# Environmental Contamination Assessment in the Process of Application of Aerosolized Therapeutic Substances

**Rafael Seitenfus** ( rafasei@hotmail.com )
Hospital Santa Rita, Santa Casa de Misericórdia
**Eduardo Dipp de Barros**
Hospital Santa Rita, Santa Casa de Misericórdia
**Viviane de Moura Linck**
Universidade Federal do Rio Grande do Sul (UFRGS)
**Thiago Franco de Oliveira**
Universidade Federal do Rio Grande do Sul (UFRGS)
**Thais Spohr Christ**
Universidade Federal do Rio Grande do Sul (UFRGS)
**Paulo Roberto Walter Ferreira**
Universidade Federal do Rio Grande do Sul (UFRGS)
**Gustavo Andreazza Laporte**
Hospital Santa Rita, Santa Casa de Misericórdia
**Marcelo Dutra Arbo**
Universidade Federal do Rio Grande do Sul (UFRGS)

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# Abstract

**Background:** PIPAC (Pressurized Intraperitoneal aerosol chemotherapy) acts by applying aerosolized chemotherapy in the peritoneal cavity, enhancing tissue penetration of chemotherapeutic agents. This method of chemotherapy delivery still raises concerns related to the operating room's environmental exposure, arousing discussions related to the occupational risks of this technique. This work aims to demonstrate the pattern of aerosolization distribution in the absence of safety mechanisms in an operating room.

**Methods**: A cross-sectional experimental work was carried out of 31 aerosol applications. Aerosolization was performed with a 1% aqueous solution of caffeine Cellulose. Nitrate membranes were used to capture the concentration of caffeine in different sites within the operating room for 5 periods of fixed exposure times.

**Results**: 930 samples obtained in 31 rounds of aerosolization. Comparing the changes in concentration per minute between the different time intervals, there were statistically significant differences between the 0-2 minutes interval and the 15-30 interval (P <0.001). Surgeon site show a significant difference between the times (P=0.010). There were no differences between changes in concentrations in the time intervals for the anesthetist site (P = 0.094). At the injector site, a statistically significant difference (P <0.001). The time assessment between 30-35 exposure showed a median of 0.

**Conclusions:** The study pointed out that the moment of greatest risk of contamination of the surgical environment occurs during aerosolization, especially during the first 15 minutes after the start of aerosolization. The sites that were most exposed to contamination were the patient, the surgeon and the injector, respectively.


# 1. Introduction

The use of intraperitoneal chemotherapy has been used as a therapeutic option in the treatment of neoplastic diseases since the 1980s.[1] Unlike the traditional intravenous use, the use in liquid form directly in the peritoneal space has been marginally performed for the treatment of carcinomatosis. This is considered a new approach to the delivery of traditionally used drugs, such as oxaliplatin, mitomycin C, cisplatin and doxorubicin.[2] However, the results in the control of peritoneal carcinomatosis in challenging scenarios, such as gastrointestinal[3], gynecological[4] and primary peritoneal carcinoma[5] highlighted the importance of pharmacokinetics and dynamic action and behavior of chemotherapeutic agents in the peritoneal space through different forms of application. In 2000,Dr. Mark Reimond *et al* presented a new procedure of delivery of chemotherapeutic agents in the peritoneal space called “Pressurized Intraperitoneal Aerosol Chemotherapy“ (PIPAC)[6]. The difference is the provision of aerosolized chemotherapy in the peritoneal cavity through video laparoscopy to enhance the penetration and distribution of therapeutic agents within that space. This new way of delivery still raises concerns related to the exposure of the operating room environment and its teams to chemotherapeutic agents .

This scenario raises discussions related to the occupational risks that did not exist before and that could affect the teams and the surgical environment.

Several articles have been written on the assessment of safety in the application of aerosolized chemotherapy for both the assistant team and the surgical environment. However, all studies focus on assessing aerosolization and its possible safety flaws during the procedure and do not demonstrate the contamination pattern during eventual inadvertent aerosolization. This study aims to demonstrate the distribution pattern of contamination during the inadvertent aerosolization of the therapeutic substance, using PIPAC in an operating room.

