

THE RESULTS OF ADJUVANT INTRAVESICAL CHEMOTHERAPY IN COMBINATION WITH DIMETHYL SULFOXIDE IN PATIENTS WITH NON-MUSCLE-INVASIVE BLADDER CANCER

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Abstract

Improving the treatment of patients with muscular non-invasive bladder cancer remains one of the most pressing issues in urology. Despite the use of a large number of drugs for intravesical instillation - the effectiveness of treatment wants better.

The aim of the study was to evaluate the efficacy of treatment in patients with low- and moderate-risk non-invasive bladder cancer after adjuvant intravesical instillation of epirubicin with dimethyl sulfoxide.

Methods and materials. A retrospective and prospective analysis of 157 patients who underwent examination, treatment and further dispensary supervision on the basis of the State Institution "Institute of Urology of the National Academy of Medical Sciences of Ukraine" in the period from 2013 to 2021. The study included patients with low- and moderate-risk non-invasive bladder cancer, which were divided into four groups. The first group (n = 46) underwent intravesical instillation of Doxorubicin, the second group (n = 41) underwent intravesical instillation of Epirubicin, the third group (n = 37) performed only transurethral resection of the bladder tumor, the fourth group (n = 33) Epirubicin in combination with Dimethyl sulfoxide. Comparison of treatment efficacy in all four groups was performed on the indicators of recurrence and disease progression.

Results. The observation time was 36 months. During the whole observation period, the recurrence rate in the group where Doxorubicin instillation was performed was -30.4% (14 patients), in the group where Epirubicin instillation was performed - 29.2% (12 patients), in the group where adjuvant intravesical chemotherapy not performed - 51.3% (19 patients) and in the group of combined treatment (Epirubicin + DMSO) -21.2% (7 patients).

Conclusions. High efficiency and safety of application allow to recommend a combination of Epirubicin with Dimethyl sulfoxide for application in clinical practice.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Key words: *dimethyl sulfoxide, bladder cancer, intravesical chemotherapy, relapse*

Introduction

Improving the treatment of patients with muscular non-invasive bladder cancer remains one of the most actual issues in urology. Because bladder cancer is an aggressive disease, all patients require adjuvant intravesical chemotherapy or immunotherapy after undergoing transurethral bladder resection [1]. Patients with musculoskeletal non-invasive bladder cancer of low and intermediate risk groups (pTa - pT1, G1 - G2) are indicated for treatment with chemotherapeutic drugs [2]. Today, among chemotherapeutics for intravesical administration, Epirubicin, Doxorubicin, Mitomycin C, and Cyclophosphamide are actively used. However, the efficacy of these drugs is better, and therefore there is a need to improve the intravesical treatment of patients with non-invasive bladder cancer.

We studied and analyzed the literature on the use of dimethyl sulfoxide (DMSO) in medicine [3]. In addition to the effective use of dimethyl sulfoxide in traumatology, surgery, dermatology, there are data on its use in urology. Back in the 80's Perez-Marrero used DMSO in the treatment of interstitial cystitis, later this experience was repeated by Peeker R. - in both studies dimethyl sulfoxide proved to be a safe and effective drug with positive results [4, 5]. Chen D, studying the problem of bladder cancer in his study in dogs, used dimethyl sulfoxide in combination with paclitaxel, which proved the ability of DMSO to deliver the chemotherapeutic agent paclitaxel in the thickness of the layers of the bladder[6].

Objective of the work was to evaluate the efficacy of treatment of patients with low and medium risk non-invasive bladder cancer after adjuvant intravesical chemotherapy with dimethyl sulfoxide compared with adjuvant intravesical chemotherapy with Epirubicin, Doxorubicin and transurethral resection of the bladder.

Materials and methods

The prospective and retrospective study included 157 patients who underwent examination, treatment and dispensary supervision at the Institute of Urology of the National Academy of Medical Sciences of Ukraine in the period from 2013

to 2021. The youngest patient was 35 years old, the oldest 86 years old. The mean age was 67.32 ± 6.8 years. The ratio between men and women was 4.2:1.

The study included patients who were at low and medium risk. These risk groups were characterized by the presence of urothelial tumor Ta, T1 stage, histologically G1-G2, the maximum score on the EORTC scale 9 points.

