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## REVIEWER'S REPORT

**Manuscript No.: IJAR- 57265**

**Title: pCR after neoadjuvant chemotherapy and survival in localized bladder cancer: A Moroccan experience**.

**Recommendation:**
**Accept after minor revision**

| Rating | Excel. | Good | Fair | Poor |
|---|---|---|---|---|
| Originality | | ✔, | | |
| Techn. Quality | | ✔, | | |
| Clarity | ✔, | | | |
| Significance | ✔, | | | |

**Reviewer Name: Dr. Bilqees Hamza**

**Detailed Reviewer's Report**

The research article titled "pCR after neoadjuvant chemotherapy and survival in localized bladder cancer: A Moroccan experience" provides a critical real-world evaluation of the treatment landscape for muscle-invasive bladder cancer (MIBC) in a middle-income setting. The author investigates the efficacy of neoadjuvant cisplatin-based chemotherapy (NAC) followed by radical cystectomy, which is the established global standard of care. By analyzing a cohort of 65 patients from the CHU Hassan II in Fez, the study establishes a direct correlation between pathological complete response (pCR) and significantly improved survival outcomes. The narrative successfully highlights that while the clinical protocols in Morocco align with international guidelines, systemic challenges regarding operability and treatment completion remain significant hurdles to optimizing patient prognosis.

The initial phase of the study focuses on the demographic and clinical characteristics of the patient population, revealing a median age of 62 years and a stark male predominance with a sex ratio of 6.2 to 1. This epidemiological profile is consistent with global trends where tobacco use—the primary risk factor for bladder cancer—is more prevalent among men. The author evaluates the "operability rate," which was found to be approximately 55.4%. This figure is particularly telling, as it suggests that nearly half of the patients who receive chemotherapy do not proceed to the curative surgical phase. The study attributes this to several factors, including disease progression during chemotherapy, patient refusal of radical surgery, and loss to follow-up, providing a sobering look at the "attrition rate" in a regional oncology department.

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A primary focus of the research involves the evaluation of pCR as a prognostic biomarker. The author finds that among the evaluable patients who underwent surgery, 34.3% achieved a pCR, meaning no residual tumor was found in the surgical specimen. The study findings reveal a dramatic difference in survival: patients with pCR had a mean overall survival (OS) of 60 months, compared to only 34.9 months for those without a complete response. This gain of over 25 months in survival is statistically significant and reinforces the "surrogate" value of pCR in predicting long-term oncological success. The author handles this data with academic rigor, noting that pCR is the ultimate goal of neoadjuvant therapy, as it essentially serves as an early indicator of whether the systemic treatment has successfully eradicated micrometastatic disease.

The discussion then moves to the specific chemotherapy regimens utilized in the Moroccan context, primarily the combination of Gemcitabine and Cisplatin. The author evaluates the "toxicity profile" and treatment adherence, noting that most patients received at least three cycles of NAC. However, the study suggests that the delay between the completion of chemotherapy and the subsequent surgery is a critical variable. In the Moroccan experience, logistical and social barriers can sometimes extend this interval, potentially allowing for tumor repopulation. The narrative effectively argues that the benefits of high-quality chemotherapy are maximized only when integrated into a seamless multidisciplinary workflow that ensures timely surgical intervention.

Furthermore, the paper addresses the survival outcomes in terms of relapse-free survival (RFS). The author explores how patients who achieved pCR not only lived longer but also remained free of disease for significantly longer periods. The study highlights that the median RFS was not even reached in the pCR group during the follow-up period, whereas the non-pCR group faced a much higher risk of early recurrence. This distinction is vital for patient counseling, as it allows clinicians to provide more accurate prognostic information following surgery. The narrative concludes that while the pCR rates in this Moroccan cohort are comparable to those reported in Western clinical trials (30–40%), the overall impact on the population is dampened by the high percentage of patients who never reach the operating table.

In summary, this article offers a robust and well-documented inquiry into the practical application of bladder cancer protocols in North Africa. It successfully bridges the gap between controlled clinical trial results and real-world hospital data. The author's ability to link pathological outcomes with specific survival gains makes this a significant contribution to the field of uro-oncology. It is an essential read for oncologists, urologists, and public health officials in low- and middle-income countries, providing a clear evidence base for the life-saving potential of neoadjuvant chemotherapy while identifying the systemic gaps that must be closed to improve operability and long-term cure rates for bladder cancer patients.

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**Recommendations**

- The author should consider conducting a follow-up study focusing specifically on the "Non-Operable Group" to identify the socio-economic and clinical reasons for surgical attrition, which would help in developing targeted interventions to improve the cystectomy rate.
- To improve the academic depth of the survival analysis, it is recommended that the author perform a Cox proportional hazards regression to determine if other factors, such as age, smoking status, or time-to-surgery, act as independent predictors of mortality alongside pCR.
- The paper would benefit from a dedicated section on "Nutritional Status and Prehabilitation," exploring whether improving the physical condition of Moroccan patients before they start NAC could lead to better chemotherapy tolerance and higher subsequent operability.
- It is suggested that the author include a visual "Consort Diagram" showing the flow of the 65 patients from diagnosis through chemotherapy and surgery, clearly marking where and why patients were excluded or lost to follow-up.
- Future research should explore the use of "Dose-Dense" chemotherapy regimens (ddMVAC) in the Moroccan setting to see if higher-intensity protocols could further increase pCR rates without significantly increasing toxicity in this specific patient population.

**Recommendation**: Recommend for publication with minor revision.