## 2. Methods

# a. Experimental design

A cross-sectional experimental study was carried out in the operation room of Hospital Santa Rita no complexo Santa Casa de Porto Alegre, from August 15, 2019, to April 15, 2020 with a total of 31 aerosolizations. PIPAC applications were simulated in a negative pressure operating room with unidirectional (laminar) airflow ventilation and open sealing doors to analyze contamination in the operating room corridor. The first stage of validation of the methodology under analysis, 10 aerosolization tests were carried out simulating different levels of leakage to assess the contamination scenarios.  The first scenario was the simulation of leakage keeping the trocar's  luer lock open throughout the procedure. In this scenario, the contamination was hard to measure. The second scenario was the aerosolization 20 cm above the center of the operating table in a 10-liter open container. The third model was free aerosolization 20 cm above the center of the operating table (Figure-1). After assessing the first 10 applications, the scenario that proved to be most suitable for the purpose was scenario 3 During all procedures, no contamination control method was used. This study was submitted to the Ethics Committee, however, it was exempt from analysis because it is an experimental study that does not involve living beings or toxic substances.

# b. Aerosolization procedure

The following equipment was used: BhioQAP registered at the Agência Nacional de Vigilância Sanitária (ANVISA) under No. 80381210072 and IV contrast injection system with remote actuation (Empower CTA-Bracco). The aerosolized equipment was kept in the center and 20 cm above the operating with the aid of a mechanical arm that supported the system (Figure-1).

The assessment of environmental contamination during the PIPAC procedure was performed using a 1% aqueous solution of caffeine (Sigma-Aldrich®). This substance was specifically chosen because caffeine has low toxicity and is easy to detect. Some physical and chemical characteristics of caffeine are described in table 1.

The injector (Empower CTA-Bracco) was configured to apply the fixed volume for each 200 ml application. The injection equipment was always programmed with fixed infusion parameters of 3.0 ml/s with a maximum pressure of 200 to 300 PSI. The injection equipment adjusts the infusion flow to keep the pressure below 300 PSI. The average injection variation was 0.6 ml/s ± 0.2 ml/s. All injections were carried out without locking the injection equipment or changing the parameters described.

Cellulose nitrate membranes (8.00 µm pores and 47 mm diameter/ UNIFIL®) were used to capture the caffeine concentration in different parts of the operating room for 5 fixed periods of exposure. The membrane exposure times after the start of aerosolization were 2, 5 15 and 30 minutes. The 5th exposure period of the cellulose membrane was started 30 minutes after the beginning of the aerosolization up to 35 minutes. A escolha do tempo foi relacionada a períodos críticos do processo de aerossolização. The time was chosen based on critical periods in the aerosolization process. Time 2 is related on average to half the aerosolization time. Time 5 regards the end of aerosolization in the vast majority of applications. Time 15 relates to half the PIPAC procedure time in clinical practice. Time 30 is related to the end of the proposed procedure in clinical practice. The time between 30-35 relates to the end of PIPAC procedure and entry of the assistant team in the surgical environment. The areas of interest for determining the contamination were established at 6 points of interest. The determination of these points was chosen according to the occupational risk of healthcare professionals or by the places of a high risk of environmental contamination. (Figure-2) The sites chosen for data collection, representing the following positions during PIPAC procedure: (1) patient, (2) surgeon site, (3) anesthetist site, (4) below the injection site near the injector, (5) at the airflow outlet (which remained turned off during the procedure) and (6) under the operating room door frame.

