ONCOLOGÍA roe-solca.ec ORIGINAL ARTICLE

End-of-life symptom control with dexmedetomidine: A single-center observational study.

Corresponding Author:

Mariana Vallejo Martinez

Email:

mariana.vallejo@cu.ucsg.edu.ec

Telephone: [593] 0998089192.
Address: Av. Pedro Menéndez Gilbert, Cdla. Atarazada, Guayaquil – Ecuador, Palliative Care Service, SOLCA-Guayaquil
Postal Code: 090505.

Guayaquil, Ecuador

Conflict of interest: The authors declare that they have no conflict of interest.

Received: May 15, 2023
Accepted: July 05, 2023
Published: August 19, 2023
Editor: Dr. Lorena Sandoya

Cite:
Miñarcaja M, Estrella A, Valencia E, Vallejo M. End-of-life symptom control with Dexmedetomidine: Single-center observational study. Oncology Journal (Ecuador) 2023;33(2):121-130.

ISSN: 2661-6653

DOI: https://doi.org/10.33821/708
SOCIEDAD DE LUCHA CONTRA EL CÁNCER.

Mirian Minarcaja [1], Adriana Estrella [1], Mariana Vallejo Martínez* [1]

1. Postgraduate Palliative Care, Santiago de Guayaquil Catholic University, Ecuador.

Abstract

Introduction: Managing refractory symptoms with dexmedetomidine (DXM) is an alternative for cancer patients in end-of-life care (AFV), which can become a great challenge, given the need to start palliative sedation. This study aims to determine the effect of DXM compared to midazolam (MDZ) in the control of refractory symptoms in patients with advanced AFV cancer as part of a palliative sedation care strategy.

Methodology: In this observational, longitudinal study, the medical reports in the medical records of hospitalized patients diagnosed with terminal advanced cancer and refractory symptoms (pain, dyspnea, and delirium) who received palliative sedation with DXM or MDZ were reviewed. The Edmonton Symptom Assessment Scale-revised (ESAS-r) scores for symptom intensity and the Richmond Sedation/Agitation Scale (RASS) for response to sedation were used.

Results: A total of 35 patients received DXM, and 18 received MDZ. Pain (32%) and delirium (30%) were the most identified refractory symptoms. Intense pain in 89.3% before DXM started; at 72 hours in 64.3%, the pain was reported as mild. Delirium was severe in 77.7%, DXM was used in 59.3%, and MDZ was used in 40.7%. At 72 hours, the DXM group presented a decrease in delirium intensity to mild and moderate, while most of the patients in the MDZ group died before 72 hours.

Conclusions: The clinical use of DXM allows a multimodal approach, expanding its usefulness in end-of-life care for managing pain and delirium since it provides a state of response for interaction with family members, a function relevant in palliative care.

Keywords:

DeCS: cancer pain, palliative care, delirium, dexmedetomidine, dyspnea, pain, midazolam.

DOI: 10.33821/708

Introduction

In the Latin American context, it is estimated that the prevalence of palliative sedation (PS) use is between 20 and 23% in palliative care units [1, 2]. Refractory symptoms have been described as the leading causes of sedation, among which delirium (60.3%), pain (44.8%), dyspnea (17.2%), seizures (3.4%), and vomiting (1.7%) stand out. In most of the region's countries, only some studies determine the use of SP [3].

Patients with terminal illnesses frequently manifest severe symptoms during the final phase of life; although many of them indeed manage to undergo adequate intervention, a percentage of cases experience uncontrollable symptoms despite the established treatment, becoming so-called refractory symptoms [4]. This generates a high emotional impact on the family and on the palliative care (PC) team, which identifies the need to start palliative sedation therapy (PS), a complex decision based on the use of drugs that provide a decreased state of consciousness to alleviate refractory symptoms without affecting patient survival [5, 6].

The most commonly used drugs are benzodiazepines with a short half-life and rapid onset of action, such as midazolam. However, levomepromazine is the choice for patients with refractory delirium [7]. Some studies suggest that DXM in end-of-life care provides sedation, treats fever, and decreases opioid requirements [8–11]. DXM acts on α2 receptors, has mild sedative and analgesic effects, and allows the patient to open their eyes to verbal stimulation and obey simple commands, thus enhancing their ability to interact with loved ones. In contrast, midazolam causes more profound sedation, limiting this interaction [12].

