ONCOLOGÍA roe-solca.ec ORIGINAL ARTICLE

Recurrence of superficial bladder cancers after intravesical chemotherapy with doxorubicin.

Corresponding Author:
Ronald Pardina Salazar.
email: ronaldpardina@gmail.com

Telephone: +593 996734147
Address: Av. Kennedy s/n and Av. Delta, in front of cdla. Bolivarian, Faculty of Medical Sciences, University of Guayaquil.
Guayaquil, Ecuador

Conflict of interest: The authors declare no conflict of interest.

Received: May 15, 2023
Accepted: July 28, 2023
Published: August 23, 2023
Editor: Dr. Lorena Sandoya

Bibliographic letterhead:
Ronald P, Jimmy L. Recurrence of superficial bladder cancers after intravesical chemotherapy with doxorubicin: a single-center observational study. Revista Oncología (Ecuador) 2023;33(2):184-193.

ISSN: 2661-6653

DOI: https://doi.org/10.33821/712
SOCIEDAD DE LUCHA CONTRA EL CÁNCER.

Ronald Pardina Salazar [1], Jimmy Labanda Muñoz [1].

1. Postgraduate Department, Gynecology and Obstetrics Specialty, Faculty of Medicine, Pontificia Universidad Católica del Ecuador, Quito, Ecuador.

Abstract

Introduction: Bladder cancer is a highly prevalent disease; its most significant problem is its tendency to recur and progress. To reduce this recurrence and progression as much as possible, many intravesical chemotherapeutics applied over months after transurethral resection of the bladder have been used with mixed results. Doxorubicin is an anthracycline antibiotic with antitumor activity produced by Streptococcus peucetius var. cesius. It can intercalate with DNA, affects many of its functions, and inhibits the synthesis of DNA and RNA, which acts intravesically to prevent the implantation of circulating tumor cells.

Methodology: The study was of an observational, descriptive, retrospective, cross-sectional type between January 1, 2018, and January 31, 2021, and developed in the Urology Service of the Teodoro Maldonado Carbo Hospital.

Results: A total of 350 cases were analyzed. The specificity of the index was 81%, with a positive predictive value (PPV) of 77% and a negative NPV of 68%. The sensitivity of ascites was 85%, and that of the palpable abdominal mass was 79%. In patients who presented CA-125 antigen values less than 1000 U/ml, the risk of obtaining optimal cytoreduction was OR: 0.15 (95% CI 0.069 - 0.307; *P*: 0.0001). The patients who presented unresectability index values between 1 and 2 points versus 3 and 4 points were OR: 7.04 (95% CI 3.33 -14.87, *P*: 0.0001).

Conclusions: Bladder cancer is a prevalent disease that presents significant challenges due to its propensity for recurrence and progression. To address this problem, various intravesical chemotherapeutics have been used after transurethral resection of the bladder, although with variable results. Doxorubicin, an anthracycline antibiotic with antitumor properties, has demonstrated the ability to interfere with DNA and RNA, making it a valuable option to prevent the implantation of circulating tumor cells when administered intravesically.

Keywords:

MeSH: urinary bladder neoplasms, doxorubicin, transurethral resection of the bladder, BCG vaccine.

DOI: 10.33821/712

Introduction

The burden of cancer incidence and mortality is proliferating worldwide; this reflects both population aging and growth and changes in the prevalence and distribution of major cancer risk factors, several of which are associated with socioeconomic development [1]. Bladder cancer is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to tenth when both sexes are considered. The worldwide age-standardized incidence rate (per 100,000 person/year) is 9.5 for men and 2.4 for women [2]. Approximately 75% of cases present with disease confined to the mucosa (stage Ta, Cis) or submucosa (stage T1); in younger patients (<40 years of age), this percentage is even higher. If bladder preservation is considered, chemoradiation is an alternative in well-selected patients without carcinoma in situ and after maximal resection [3].

Bladder cancer is the most common urological neoplasia and one of the most frequent causes of death from cancer. Its incidence has increased steadily, especially in developed countries [2]. Approximately 70% to 80% of newly diagnosed bladder cancer patients have nonmuscle-invasive tumors, and it is estimated that 50% to 70% of cases will have a high rate of recurrence and progression [1].

According to the latest GLOBOCAN data, bladder cancer accounts for 3% of cancer diagnoses worldwide and is especially common in developed countries. In the United States, bladder cancer is the sixth most common neoplasm. Ninety percent of bladder cancer diagnoses are made in people over 55, four times more common in men than women. While the median 5-year survival in the US is 77%, the 5-year survival for people with metastatic disease is only 5% [4].

