy had a pT2 stage on TURB before taking chemotherapy and being operated on for a cystectomy. There were no cases of pCR in patients who did not receive neoadjuvant chemotherapy.

Discussion and conclusions

The interest of this study was to discuss the international recommendations for the management of MIBC, especially those concerning neoadjuvant chemotherapy, as well as to analyze the adherence to them by doctors in Lebanon. In addition, the efficacy of neoadjuvant chemotherapy was evaluated in the study sample. Moreover, the histological, demographic, and therapeutic characteristics of the study population were compared to those in the literature.

Several similarities exist between the studied population and those in the literature from a demographic point of view: the median age at the time of diagnosis of the population was 66 compared to the median age of 65–70 in literature. 79% of the patients in the study were males and 21% females, equivalent to the sex distribution in literature, which reports that BC is 3 to 4 times more common in men than in women. ⁽⁷⁾

From a histological point of view, the most frequent histologic type in the study population was the urothelial type at 92% followed by the squamous type (8%), comparable to the figures for developed countries (90% and 1–7%, respectively). ⁽¹⁹⁾

From a therapeutic point of view, and despite strong international recommendations, the high level of evidence and evidence of improved survival, only 20% of the cases in the study received chemotherapy neoadjuvant to cystectomy. It should be noted that, nevertheless, this figure is identical to the percentage of patients in the United States, where only 20% of patients receive neoadjuvant chemotherapy before cystectomy. ^(20–22)

Despite the small number of patients in the study, 29% of patients who received neoadjuvant chemotherapy presented a pCR (TONOMO) with a pT2 stage on diagnostic TURB, consistent with the 30% described in Yin et al. ⁽²³⁾ There were no cases of pCR in patients who did not receive neoadjuvant chemotherapy.

Although the statistical power of the study is limited, this number is still not negligible, especially since these patients, after neoadjuvant chemotherapy, had greater overall survival with a lower risk of tumor recurrence. ⁽²⁴⁾

It is also worth noting that there are overall 10 urologists at our institution, of whom 6 were involved in the decision making of performing a cystectomy on the study patients.

Reluctance to prescribe neoadjuvant chemotherapy

could be partly explained by its side effects. Therefore, it could be useful if in future trials, fewer cycles of neoadjuvant chemotherapy could be compared with the usual 4 cycles. Moreover, immunotherapy could also benefit from further studies regarding its use as a neoadjuvant agent.

We can note a reluctance of urologists at our institution to prescribe neoadjuvant chemotherapy. It would therefore be interesting to extend the study to the national level and therefore to analyze a larger number, as well as to evaluate the survival in patients who received neoadjuvant chemotherapy, especially in those who had a pCR. Our study can serve as a basis for improving the practice of urologists in Lebanon regarding BC.

Funding and Conflict of Interest

The authors declare that they have no conflict of interests.

Ethical Disclosure

The study has an IRB approval from the Saint Joseph's University (Beirut) Research Ethics Committee. It has been performed in accordance with the ethical standards laid down in an appropriate version of the 1964 Declaration of Helsinki.

All the corresponding authors have consented for the study to be published.

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