For this reason, this study aims to determine the effect of dexmedetomidine and midazolam in controlling refractory symptoms in patients with advanced cancer in the last days of life as part of a palliative sedation care strategy.

Materials and methods

Study design

The methodology used corresponds to an observational, longitudinal study.

Study area

The study was conducted in the palliative hospitalization area at the National Oncology Institute "Dr. Juan Tanca Marengo," SOLCA -Guayaquil, from May 1 to December 31, 2022.

Universe and Sample

The universe was made up of all the cases registered in the institution. The sample size was nonprobabilistic and discretionary and included all incident cases in the study period.

Participants

Cases of patients with the following characteristics are included:

- Patients of either sex with histological confirmation of cancer.
- Age greater than ten years.
- Terminal-stage patients with refractory symptoms (pain, dyspnea, and delirium).
- Life expectancy is less than three weeks.
- Informed consent of the patient or family.

The following cases were excluded:

- Cancer patients undergoing active treatment.
- Having previously received intravenous benzodiazepines.
- Patients and relatives who rejected the alternatives.

Two natural groups were formed with the intention of treating with
Group 1: Dexmethomedine
Group 2: Midazolam.

Variables

The variables were age, sex, oncological diagnosis, assessment with the RASS scale, reason for sedation, duration of the infusion, basal dose, dose at 34 and 72 hours, and response to pain in both groups.

Procedure, techniques, and instruments.

The data collection of the study sample was obtained through the hospital system and from the review of medical records, explicitly using the information on the required variables.

To carry out the baseline and evolutionary evaluation of each case, the medical reports in the medical records were reviewed using the forms of the Edmonton Symptom Assessment Scale-Revised (ESAS-r), which is applied to all patients admitted to the Palliative Hospitalization Area and the Richmond Agitation/Sedation Scale (RASS), which is administered to all patients who receive sedation or who present refractory symptoms.

The data obtained were recorded in a Microsoft Excel document, which included demographic data, diagnosis, heart rate, drug dose, and intensity of symptoms before sedation plus control at 24 and 72 hours after its onset. The end of the study was established as 72 hours. All cases received continuous monitoring and psychological support from the patient and family.

ESAS-r SCALE: This is a validated instrument that uses numerical visual scales to explore frequent symptoms and their intensity in a period determined according to the patient's condition and is scored from 1 to 10 depending on the intensity of the symptom: 0 absent, 1 to 3 mild, 4 to 6 moderate, and 7 to 10 severe [13].

RASS SCALE: validated scale to detect a state of agitation or delirium, whose positive values from +1 to +4 indicate agitation and negative values from -1 to -5 are used to analyze sedation [14].

Avoidance of bias

To avoid study bias, the registration of medical records in a Microsoft Excel database was guaranteed, as well as a double checklist to include only the cases of the palliative care service that met the study variables. To avoid interviewer, information, and memory biases, the principal investigator always kept the data with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their concordance was verified.

Statistical analysis

Continuous variables are reported as the mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate; frequencies and percentages were used to notify the categorical variables. The means were compared with Student's t test, and the proportions were compared with chi-square tests. SPSS 26.0 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) was used.

Results

Participants

Of 264 patients admitted to the palliative hospitalization service from May to December, 53 presented refractory symptoms and palliative sedation criteria; they were assigned into two groups. MDZ was administered more frequently to manage dyspnea and delirium, while DXM was administered for pain and dyspnea. Thirty-five patients received DXM, and 18 received MDZ. During the study period, 17 patients died due to being in the final phase of life.

Demographic characterization

Table 1 details the clinical and demographic variables of the two groups. The average age was 51 years, with a range between 10 and 87 years, and the gender ratio was 1.6 to 1, with a more significant number of women. The most frequent oncological diagnosis was digestive cancer (37.7%), including pancreas, stomach, and liver cancer. Pain (32%) and delirium (30%) were the most frequently identified refractory symptoms that motivated the use of palliative sedation. Of the 53 patients, 25% presented more than one refractory symptom at the end of life as a reason for sedation.

