Comparison Between Intravesical Chemotherapy Epirubicin and Mitomycin-C after TURB vs TURB Alone With Recurrence Rate of Non-Muscle Invasive Bladder Cancer: Meta-Analysis

Besut Daryanto¹, Athaya Febriantyo Purnomo¹, Kurnia Penta Seputra¹, Taufiq Nur Budaya¹

ABSTRACT

Background: Bladder cancer is still a burden on the world of oncology medicine, which every year affects about 3.4 million people globally with 430,000 new cases per year. It is the fourth most common cancer in men and eighth most common women malignancy in the world. This makes bladder cancer a “silent killer” and it needs appropriate treatment planning. Single immediate instillation of chemotherapy after transurethral resection of the bladder (TURB) is recommended by EAU guideline, but its use remains a controversy.

Objective: Study aimed to analyze benefit of intravesical chemotherapy following TURB in terms of recurrence of non-muscle invasive bladder cancer (NMIBC). Methods: Systematic review and meta-analysis of randomized controlled trials comparing the efficacy of a single instillation after TURB with TURB alone in NMIBC (pTa-pT1) patients was conducted. Studies searched throughout Medline, PubMed, Embase, and Cochrane in December 2018. Keywords were intravesical chemotherapy, combination, transurethral resection, bladder cancer. Inclusion criteria were RCT studies, subjects in study were treated single immediate chemotherapy instillation after TURB compared to TURB alone in patient with pTa-pT1 urothelial carcinoma of the bladder. Trials with additional treatment prior to first recurrence were not eligible. Studies using recurrence rate as dependent variable. From 361 studies, in total 11 studies were eligible for this meta-analysis.

Results: From those 11 studies, it is shown that intravesical chemotherapy using Epirubicin and Mitomycin-C following TURB showed significant decrease of recurrence rate of bladder cancer even to progression of the disease compared to TURB alone (p<0.05) with pooled Risk Ratio were 0.69 and pooled heterogeneity (I²) were 26.6%. Conclusion: This meta-analysis study showed that combination therapy of intravesical chemotherapy after TURB is superior to TURB alone in showing the recurrence rate of NMIBC.

Keywords: Intravesical Chemotherapy, TURB, Non-muscle Invasive Bladder Cancer.

1. BACKGROUND

Bladder cancer is still a burden on the world of oncology medicine, which every year affects about 3.4 million people globally with 430,000 new cases per year. It is the fourth most common cancer in men and eighth most common women malignancy in the world (1).

This makes bladder cancer a “silent killer” and it needs appropriate treatment planning. Single immediate instillation of chemotherapy after transurethral resection of the bladder (TURB) is recommended by EAU guideline, but its use remains a controversy (2, 3). In low and intermediate risk patient with non-muscle invasive bladder cancer (NMIBC) EAU Guidelines panel recommends a single immediate instillation of chemotherapy after a single immediate instillation of chemotherapy after a complete trans-urethral resection of bladder (TURB) (2). American Urological Association (AUA) support the chemotherapy instillation as well to lower the risk of recurrence after TURB in patients with small volume, low grade tumor (3). Even though there are
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some recommendations, the instillation is still not uni-
versally used in daily clinical practice.
Epirubicin and Mitomycin-C is well-known chemother-
apy used for oncology medicine that prior to be
recommendation from guideline for single immediate
instillation from some RCTs (1, 2).

2. OBJECTIVE
Study aimed to analyze benefit of intravesical che-
motherapy following TURB in terms of recurrence of
non-muscle invasive bladder cancer (NMIBC).

3. MATERIAL AND METHODS

Information Sources and Search Strategy
This systematic review and meta-analysis was con-
ducted based on PRISMA guidelines (9). Studies were
obtained by searching electronic databases, Medline,
PubMed, Embase, and Cochrane in December 2018.
Only articles in English were included. Authors used the
following search keywords to search all trials registers
and databases: “intravesical chemotherapy”, “combina-
tion”, “transurethral resection”, and “bladder cancer”. No
ethical clearance is needed for this study.