Exclusion criteria were high-risk patients, as well as those who had previously undergone intravesical chemotherapy or immunotherapy, had an EORTC score of more than 10, histologically G3, T2-T4 formation, and had the presence of upper urinary tract tumors and metastases.

In a previous comparative study [7], we proved that there is no significant difference in the effectiveness of treatment between Epirubicin and Doxorubicin. Based on our own observations, it was found that when Doxorubicin was administered intravesically, some patients noted side effects (frequent urge to urinate, gripes during urination, increase in body t on the day of instillation, nausea), while intravesical administration of Epirubicin showed fewer symptoms. That is why for the combined treatment with dimethyl sulfoxide we preferred Epirubicin.

All 157 patients were divided into 4 groups depending on the treatment offered to them. Characteristics of the groups are shown in Table 1.

At the first stage of treatment, all patients underwent transurethral resection of the bladder according to the conventional method with the removal of all visible tumors. This tabulation is shown in Figures 1, 2, 3.

If hematuria, perforation of the bladder, or suspected perforation of the bladder were not observed in the early postoperative period, we began the second stage of treatment - adjuvant intravesical chemotherapy. Unfortunately, there is no clear data in the literature on how much and how long the course of instillations should last, and therefore in our study we were guided by our own experience and capabilities of the patient.

In the first group, instillations were performed with the drug Doxorubicin 50 mg 25 ml, previously diluted with 30 ml 0.9% NaCl. The instillation course was performed according to the following scheme once a week for 4 weeks, then once a month for 4 months.

The second group of patients received instillation of Epirubicin 50 mg 25 ml, which was also diluted with 30 ml 0.9% NaCl. Instillation was performed according to the scheme once a week for 4 weeks, then once a month for 4 months.

The third group underwent only transurethral resection of the bladder, as patients in this group refused to undergo intravesical chemotherapy.

The fourth group was instilled with Epirubicin 50 mg 25 ml, which was diluted with 20 ml of 0.9% NaCl and added 10 ml of 50% dimethyl sulfoxide. The instillation scheme was similar to the first and second groups.

The exposure time of the chemotherapeutic drug in the bladder in the first, second and fourth groups was 2 hours. During this time, patients were advised to change body position - lying on their back, abdomen and sides for better distribution of the drug on the walls of the bladder.

Patients were examined during and after adjuvant intravesical chemotherapy by cystoscopy once every 3 months for the first year and once every 6 months for the next two years. Also, once a year, patients underwent CT to monitor the prolongation of the process and control of upper urinary tract lesions. The scope of the examination included: general urinalysis, general blood test, physical examination, ultrasound examination of the abdominal organs, kidneys, bladder, lymph nodes. If recurrence or progression was suspected, patients underwent transurethral resection of the bladder.

When recurrence is detected, the degree of invasion (pT) and histological gradation (G) of the tumor must be established. Invasion into a deeper layer from Ta to T1 or from T1 to T2, as well as the detection of regional or distant metastases was regarded as disease progression.

Data processing and calculation of results were performed using Microsoft Word, Excel and online service medstatistica.ru. the χ^2 - criterion was used to determine differences between qualitative variables.

Results

The median follow-up in all three groups was 36 months. As shown in table 1, the groups were well balanced in terms of basic clinical and morphological characteristics. Indicators of recurrence rate,

recurrence-free survival and progression are shown in Table 2.

The total number of relapses during the first year of follow-up in the group where instillation of Doxorubicin was performed was - 17.3% (8 patients), in the group where instillation of Epirubicin was performed - 19.5% (8 patients), in the group where only TUR was performed - 32.4% (12 patients) and in the combined treatment group (Epirubicin + DMSO) - 12.1% (4 patients).

The study found that the number of relapses during intravesical instillation is lower. As soon as the intravesical instillations end (4-5 months), the number of relapses begins to increase (as shown in Figure 4). From this we can conclude that intravesical instillations prolong the recurrence-free period.

At 36 months of follow-up, recurrence in the group where Doxorubicin was instilled was -30.4% (14 patients), in the group where Epirubicin was instilled was 29.2% (12 patients), in the group where TUR was performed -- 51.3 % (19 patients) and in the combination treatment group (Epirubicin + DMSO) - 21.2% (7 patients). Data are presented in Figure 5.