Most (90%) bladder cancers comprise urothelial carcinoma as the predominant histology in Western Europe and the United States. However, squamous cell bladder cancer is more common in Africa, where schistosomiasis infections are more common [2]. Recent studies showed that North America and Western Europe reported exceptionally high incidence rates, while Eastern Europe and Asian countries had the lowest rates [4].

In Latin America, the figures do not differ from world statistics; prostate (21%), colon and rectal (12%), and lung (8%) cancers are the most commonly diagnosed cancers in Hispanic men. In comparison, breast cancers (29%), thyroid (8%), and uterine corpus (8%) are more common in women, while bladder cancer accounts for 4% of estimated new cases in men [5].

In Mexico, it is in the fourth place of presentation, with 14.4% of diagnosed tumors behind prostate, testicular, and kidney cancer and a male-to-female ratio of 3.8 to one. Approximately 75% of newly diagnosed cases are nonmuscle invasive and have a high rate of recurrence and progression despite local therapy [5]. In 2015, 534 deaths from bladder cancer were registered in Chile, representing 2% of the total cancer deaths of the same year (Ministry of Health, 2021). In Ecuador, according to data from the World Health Organization (WHO), in 2018, deaths caused by bladder cancer accounted for 0.21% of all registered deaths; the mortality rate was 1.08 per 100,000 inhabitants [6].

The mainstay of nonmuscle-invasive bladder cancer treatment is transurethral resection. The first intervention is essential for diagnosis and prognosis. Complete microscopic and macroscopic removal is the goal of this procedure [5]. On the other hand, standard chemotherapy in advanced soft tissue sarcomas (STS) should include doxorubicin with another drug, ifosfamide, which is the most widely used [7]. The factors that predict recurrence are the number of tumors ≥ 8 and the pathological tumor stage T1, and the factors that predict progression are renal ectasia and advanced stage T2 [5]. Doxorubicin (DOX) is considered one of the most effective chemotherapeutic agents and is used as a first-line drug in many types of cancer. However, it has serious adverse effects, such as lethal cardiotoxicity and dose-limiting myelosuppression [8].

The objective of this study was to demonstrate whether intravesical adjuvant treatment with doxorubicin in patients with superficial bladder tumors (Ta, T1, and Cis) decreases or increases recurrence and to evaluate the long-term quality of life of patients treated with this drug.

Materials and methods

Location
The research was conducted at the "Teodoro Maldonado Carbo" hospital in Guayaquil – Ecuador, located at Av. 25 de Julio and Av. Ernesto Albán, with data collected from the urology department.

Investigation period
The period was from January 1, 2018, to January 31, 2021.

Sample
Sample of patients with superficial bladder cancer. To calculate the sample size, the following formula was applied:

n = (Z^2.p(1-p).N)/(e^2.(N-1)+Z^2.p. (1-p))

where:
(N) population = 4,500
(Z) reliability value = 1.96
(e) expected error = 5%
(p) probability of occurrence = 50%
(〖 1.96 〗 ^2.0.5(1-0.5).4.500)/(〖 0.05 〗 ^2. (4.500-1)+ 〖 1.96 〗 ^2.p. (1-0, 5)
(n) sample = 350
Considering that the population of (N) is 4,500, the 95% confidence interval is represented by a Z value of 1.96 and a margin of error of 5%, where the occurrence (p) is 50% for a total sample of 382 patients.

Design of the investigation
This research is observational; the source is retrospective. Patient follow-up was cross-sectional.

Investigation procedure
First, the data from the medical records of the patients who underwent transurethral resection of a superficial bladder tumor and subsequent bladder instillation with doxorubicin in the Urology area of the Teodoro Maldonado Carbo Hospital - IESS from January 2018 to January 2021 were requested using the system digital medical records of the institution AS400. Then, the collected data were tabulated and filtered in an Excel sheet, where the patient's demographic data, associated comorbidities, main complications after chemotherapy, and the degree of quality of life through the ECOG Scale for the quality of life were recorded. Once the data were collected, they were analyzed with the statistical tests pertinent to the study group using correlation measures and differences of means and variances.

Inclusion criteria
Patients undergoing transurethral resection of a superficial bladder tumor and subsequent bladder instillation with doxorubicin. Patients with stage ≥ Ta or < T2, tumor grade ≥ I, and tumor size > 1 cm. Multiple or recurrent tumors were also included.