Table 1. Clinical and demographic characteristics.

Characteristics	Dexmedetomidine No.=35	Midazolam N=18	*P value*
Age (years) ± SD	49 ± 20	56 ± 19	0.19
Men	14 (40%)	6 (33%)	0.63
Women	21 (60%)	12 (67%)	
Oncological diagnosis, n (%)			
Breast cancer	4 (8%)	4 (8%)	0.25
Lung cancer	2 (4%)	-	
Prostate cancer	2 (4%)	1 (2%)	
Uterus Cancer	1 (2%)	3 (6%)	
Digestive cancer	13 (24%)	7(12%)	
Other Tumors	13 (24%)	3 (6%)	
Initial Ras , n (%)			
+3 (Very agitated)	33 (62.2%)	17 (32.1%)	0.98
0 (Awake, helpful)	2 (3.8%)	1 (1.9%)	
Reason for sedation	**ESAS-r SCALE**		
Severe pain	17 (32%)	0 (0%)	
Delirium	7 (13%)	9 (17%)	
Mild	0	0	
Moderate	1	1	
Severe	6	8	
Severe dyspnea	0	7 (13%)	
More than one symptom	11 (21%)	2 (4%)	
Characteristic of use of the drug			
Infusion duration (days) mean ± SD	5±2	3±3	0.017
Basal dose (ug/mg) mean ± SD	120 ± 38.7	25.7 ±14.5	NC
24-h dose (ug/mg) mean ± SD	148.57 ± 87.8	36.5 ±12.9	NC
72-h dose (ug/mg) mean ± SD	177.5 ± 90	37.5±13.3	NC

ESAS-r: Edmonton Symptom Assessment Scale; RASS, Richmond Agitation and Sedation Scale; h, hour; ug micrograms; mg milligrams.NC: Not comparable.

Table 2 evaluates the intensity of the symptoms and their evolution 72 hours after starting the medication. Severe pain was identified in 25/28 (89.3%) patients before the start of the DXM infusion; at 72 hours, it was possible to show that in 18/28 (64.3%) patients, the pain was reported as mild intensity. Delirium was identified in 27 patients and was severe in 77.7%. DXM was used in 16/27 (59.3%) and MDZ in 11/27 (40.7%); it was possible to establish that, at 72

hours, the patients in the DXM group presented a decrease in the intensity of delirium, ranging from mild to moderate, while most of the patients in the MDZ group died within 72 hours; however, it is worth mentioning that 7.4% had complete control of the symptom, and 11.6% reported it as mild and moderate.

Table 3 specifies the initial RASS scale and control records at 72 hours. It was possible to determine that most of the patients were initially located in Rass +3 (very agitated), and 72 hours after the start of the infusion, 96% went to a RASS of 0 to -4; DXM-infused patients remained at a higher rate with RASS 0 to -2 compared to the midazolam group with RASS between -3 and -4. The heart rate between the groups was not significantly different (Table 4).

Table 2. Refractory symptoms in the study groups.

		DMX	MDZ
Initial pain data	Mild	1 (3.6%)	0
	Moderate	2 (7.1%)	0
	Severe	25 (89.3%)	0
Initial dyspnea data	Mild	1(9.1%)	0
	Moderate	1(9.1%)	1 (9.1%)
	Severe	0	8 (72.7%)
Initial delirium data	Moderate	5(18.5%)	1 (3.7%)
	Severe	11(40.7%)	10 (37%)
Data at 72 hours of pain	Mild	18 (64.3%)	0
	Moderate	4 (14.3%)	0
	Severe	0	0
	Deceased	6 (21.4%)	0
Data at 72 hours of dyspnea	No symptom	0	3 (27.3%)
	Mild	0	1 (9.1%)
	Deceased	2 (18.2%)	5 (45.5%)
Data at 72 hours of delirium	No symptom	0	2 (7.4%)
	Mild	7 (25.9%)	2 (7.4%)
	Moderate	7 (25.9%)	1(4.2%)
	Deceased	2 (7.4%)	6 (22.2%)

Table 3. Agitation and sedation scale.