During the whole period of observation the progression of the disease was detected in 6.5% (2 patients) - in the group where instillation was performed with Doxorubicin, 7.3% (2 patients) - in the group where instillation with Epirubicin was performed, 13.5% (5 patients) - in in the group where only TUR was performed and 3.0% (1 patient) - in the group where Epirubicin was instilled in combination with Dimethyl sulfoxide. The data are presented in Figure 6.

Discussion

Bacillus Calmette-Guerin (BCG) is known for intravesical use in bladder cancer. However, the use of BCG is recommended for high-risk non-invasive bladder muscle cancer [8]. In our case, patients who belong to the low and intermediate risk groups are subject to treatment.

One study reported that an hourly session of Mitomycin C was more effective than a 30-minute session [9]. We can agree with this, and therefore in this study, the exposure of the drug in the bladder was 2 hours.

In another randomized study using Epirubicin, it was found that the concentration of the drug is

more important than the duration of the session [10]. In our opinion, this statement is not entirely true, because the concentration of the drug will affect only the mucous layer of the bladder, and we use DMSO to transport the chemotherapy into the submucosal layer.

It is no secret that changes in urine pH, decreased diuresis and buffering of intravesical solution reduce the recurrence rate [11]. These are auxiliary methods for the use of intravesical chemotherapy. In our study, we did not use changes in urine pH, but we resorted to a decrease in diuresis in the patient by instillation in the morning, after waking up and reduced fluid intake the day before.

The literature describes various technologies for raising the temperature of the injected chemotherapy. This effect is achieved through the use of microwave hyperthermia, electrophoresis [12, 13]. However, these studies are still being conducted and so far has no reliable results on their effectiveness.

Conclusions

Despite the adjuvants administered to all patients intravesical instillation of chemotherapeutics relapses were observed in all three groups in the first 3 months and with certain wave fluctuations during all 36 months of follow-up. Unfortunately, intravesical chemotherapy cannot completely prevent the progression of bladder cancer, which was also found in all three groups.

Recurrence analysis showed a higher efficacy in the treatment of non-invasive muscular bladder cancer with intravesical Epirubiin in combination with Dimethyl sulfoxide compared to intravesical Epirubicin or Doxorubicin.

High efficacy, safety of usage, reduction of relapses, no side effects, ease of use - allow us to recommend the combination of Epirubicin with Dimethyl sulfoxide for implementation in clinical practice to improve the treatment of patients with non-invasive bladder cancer in low and medium risk groups.

Acknowledgments

The authors declare that there are no conflicts of interest.

References

1. Babjuk M., Burger M., Comperat E. M. et al. European Association of Urology Guidelines on Nonmuscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ): 2019 update. *Eur Urol* 2019;76(5):639–57. DOI: 10.1016 / j.euro.2019.08.016.
2. Oddens J., Brausi M., Sylvester R. et al. Final results of an EORTC-GU CancerGroup randomized study of maintenance bacillus Calmette–Guerin intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. *Eur Urol* 2013;63(3):462–72. DOI: 10.1016/j.euro.2012.10.039. PMID: 23141049
3. Shulyak A.V., Goydyk V.S., Gusakovsky S.S., Grygorenko V.N., Mytsik Y.O., Badiuk, N.S. Modern aspect of the use of Dimethyl sulfoxide (DMSO). *Pharmacologyonline* 2021; Vol. 1; P. 82–89.
4. Perez-Marrero R, Emerson LE and Feltis JT: A controlled study of dimethyl sulfoxide in interstitial cystitis. *J Urol* 1988; 140: 36.
5. Peeker R, Haghsheno MA, Holmang S et al: Intravesical bacillus Calmette-Guerin and dimethyl sulfoxide for treatment of classic and nonulcer interstitial cystitis: a prospective, randomized double-blind study. *J Urol* 2000; 164: 1912.
6. Chen D., Song D., Wientjes M.G., Au J.L. Effect of dimethyl sulfoxide on bladder tissue penetration of intravesical paclitaxel. *Clin Cancer Res* 2003; 9(1):363–9.
7. Shulyak A.V., Gusakovsky S.S., Grygorenko V.N., Kurilenko V.N., Mytsik Y.O., Goydyk V.S., Badiuk, N.S. Comparative characteristics of adjuvant internal bladder chemotherapy in with muscle-non-invasive bladder cancer. *Pharmacologyonline* 2020; Vol. 3; P. 261-269.
8. Chang S. S., Boorjian S. A., Chou R. et al. Diagnosis and treatment of non-muscle invasive bladder Cancer: AUA / SUO guideline. *J Urol* 2016;196 (4):1021–9. DOI: 10.1016 / j.juro.2016.06.049.
9. Giesbers, A.A., et al. Recurrence of superficial bladder carcinoma after intravesical instillation of mitomycin-C. Comparison of exposure times.