Exclusion criteria
Open approach surgery and emergency surgery.
Wide tumor bed.
High-grade tumor with a solid appearance and an infiltrating appearance.
Frank hematuria.
Resection of the urinary meatus.

Excessive bladder perforation.
Demented and noncooperative patient.
No indication or prescription for doxorubicin.
Noncompliance with informed consent.

Statistical analysis

The data were collected using the institution's clinical records in the AS400 databases. Once collected, the data will be refined in an Excel sheet to proceed to the analysis using the SPSS statistical program. The results will be presented through measures of mean central tendency, data dispersion, and tables of relative and absolute frequencies. Correlation tests, chi-square, Student's t test and ANOVA will be conducted to verify hypotheses appropriate to the variables' operationalization. For the statistical verification of the hypothesis, a reliability index of 95% and a P value less than 0.05 will be taken as a reference. The measurement will be made with the results of the clinical histories. The chi-square test will be applied to assess the dependence of the dependent variable (recurrence), a binomial variable, with the application of doxorubicin, another binomial variable. Student's t test and ANOVA will be applied to assess the differences in patients' quality of life intravesically instilled with doxorubicin compared to those not. Both tests evaluate differences between groups, the first through the mean values of the ECOG quality of life questionnaire and the second through their variances.

Results

A total of 350 patients participated, 286 men (81.6%), more frequently in patients older than 73 years (50%) (Table 1).
Of the 350 patients in the sample, 286 were men (81.6%), and 64 were women (18.4%). The highest prevalence of superficial bladder cancer is observed.

The most frequent age range corresponds to patients over 73 years of age, followed by patients between 62 and 72, with a percentage of 36.8%. The analysis shows that older patients have a greater tendency to suffer from superficial bladder cancer. A total of 65.8% of the clinical histories taken in the sample had a tumor between 0 and 3 cm, and 34.2% had tumors more extensive than three centimeters. A more excellent location was observed in the left lateral wall; of the 350 clinical histories, 124, corresponding to 35.5%, had the tumor in this section.

Of the total clinical histories in the sample, 101 patients presented noninvasive papillary carcinoma (Ta) (28.9%). Fourteen patients had carcinoma in situ (Cis) and, more frequently, 235 patients had tumors that had spread to the connective tissue (T1). Of the 350 patients, 180 were grade I, corresponding to 51.3%, 32 were grade II, and 138 were grade III. There were no patients with grade IV.

As risk factors, according to the records of the clinical histories, 277 patients had a history of smoking, 53 patients were previous carriers of a bladder catheter, and 20 patients reported activities with exposure to polycyclic aromatic hydrocarbons, mainly related to the actions of automotive mechanics and the transport sector.

According to the medical records, 111 patients underwent transurethral resection (TUR) alone, 64 patients underwent TUR plus bacillus Calmette-Guérin (BCG) therapy, and 175 patients underwent TUR plus chemotherapy (CTX). The chi-square tests between the type of treatment and cancer recurrence showed no dependency relationship between the variables (P = 0.852). Similarly, the independence between the kind of treatment and the patient's state (P=0.078) was corroborated.

Regarding the histological type of the patients, according to the medical records, 212 patients presented urothelial carcinomas, 60 patients presented transitional cell carcinoma, 69 patients presented papillary carcinomas, and, less frequently, ten patients presented a rare and aggressive variety of carcinoma. This is plasmacytoid carcinoma.

Of the 350 medical records, 207 patients were still alive at the time of data collection, while 143 were reported deceased.

To determine the recurrence of superficial bladder cancers after intravesical chemotherapy with doxorubicin. After doxorubicin instillation, 147 patients reported cancer recurrence, while 203 had no recurrence.

Table 1. Demographic, clinical and pathological characteristics of the study population.

Category	Variable	Frequency No.=350	Percentage
Sex	Man	286	81.6%
	Women	64	18.4%
Age (years)	18-28	5	1.3%
	29-39	9	2.6%
	40-50	5	1.3%
	51-61	28	7.9%
	62-72	129	36.8%
	> 73	175	50.0%
Tumor size _	0-3CM	230	65.8%
	>3CM	120	34.2%
Tumor location	Left sidewall	124	35.5%
	Right sidewall	101	28.9%
	trine	64	18.4%
	Dome	46	13.2%
	Back wall	5	1.3%
	Multiple	9	2.6%
Pathological stage	Ta	101	28.9%
	Cis	14	3.9%
	T1	235	67.1%
Tumor grade	Grade I	180	51.3%
	Grade II	32	9.2%
	Grade III	138	39.5%
Risk factors	smoking	277	79.1%
	Chronic bladder catheter carrier	53	15.2%
	Exposure to polycyclic aromatic hydrocarbons	20	5.7%
Type of treatment	RTU	111	31.6%
	TUR + BCG	64	18.4%
	TUR + QT	175	50.0%
Histological type	Urothelial	212	60.5%
	Transitional	60	17.1%
	Papillary carcinoma	69	19.7%
	Plasmacytoid	10	2.6%
Patient's status	Alive	207	59.2%
	Deceased	143	40.8%
Recurrence/recurrence	Yes	147	42.1%
	No	203	57.9%
Tumor progression	Yes	55	15.8%