	Initial		24 hours		72 hours	
	Cluster DXM No.=35	Cluster MDZn=18	Cluster DXM n=35	Cluster MDZn=14	Cluster DXM n=28	Cluster MDZn=8
RASS +3 (Very agitated)	33	17	6	2	-	2
RASS 0 (Alert and calm)	2	1	14	3	9	2
RASS -1 (sleepy)	-	-	5	2	6	-
RASS -2 (Mild sedation)	-	-	1	-	6	-
RASS -3 (Moderate sedation)	-	-	4	1	1	1

RASS-4 (Deep sedation)	-	-	5	6	6	3

Table 4. Agitation and sedation scale.

	DXM Group	MDZ Group
Basal HR (beats per minute) median-ranges.	105 (81-146)	101 (60 - 145)
HR 24 hours (beats per minute) median-ranges.	85 (57-115)	86 (60 - 105)
HR 72 hours (beats per minute) median-ranges.	76 (58-100)	77 (57-88)

HR: Heart rate.

Discussion

Research describes the effects of dexmedetomidine and midazolam in controlling refractory symptoms at the end of life. Regarding the indication of sedation, the requirements were met, including being in the terminal stage, suffering from one or more refractory symptoms, that is, not responding to other therapeutic alternatives, and having signed an informed consent form [15]. The leading cause for the use of palliative sedation was pain, followed by delirium, unlike the literature consulted, where delirium was the most frequently identified reason [2, 16, 17]; however, it is essential to consider that in this study, the pain was concurrent with other symptoms such as delirium and dyspnea.

DXM was used to manage refractory pain and delirium due to its sympatholytic, sedative, amnesic, and analgesic properties that provide "conscious sedation" without respiratory depression [18]. This fact has been demonstrated in the results of this investigation, in which both pain and delirium reported a decrease in their intensity at the 72-hour control, which allowed the patient to be kept awake between a state of alert and calm until a form of mild sedation, which facilitated interaction with the family.

In the palliative care setting, multiple case reports have demonstrated the utility of DXM for refractory pain and delirium [8, 19, 20]. One of them was carried out by Hofherr et al., where a favorable response was evidenced for refractory pain, opioid-induced hyperalgesia, and delirium at the end of life; with a dose ranging from 0.3 to 0.5 mcg/kg/h, it achieved a decrease in pain intensity [21, 22]. In this investigation, the drug was used in a continuous infusion, with low doses, without induction boluses (mean amount of 177.5 mcg/day), which made it possible to demonstrate the decrease in the intensity of symptoms through ESAS-r at 24 and 72 hours. In addition, according to the results obtained, the heart rate did not change significantly, possibly due to this continuous low-dose infusion, which allowed pharmacokinetic stability.

A systematic review from 2000 to 2020, carried out in 7 countries, on implementing palliative sedation at the end of life reveals that most of its use was in men, contrary to the present study in which more women received SP. On the other hand, age, hospitalization conditions, and refractory symptoms were similar [20-22].

International evidence in the palliative field is increasing, but at the local level, studies in clinical practice are unknown, so it seems justified to carry out controlled clinical trials. In addition, in pediatrics, DXM has demonstrated safety and efficacy, considering it an advantage for alleviating the child's suffering at the end of life, but not before analyzing ethical and clinical aspects in decision-making [23 – 25].

One of the study's strengths was having information about using a pharmacological alternative to comfort patients. The limitation was focused on the small number of patients, which did not allow for establishing firm recommendations about the efficacy of other drugs due to the terminal and end-of-life status of the patients in a short time.

Conclusions

The clinical use of DXM is helpful in several scenarios, both in adults and children with oncological pathology, for managing pain with opioids and refractory delirium, allowing a multimodal approach and expanding its usefulness in end-of-care life due to its mild sedative effects, allowing interaction with family members, and turning out to be a relevant function in palliative care.

Abbreviations

ESAS-r: Edmonton Symptom Assessment Scale.
RASS: Richmond agitation and sedation scale.
DXM: Dexamethasone.
MDZ: Midazolam.

Administrative information

Additional Files

None declared by the authors.

Acknowledgments

We thank the patients, managers, and staff of the SOLCA-Guayaquil Hospital, where the study was conducted.