- Br J Urol, 1989. 63: 176.
<https://www.ncbi.nlm.nih.gov/pubmed/2495144>
10. Kuroda, M., et al. Efficacy of prophylactic treatment with intravesical epirubicin on recurrence of superficial bladder cancer: The 6th Trial of the Japanese Urological Cancer Research Group (JUICRG): a randomized trial of intravesical epirubicin at dose of 20mg/40ml, 30mg/40ml, 40mg/40ml. Eur Urol, 2004. 45:600.
<https://www.ncbi.nlm.nih.gov/pubmed/15082202>
11. Au, J.L., et al. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase III trial. J Natl Cancer Inst, 2001. 93: 597.
<https://www.ncbi.nlm.nih.gov/pubmed/11309436>
12. Arends, T.J., et al. Combined chemohyperthermia: 10-year single center experience in 160 patients with nonmuscle invasive bladder cancer. J Urol, 2014. 192: 708.
<https://www.ncbi.nlm.nih.gov/pubmed/24704017>
13. Arends, T.J., et al. Results of a Randomised Controlled Trial Comparing Intravesical Chemohyperthermia with Mitomycin C Versus Bacillus Calmette-Guerin for Adjuvant Treatment of Patients with Intermediate and High risk Non-Muscle-invasive Bladder Cancer. Eur Urol, 2016. 69: 1046.

Table 1. Characteristics of patients by groups

Characteristic	Group of Doxorubicin (n=46)	Group with Epirubicin (n=41)	Group TUR (n=37)	Group Epirubicin + Dimethyl sulfoxide (n=33)
Median Observation, months	36	36	36	36
Men	37	34	29	27
Women	9	7	8	6
Degree				
Ta	19	22	21	19
T1	27	19	16	14
Differentiation				
G1	25	23	23	18
G2	21	18	14	15
The number of tumors				
One	28	21	20	24
Multiple	18	20	17	9
Tumor size				
≤ 3 CM	29	24	22	14
≥ 3 CM	17	17	15	19

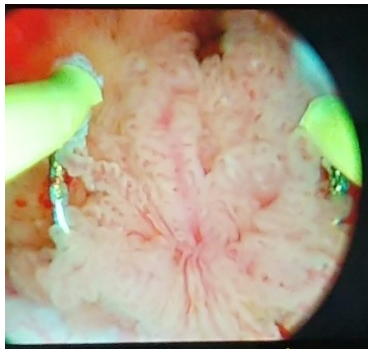
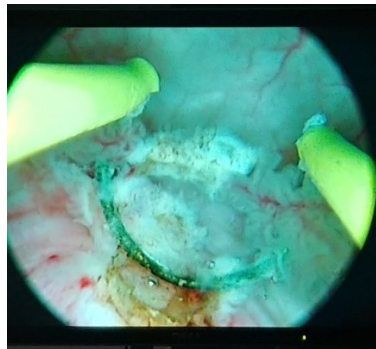
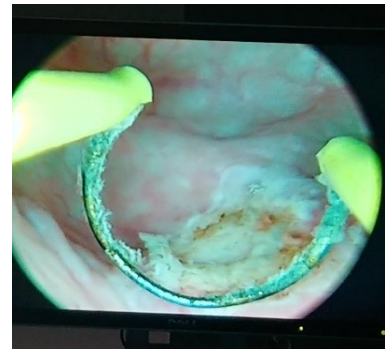
**Figure 1.** Tumor**Figure 2.** Tumor resection**Figure 3.** Resection site