	No	295	84.2%

TUR: transnurethral resection. BCG: bacillus Calmette-Guérin. QT: Chemotherapy.

Table 2. Recurrence and progression of bladder cancer in the study group.

Category	Variable	Frequency n=350	Percentage
Recurrence	No recurrence	203	56.6%
	3 months	24	6.6%
	6 months	10	2.6%
	12 months	56	15.8%
	24 months	29	7.9%
	36 months	15	3.9%
	48 months	23	6.6%
Progression	No progression	295	84.2%
	3 months	5	1.3%
	6 months	9	2.6%
	12 months	9	2.6%
	24 months	18	5.3%
	36 months	5	1.3%
	48 months	9	2.6%

Table 2 shows that 203 patients did not present recurrence. Of the 147 patients with a recurrence, 56 had a repeat at 12 months, representing 15.8% of the total medical records. However, a relatively large proportion of 24 patients showed recurrence at three months. Despite the recurrence, it should be noted that most patients did not show replay after treatment. Based on the analysis of the medical records, of the 350 patients, 295 did not show cancer progression, and a minority of 55 patients did show progression. Observing the time of progression, a minority showed progression after three months (5 patients; 1.3%), and 2.6% (9 patients) continued to progress at six months and in the same proportion at 12 months. Most patients progressed at 24 months (5.3%), and five progressed at 36 months.

Discussion

Regarding the first objective, it was possible to conclude in this study that, of the total of 350 patients in the sample, 81.6% corresponded to the male population (286 patients), and 64, which is equivalent to 18.4%, were women, which allows us to infer a greater prevalence of superficial bladder cancer in men, with a ratio of 4.45 times men to women, which coincides with [4]. The disease is four times more common in men than in women. In turn, a study [5] identified thirty-six patients (72%) males and 14 (28%) females, with a relationship similar to that of this study.

This research's most frequent age range corresponds to patients over 73 years of age, followed by patients between 62 and 72, with a percentage of 36.8%. The analysis shows that older patients have a greater tendency to suffer from superficial bladder cancer. Regarding empirical referents [4], they found that 90% of bladder cancer diagnoses are made in people 55 or older, and the mean age was 59.4 years. On the other hand, Reyna-Blanco et al. [13]

categorized patients between 35 and 76 years, with a mean of 53 years, with a 60% incidence in males.

Regarding the clinical manifestations and risk factors, 65.8% of the medical records in the sample had a tumor between 0 and 3 cm, and 34.2% had tumors larger than 3 cm. A more excellent location was observed in the left lateral wall; of the 350 medical records, 124, corresponding to 35.5%, had the tumor in this section. Of the total clinical histories of the sample, 101 patients presented noninvasive papillary carcinoma (Ta) (28.9%). Fourteen patients had carcinoma in situ (Cis), and 235 patients had tumor spread to the connective tissue (T1) more frequently. Of the 350 patients, 180 were grade I, corresponding to 51.3%, 32 were grade II, and 138 were grade III. Regarding the histological type of the patients, according to the medical records, 212 patients presented urothelial carcinomas, 60 patients presented transitional cell carcinoma, 69 patients presented papillary carcinomas, and, less frequently, ten patients presented a rare and aggressive variety of carcinoma: plasmacytoid carcinoma. Regarding the empirical referents [4], they identified patients with high histological grade (62%), low grade (28%), and low malignant potential (10%).

As risk factors, according to the records of the clinical histories, 277 patients had a history of smoking, 53 patients were previous carriers of a bladder catheter, and 20 patients reported activities with exposure to polycyclic aromatic hydrocarbons, mainly related to the actions of automotive mechanics and the transport sector. Regarding the referents consulted, [3] observed an immediate decrease in the risk of bladder cancer in those patients who quit smoking. The reduction was approximately 40% within 1-4 years of leaving and 60% after 25 years. Regarding smoking as a risk factor [4], they point out that increased exposure to tobacco smoke and occupational risks in men may help explain the four-sex discrepancy in bladder cancer incidence.