Author contributions

Mirian Miñarcaja: Conceptualization, formal analysis, research, project management, resources, software.

Adriana Estrella: Conceptualization, methodology, validation, visualization, writing-review, and editing.

Marina Vallejo Martínez: Conceptualization, methodology, validation, visualization.

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

Not required in studies of databases or medical records.

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. Pérez J, Utor L, Gatón L. Guía de sedación paliativa [Internet]. Instituto Nacional de Gestión Sanitaria. Madrid, España; 2022. Disponible en: paliativa
2. Santos D, Della A, Barlocco B, Pereyra J, Bonilla D. Sedación paliativa: experiencia en una unidad de cuidados paliativos de Montevideo. Rev. Méd. Urug. 2009;25(2):78-83. SciELO: S1688.
3. Quintero Carreño Valeria, Martínez Vásquez Catalina, Agámez Insignares Claudia. Sedación paliativa en enfermedad terminal. Rev. Colomb. Cancerol. 2022;26(1):3-13. SciELO: S0123. Epub Sep 02, 2022. doi: 10.35509/01239015.702.
4. Villarroel P, Contreras V, Carbonell P. Rol de la dexmedetomidina en el tratamiento del dolor. Dolor. 2013;22(60): 34-40. LILACS: 779247.
5. Arantzamendi M, Belar A, Payne S, Rijpstra M, Preston N, Menten J, Van der Elst M, Radbruch L, Hasselaar J, Centeno C. Clinical Aspects of Palliative Sedation in Prospective Studies. A Systematic Review. J Pain Symptom Manage. 2021 Apr;61(4):831-844.e10. doi: 10.1016/j.jpainsymman.2020.09.022. Epub 2020 Sep 19. PMID: 32961218.
6. Eun Y, Hong IW, Bruera E, Kang JH. Qualitative Study on the Perceptions of Terminally Ill Cancer Patients and Their Family Members Regarding End-of-Life Experiences Focusing on Palliative Sedation. J Pain Symptom Manage. 2017 Jun;53(6):1010-1016. doi: 10.1016/j.jpainsymman.2016.12.353. Epub 2017 Feb 10. PMID: 28192224.
7. Santacruz JG. La importancia del alivio del sufrimiento: acerca de la sedación paliativa. Rev Colomb Cancerol. 2022;26(1):1-2. doi: 10.35509/01239015.871.
8. Mato M, Perez A, Otero J, Torres L. Dexmetomidina: un fármaco prometedor. Rev. Esp. Anestesiol. Reanim; 2002;49(8): 407-420. LILACS: 19024.
9. Lemus R, Jacobowski NL, Humphrey L, Tobias JD. Applications of Dexmedetomidine in Palliative and Hospice Care. J Pediatr Pharmacol Ther. 2022;27(7):587-594. doi: 10.5863/1551-6776-27.7.587. Epub 2022 Sep 26. PMID: 36186237; PMCID: PMC9514772.
10. Soares LG, Naylor C, Martins MA, Peixoto G. Dexmedetomidine: a new option for intractable distress in the dying. J Pain Symptom Manage. 2002 Jul;24(1):6-8. doi: 10.1016/s0885-3924(02)00423-2. PMID: 12183087.
11. Lemus R, Jacobowski NL, Humphrey L, Tobias JD. Applications of Dexmedetomidine in Palliative and Hospice Care. J Pediatr Pharmacol Ther. 2022;27(7):587-594. doi: 10.5863/1551-6776-27.7.587. Epub 2022 Sep 26. PMID: 36186237; PMCID: PMC9514772.
12. Romera Ortega MA, Chamorro Jambrina C, Lipperheide Vallhonrat I, Fernández Simón I. Indicaciones de la dexmedetomidina en las tendencias actuales de sedoanalgesia en el paciente crítico [Indications of dexmedetomidine in the current sedoanalgesia tendencies in critical patients]. Med Intensiva. 2014 Jan-Feb;38(1):41-8. Spanish. doi: 10.1016/j.medin.2013.03.008. Epub 2013 May 15. PMID: 23683866.