Eligibility Criteria
Inclusion criteria were RCT studies, subjects in study
were treated single immediate chemotherapy instillation
after TURB compared to TURB alone in patient with
pTa-pT1 urothelial carcinoma of the bladder. Trials with
additional treatment prior to first recurrence were not
eligible. Unpublished articles, abstracts, study not writ-
en in English were excluded from the study. Study char-
acteristics were presented as PICO in Table 1.

Quality Assessment
The methodological quality in each of these stud-
ies was assessed using the risk-of-bias assessment tool
based on the Cochrane Handbook for Systematic Re-
views of Interventions (version 5.1.0) by 2 reviewers
(A.F.P. and B.D.).

Study selection and data collection
Study selection and data collection were performed
independently in an unblinded standardized manner by
4 reviewers (A.F.P., B.D., K.P.S and T.N.B) with the same
portion. Discrepancies between the two authors were
resolved by discussion. All studies were screened for du-
plicate together after being collected in a single folder.
After that, the selected articles will be judged on their
title and abstract using the inclusion and exclusion cri-
teria described earlier. Selected studies will be reviewed
based on their full-text version. Statistical analysis was
done by Review Manager 5. From 361 studies, total 11
studies were eligible for this study.

Outcomes
The primary outcome was recurrence rate of those
NMIBC patient who got Intravesical Chemotherapy and
those not. This outcome was evaluated for all studies for
which an Risk Ratio (RR) could be calculated.

Table 1. PICO of the study.

| Patient                  | Patients diagnosed with Non-Muscle Invasive Bladder Cancer and treated with primary TURB and survived. |
|-------------------------|----------------------------------------------------------------------------------------------------------------|
| Intervention            | Given single immediate chemotherapy (Epirubicin and Mitomycin C) instillation after TURB.                      |
| Comparison/ Control     | Not given instillation after TURB                                                                          |
| Outcome                 | Recurrence Rate                                                                                             |

Table 2. Characteristics of the included studies.

| Study, Publication Year | Country    | Chemotherapy after TURB |
|-------------------------|------------|-------------------------|
| Ali-El-Dein, 1997       | Egypt      | Epirubicin 50 mg / 50 mL |
| Berrum-Svennung, 2008   | Sweden     | Epirubicin 50 mg / 50 mL |
| Gudjonsson, 2009        | Sweden     | Epirubicin 80 mg / 50 mL |
| Oosterlinck, 1993       | Multination| Epirubicin 80 mg / 50 mL |
| Rajala, 2002            | Finland    | Epirubicin 100 mg / 100 mL |
| Barghi, 2006            | Iran       | Mitomycin C 30 mg / 30 mL |
| De Nunzio, 2011         | Italy      | Mitomycin C 40 mg / 50 mL |
| El-Ghobashy, 2007       | Egypt      | Mitomycin C 30 mg / 50 mL |
| Solsona, 1999           | Spain      | Mitomycin C 30 mg / 50 mL |
| Tatar, 2011             | Turkey     | Mitomycin C 40mg / 50 mL |
| Tolley, 1996            | United Kingdom | Mitomycin C 40 mg / 40 mL |

Figure 1. Study flow chart.
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Assessment of bias and statistical methods
The quality of this study was assessed by B.D. and A.F.P with the same portion by using Cochrane-risk-of-bias tool (10). Bias assessed include random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other sources of bias.

Effect size using Risk Ratio (RR) and 95% confidence interval (CI) for Recurrence rate of patients treated with intravesical chemotherapy, compared to who were not given treatment. Homogeneity of study results is determined using Cochran Q test. Random Effect Model (REM) was used because statistical heterogeneity was found in the study ($I^2 > 75\%$). Otherwise, Fixed Effect Model (FEM) was used. $P \leq .05$ (2-sided) was considered statistically significant.

### 4. RESULTS

#### Literature Search

A flow diagram of study selection is shown in Figure 1. After initially identifying 361 articles, 218 were excluded and the full texts of 143 were reviewed. Subsequently, 132 studies were excluded, and 11 studies were included in the systematic review and meta-analysis (Table 2).