Regarding the third objective, according to the medical records, 111 patients underwent transurethral resection (TUR) alone, 64 patients underwent TUR plus bacillus Calmette-Guérin (BCG) therapy, and 175 patients underwent TUR plus chemotherapy (CTX).The chi-square tests between the type of treatment and cancer recurrence show no dependency relationship between the variables (sig. = 0.852). This means that there are no differences in the effectiveness of the treatments; that is, they all demonstrate the same efficacy. Similarly, the independence between the type of treatment and the patient's condition is corroborated. This means that the patient's condition does not depend on the kind of treatment, i.e., all treatments have the same result on the patient's condition. Of the 350 medical records, 207 patients were still alive at the time of data collection, while 143 were reported deceased.

The results coincide with [10], who determined that cisplatin-based chemotherapy protocols, especially the 4-drug regimen (methotrexate, vinblastine, doxorubicin, and cisplatin) called M-VAC, have been the one with the best data regarding response rates but with a poor tolerability profile. The benefit of this intervention has been seen both in rates of pathological complete response or cytoreduction and in disease-free survival and overall survival.

Regarding the last objective, 203 patients did not present recurrence in this research work. Of the 147 patients who had a recurrence, 56 had a recurrence at 12 months, representing 15.8% of the total medical records. However, a relatively large proportion of 24 patients showed recurrence at three months. Despite the recurrence, it should be noted that most patients did not show recurrence after treatment. Based on the analysis of the medical records, of the 350 patients, 295 did not show cancer progression, and a minority of 55 patients did show progression. Observing the time of progression, a minority showed progression after three months (5 patients; 1.3%), and 2.6% (9 patients) continued to progress at six months and in the same proportion at 12 months. The majority of patients showed progression at 24 months (5.3%), five patients showed progression at 36 months, and finally, 2.6% of patients maintained progression at 48 months.

Most patients who showed recurrence were in a T1 stage, consistent with medical theory. Carcinomas in situ did not present recurrence. The chi-square and Cramer's Phi V depend-

ency tests show a dependency on the pathological stage and cancer recurrence, with a significance value of 0.05 in both tests, demonstrating the variables' dependence. This means that the risk of recurrence increases with each stage, which is consistent with the theory. Recurrence according to the tumor grade. It was observed that 92 grade one patients showed recurrence compared to 88 who did not; 23 grade two patients showed recurrence and no recurrence; and 32 grade III patients showed recurrence and 106 did not.

In the same way, the chi-square dependency tests allowed us to corroborate the dependency between the grade of the tumor and recurrence. The value of the test statistic (0.17), which is less than the significance value of 0.05, determines a dependency between tumor grade and recurrence. One study [10] identified an overall recurrence rate of 23%. The recurrence rates by status were 56% in Grade 3 and 0% in Grade 1. The recurrence rate was 41% in patients with large tumors versus 17% in those with small tumors and 44% in those with multiple tumors compared with 18% in those with solitary tumors; 30% of stage Ta tumors and 21% of stage T1 tumors recurred. Recurrence-free, progression-free, and disease-specific survival did not differ significantly between groups. The 10-year Kaplan–Meier estimates for recurrence-free, progression-free, and disease-specific survival were 67%, 84%, and 92%, respectively, for the doxorubicin group. Tumor size predicted recurrence (P = 0.013) and grade predicted progression (P = 0.004) with multivariate analysis, which is consistent with the findings of this investigation.

Conclusions

This study hypothesized that intravesical instillation with doxorubicin reduces the recurrence of superficial bladder cancers. The results of the chi-square dependency tests and Cramer's Phi V allowed us to corroborate the dependence between the grade of the tumor and the recurrence and the reliance of the pathological stage and the recurrence of the cancer with bilateral significance values of 0.050 and 0.017. However, no dependence was shown between the type of treatment and cancer recurrence (sig. = 0.852); that is, the efficacy of treatments is demonstrated, particularly with doxorubicin and the reduction of recurrence and progression of superficial bladder cancer.

Abbreviations

TUR: transurethral resection.
BCG: bacillus Calmette-Guérin.
QT: Chemotherapy.
Cis: Carcinoma in situ

Administrative information

Additional Files

None declared by the authors.