Table 2. Indicators of recurrence and progression in groups

Indicator	Group with Doxorubicin n= 41	Group with Epirubicin n= 41	Group TUR n= 37	Group Epirubicin + DMSO n= 33	p
Recurrence rate,% 3 months	6,5 %	7,3 %	10,8 %	6,06 %	$p_1 \geq 0,05$ $p_2 \geq 0,05$ $p_3 \leq 0,05$
Recurrence rate,% 6 months	10,8 %	9,7 %	18,9 %	9,1 %	$p_1 \geq 0,05$ $p_2 \geq 0,05$ $p_3 \leq 0,05$
1 year recurrence-free survival, %	82,7 %	80,5 %	67,6 %	87,9 %	$p_1 \geq 0,05$ $p_2 \geq 0,05$ $p_3 \leq 0,05$
2-year recurrence- free survival,%	76,1 %	78,1 %	56,8 %	84,8 %	$p_1 \geq 0,05$ $p_2 \geq 0,05$ $p_3 \leq 0,05$
3-year recurrence- free survival,%	69,6 %	70,8 %	48,7 %	78,8 %	$p_1 \geq 0,05$ $p_2 \geq 0,05$ $p_3 \leq 0,05$
Frequency of progression, from Ta, T1 to T2%	6,5 %	7,3 %	13,5 %	3,0 %	$p_1 \geq 0,05$ $p_2 \geq 0,05$ $p_3 \leq 0,05$

p1 - significance of comparison between the group Epirubicin + DMSO and the group Doxorubicin

p2 - reliability of the comparison between the group Epirubicin + DMSO and the group Epirubicin