From those 11 studies, it is shown that intravesical chemotherapy using Epirubicin and Mitomycin-C following TURB showed significant decrease of recurrence rate of bladder cancer even to progression of the disease compared to TURB alone ($p<0.05$) with pooled Risk Ratio were 0.69 and had narrow heterogeneity ($I^2$) were 26.6%.

![Figure 2. Forest plot comparing AKI incidence.](image)

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**Table 2. Characteristics of the included studies**

| Study or Subgroup | Institution - Events | Institution - Total | Risk Ratio | Risk Ratio |
|-------------------|----------------------|---------------------|------------|------------|
| **Epirubicin**    |                      |                     |            |            |
| Ali-El-Dein 1997  | 10                   | 55                  | 0.48 [0.30, 0.76] |            |
| Berrum-Svennung 2008 | 79 | 155 | 0.81 [0.66, 0.96] |            |
| Gudjonsson 2000 | 63 | 102 | 0.80 [0.67, 0.96] |            |
| Oosterlinck 1993 | 82 | 208 | 0.83 [0.77, 0.95] |            |
| Rajala 2002 | 31 | 69 | 0.83 [0.75, 0.95] |            |
| Subtotal (95% CI) | 506 | 1004 | 0.69 [0.59, 0.81] |            |
| Total events | 271 | 370 |            |            |
| **Mitomycin-C**   |                      |                     |            |            |
| Berrum-Svennung 2008 | 10 | 57 | 0.24 [0.13, 0.44] |            |
| El-Ghobashy 2007 | 12 | 31 | 0.73 [0.42, 1.28] |            |
| Solsona 1999 | 25 | 57 | 0.76 [0.53, 1.09] |            |
| Tatar 2011 | 2 | 21 | 0.70 [0.43, 1.17] |            |
| Tolley 1996 | 76 | 140 | 0.89 [0.68, 1.17] |            |
| Subtotal (95% CI) | 377 | 701 | 0.57 [0.37, 0.88] |            |
| Total events | 126 | 211 |            |            |

**Figure 3: Risk of bias**

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![Figure 3: Risk of bias](image)
Quality Assessment of the Included Studies
The quality assessment assessed included selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias (Figure 3). In 11 studies, reporting bias weren’t adequately generated. But all studies had good quality in attrition bias, performance bias, and reporting bias.

5. DISCUSSION
In this meta-analysis study, there are 11 studies included in terms of inclusion criteria. Studies used Epirubicin as intravesical chemotherapy were 5 studies, and using Mitomycin C were 6 studies. Whether the study used Epirubicin or Mitomycin C, we calculated to pooled risk ratio to overlook the recurrence rate after being treated by respective chemotherapy agents. Five studies were using Epirubicin ranged from 1993-2009 was overall weighted to be less recurrent in groups were using instillation of Epirubicin (5-9). Total effect of the studies used Epirubicin were 3.98 with significant different between the group treated with Epirubicin instillation and not given treatment (p < 0.0001) with heterogeneity 42%. Studies elaborated into the other resources of chemotherapy, were using Mitomycin C, 6 studies were conducted and we got the pooled total effect was 2.54 with significantly better for the instilled groups of patient (p = 0.01) with broader heterogeneity 73%. It showed Mitomycin C instillation were also better than the group not being treated (10-15). The pooled risk ratio was 0.69 with total effect was quite high 4.45 (p < 0.00001), the data showed there were significant different between the groups used instillation were better in recurrence rate rather than groups not being treated.

6. CONCLUSION
Our current study has identified that intravesical chemotherapy using epirubicin and mitomycin-C after TURB significantly lower recurrence rate of NMIBC and it could serve as potential progressivity suppressor.

- Author’s contribution: The investigation was arranged by BD, AFP, KPS, and TNB who also performed research, provided research materials, and collated and processed data. BD and AFP were responsible for data analysis and interpretation. BD, AFP, KPS, and TNB contributed with the initial and final versions of the article as well as practical assistance. All authors were in control of the manuscript’s substance after critically reviewing and approving the final text.
- Conflicts of interest: There are no conflicts of interest.
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