Acknowledgments

We thank the managers and staff of the "Teodoro Maldonado Carbo" Hospital in Guayaquil, Ecuador, where the study was conducted.

Author contributions

Ronald Pardina: Conceptualization, formal analysis, research, project management, resources, software.

Jimmy Labanda Muñoz: Conceptualization, methodology, validation, visualization, writing-review, and edition.

All the authors have read and approved the final version of the manuscript.

Financing

The researchers funded the study. The authors did not receive any financial recognition for this research work.

Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Statements

Ethics committee approval

No studies of databases or medical records are needed.

Consent for publication

It is not required when images, resonances, or tomographic studies of specific patients are not published.

Conflicts of interest

The authors declare that they have no conflicts of competence or interest.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660. Epub 2021 Feb 4. PMID: 33538338.

2. Wong MCS, Fung FDH, Leung C, Cheung WWL, Goggins WB, Ng CF. The global epidemiology of bladder cancer: a joinpoint regression analysis of its incidence and mortality trends and projection. Sci Rep. 2018 Jan 18;8(1):1129. doi: 10.1038/s41598-018-19199-z. PMID: 29348548; PMCID: PMC5773684Bernal, C. (2010). Metodología de la Investigación. Bógota: Pearson Education.

3. Witjes JA, Bruins HM, Cathomas R, Compérat EM, Cowan NC, Gakis G, Hernández V, Linares Espinós E, Lorch A, Neuzillet Y, Rouanne M, Thalmann GN, Veskimäe E, Ribal MJ, van der Heijden AG. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2021 Jan;79(1):82-104. doi: 10.1016/j.eururo.2020.03.055. Epub 2020 Apr 29. PMID: 32360052.

4. Saginala K, Barsouk A, Aluru JS, Rawla P, Padala SA, Barsouk A. Epidemiology of Bladder Cancer. Med Sci (Basel). 2020 Mar 13;8(1):15. doi: 10.3390/medsci8010015. PMID: 32183076; PMCID: PMC7151633.

5. De la Rosa C, Viveros C, Torres J, Hernández O, Arellano R, Martínez GExperiencia en el tratamiento de cáncer vesicalExperience in the treatment of bladder cancer. Revista Mexicana de Urología, 2015;75(2):58-63. doi: 10.1016/j.uromx.2015.01.001

6. Corral Cordero Fabián, Cueva Ayala Patricia, Yépez Maldonado José, Tarupi Montenegro Wilmer. Tendencias en incidencia y mortalidad por cáncer durante tres decadas en Quito - Ecuador. Colomb. Med. [Internet]. 2018 Mar [citado 2023 Ago 23] ; 49(1): 35-41. Disponible en: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S1657-95342018000100035&lng=es. https://doi.org/10.25100/cm.v49i1.3785.

7. Calderillo-Ruiz et al. (2009). Cisplatino y doxorrubicina en sarcomas avanzados de partes blandas: esquema de primera línea. Gaceta Mexicana de Oncología, 81, 12-18.

8. Cagel M, Grotz E, Bernabeu E, Moretton MA, Chiappetta DA. Doxorubicin: nanotechnological overviews from bench to bedside. Drug Discov Today. 2017 Feb;22(2):270-281. doi: 10.1016/j.drudis.2016.11.005. Epub 2016 Nov 23. PMID: 27890669.

9. Hernández, R., Fernández, C., & Baptista, P. (2014). Metodología de la Investigación (6 ed.). Mc Graw Hill. Obtenido de http://observatorio.epacartagena.gov.co/wp-content/uploads/2017/08/metodologia-de-la-investigacion-sexta-edicion.compressed.pdf

10. Pino, L. (2015). Quimioterapia perioperatoria en cáncer de vejiga: más evidencia que realidad. Urología Colombiana, 24(2), 106-112. doi:https://www.elsevier.es/es-revista-urologia-colombiana-398-articulo-quimioterapia-perioperatoria-cancer-vejiga-mas-S0120789X15000702

11. Sociedad Americana Contra El Cáncer (TM). (2018). Datos y Estadísticas sobre el Cáncer entre los Hispanos/Latinos 2018-2020. Atlanta.

12. Bernal, C. (2010). Metodología de la Investigación. Bógota: Pearson Education.

13. Reyna-Blanco E.. Tumores de vejiga no uroteliales, como reto diagnóstico y terapéutico. Revista Mexicana de Urología 2019: 79(4), 1-8.

Editor's Note

Oncology Journal (Ecuador) remains neutral regarding jurisdictional claims in published maps and institutional affiliations.