p3 - significance of comparison between Epirubicin + DMSO group and TUR group \

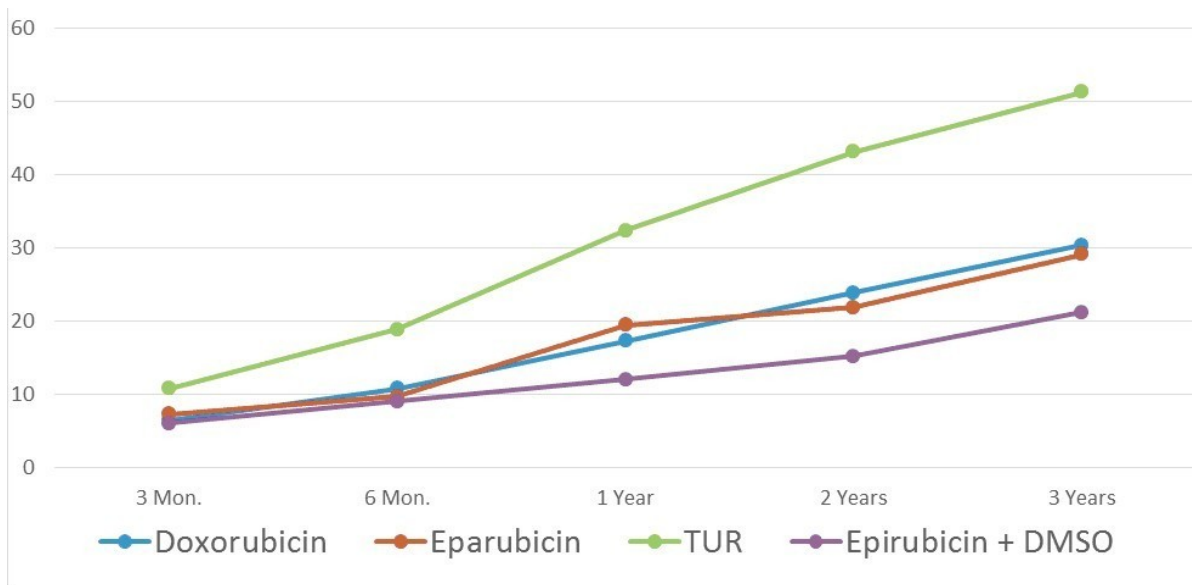


Figure 4. Relapse rates in groups

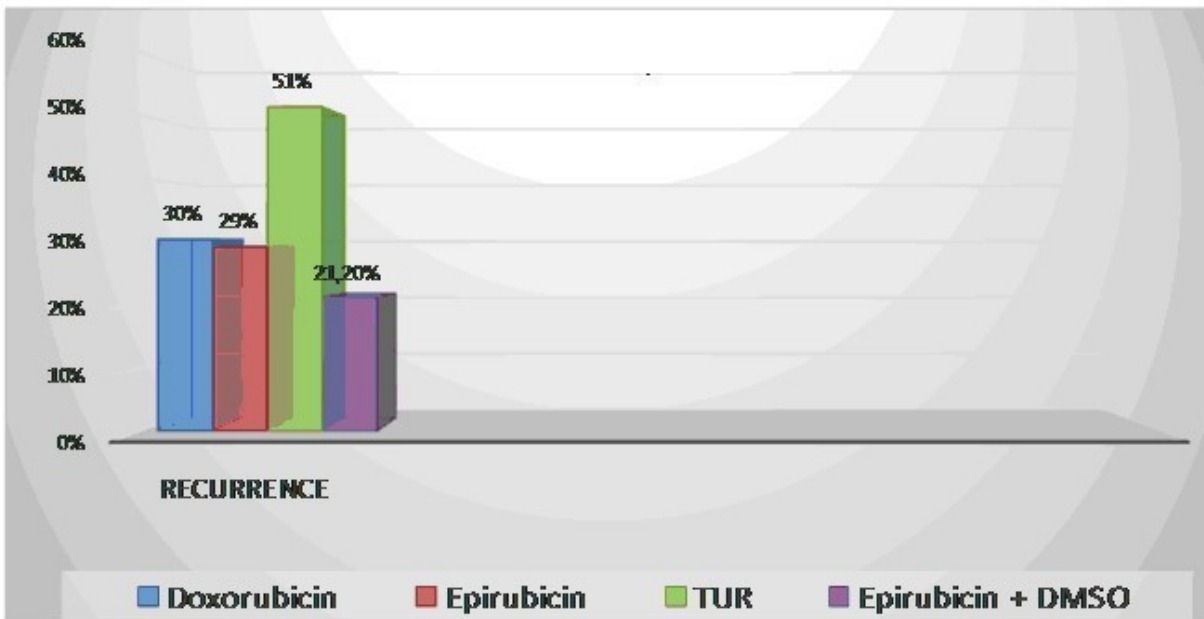


Figure 5. Relapse rates

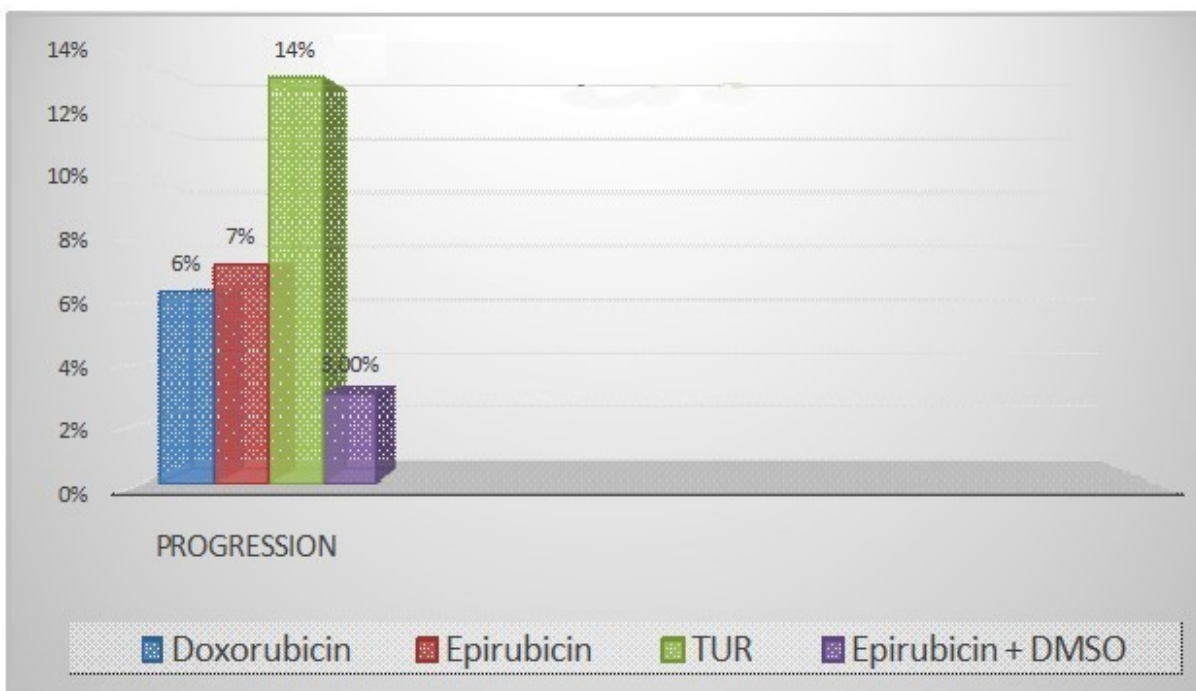


Figure 6. Relapse progression