13. Carvajal Valcárcel A, Martínez García M, Centeno Cortés C. Versión española del Edmonton Symptom Assessment Sytem (ESAS): un instrumento de referencia para la valoración sintomática del paciente con cáncer avanzado. Med Paliativa. 2013;20(4):143-9. doi: 10.1016/j.medipa.2013.02.001.

14. Rojas-Gambasica JA, Valencia-Moreno A, Nieto-Estrada VH, Méndez-Osorio P, Molano-Franco D, Jiménez-Quimbaya ÁT, et al. Validación transcultural y lingüística de la escala de sedación y agitación Richmond al español. Rev Colomb Anestesiol. 2016;44(3):218-23. SciELO: S0120.

15. Patel C, Kleinig P, Bakker M, Tait P. Palliative sedation: A safety net for the relief of refractory and intolerable symptoms at the end of life. Aust J Gen Pract. 2019 Dec;48(12):838-845. doi: 10.31128/AJGP-05-19-4938. PMID: 31774984.

16. Won YW, Chun HS, Seo M, Kim RB, Kim JH, Kang JH. Clinical Patterns of Continuous and Intermittent Palliative Sedation in Patients With Terminal Cancer: A Descriptive, Observational Study. J Pain Symptom Manage. 2019 Jul;58(1):65-71. doi: 10.1016/j.jpainsymman.2019.04.019. Epub 2019 Apr 23. PMID: 31026509.

17. Elsayem A, Curry Iii E, Boohene J, Munsell MF, Calderon B, Hung F, Bruera E. Use of palliative sedation for intractable symptoms in the palliative care unit of a comprehensive cancer center. Support Care Cancer. 2009 Jan;17(1):53-9. doi: 10.1007/s00520-008-0459-4. Epub 2008 May 7. PMID: 18461370.

18. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. Rev Bras Anestesiol. 2012 Jan-Feb;62(1):118-33. doi: 10.1016/S0034-7094(12)70110-1. PMID: 22248773.

19. Mupamombe CT, Luczkiewicz D, Kerr C. Dexmedetomidine as an Option for Opioid Refractory Pain in the Hospice Setting. J Palliat Med. 2019 Nov;22(11):1478-1481. doi: 10.1089/jpm.2019.0035. Epub 2019 Jun 13. PMID: 31194614.

20. Hilliard N, Brown S, Mitchinson S. A case report of dexmedetomidine used to treat intractable pain and delirium in a tertiary palliative care unit. Palliat Med. 2015 Mar;29(3):278-81. doi: 10.1177/0269216314556923. Epub 2014 Dec 2. PMID: 25467740.

21. Hofherr ML, Abrahm JL, Rickerson E. Dexmedetomidine: A Novel Strategy for Patients with Intractable Pain, Opioid-Induced Hyperalgesia, or Delirium at the End of Life. J Palliat Med. 2020 Nov;23(11):1515-1517. doi: 10.1089/jpm.2019.0427. Epub 2020 Jan 16. PMID: 31944877.

22. Wu SH, Lu DV, Hsu CD, Lu IC. The Effectiveness of Low-dose Dexmedetomidine Infusion in Sedative Flexible Bronchoscopy: A Retrospective Analysis. Medicina (Kaunas). 2020 Apr 23;56(4):193. doi: 10.3390/medicina56040193. PMID: 32340204; PMCID: PMC7231242.

23. Cuviello A, Johnson LM, Morgan KJ, Anghelescu DL, Baker JN. Palliative Sedation Therapy in Pediatrics: An Algorithm and Clinical Practice Update. Children (Basel). 2022 Dec 1;9(12):1887. doi: 10.3390/children9121887. PMID: 36553328; PMCID: PMC9776759.

24. Zhao Y, He J, Yu N, Jia C, Wang S. Mechanisms of Dexmedetomidine in Neuropathic Pain. Front Neurosci. 2020 May 5;14:330. doi: 10.3389/fnins.2020.00330. PMID: 32431587; PMCID: PMC7214625.

25. Prieto C, Pedroza N, Gómez E, Tavera T, Hernández J, Melo M, Moreno H. Sedación paliativa aspectos éticos, clínicos y médicos en el paciente paliativo. Scientific and Educational Medical Journal 2021;3(1):125-134. 61/139

Editor's Note

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