# c. Environment contamination analysis

Cellulose nitrate membranes collected in each situation were analyzed to determine the environmental concentration of caffeine. After the collection period in each different scenario, the membranes were separately packed in plastic bags and sent to Central Analítica da Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA). Immediately after arriving at the assessment site, the samples were placed in an amber flask containing 3 ml of water supplemented with 0.1% formic acid, protected from light and incubated at 4-8 ºC for 24 hours. Aliquots of the solutions were directly injected into a liquid chromatography system together with high-resolution mass spectrometry (LC-HRMS). This system was integrated into a mass spectrometer composed of a hybrid system with quadrupole analyzer and TOF (time of flight, Bruker Daltonics, micrOTOF-QIII model) in series and in an orthogonal position for high resolution and mass accuracy. Data were processed using Data Analysis e HyStar™ software. The analyses were carried out through electrospray ionization (ESI) and the parameters such as ionization method, temperature, gas flow, collision energy and capillary energy were tested and optimized. Elution was made on a Shim-pack XR-ODS II chromatography column (75 x 2 mm, particle size 2.2 µm, Shimadzu®, Tokyo, Japan) with a water and methanol gradient supplemented with 0.1% formic acid, 0.4 ml/min flow, and temperature of 50 ºC. The total assessment time was on average 4 minutes.

# d. Statistical analysis

The sample size was calculated using the WINPEPI program (Abramson, J.H. WINPEPI updated: computer programs for epidemiologists, and their teaching potential. Epidemiologic Perspectives & Innovations 2011, 8:1) considering a 5% significance level and 90% power. The first 10 aerosolizations were used to validate the experimental design and optimize the analytical methodology, define better packaging, train the research team, and choose the best-proposed scenario. After the tenth aerosolization, 21 consecutive aerosolizations were considered for analysis. The variable distribution was assessed by the Kolmogorov-Smirnov test. Differences in the intervals of 0 to 2 minutes, 2 to 5 minutes, 5 to 15 minutes, and 15 to 30 minutes were calculated, and this difference was divided by 2, 3, 10 and 15 minutes to determine the variation per minute. The variations per minute were described by the median and the 25-75% interquartile range and compared using the Friedman test between the intervals. A 5% significance level was considered.

# 3. Results

The 930 samples obtained in 31 rounds of aerosolization with 5 different exposure times and 6 different sites in the operating room were analyzed. The median of the concentration of each site in different time analysis was presented by the median of the contamination values and the differences in the intervals were calculated and corrected for the exposure time interval and its interquartile range from 25–75% due to the large variability of the assessment. Comparing the changes in concentration per minute between the different time intervals, there were statistically significant differences between the 0–2 minutes interval and the 15–30 interval ($P < 0.001$); and between the interval 2–5 and the intervals 5–15 ($P = 0.014$) and 15–30 ($P < 0.001$). (Table 2)

Table 2
-Comparative table of variations in concentrations over time intervals for different sites (n = 31). Data given by the median (interquartile range: 25th and 75th percentiles) and compared using Friedman test

| Interval | 0–2 | 0–5 | 0–15 | 0–30 | P |
|---|---|---|---|---|---|
| Patient | 5.57(2.01–12.57)[a,b] | 7.34(0.53–14.46)[a] | 1.56 (-0.86–4.78)[b,c] | -1.08(-2.09–0.54)[c] | **< 0.001** |
| Surgean | 0.50 (0–2.65) | 0.56 (0–2.91) | 0 (-0.74–0.27) | 0 (-0.25–0.15) | **0.010** |
| Anesthetist | 0 (0–4.19) | 0 (-0.02–0.81) | 0 (-0.11–0.17) | 0 (-0.14–0.07) | 0.094 |
| Injetcor | 0.87 (0–5.07)[a] | -0.01(-1,24–0.11)[b] | 0 (-0.12–0.10)[b] | 0 (0–0.18)[a,b] | **< 0.001** |
| Air Conditioning | 0 (0–0) | 0 (0–0.32) | 0 (-0.02–0) | 0 (0–0.03) | 0.097 |
| Outside operating room | 0 (0–0.25) | 0 (-0.01–0) | 0 (0–0) | 0 (-0.02–0) | 0.124 |

Although the changes in concentrations at the surgeon-2- site show a significant difference between the times (P = 0.010), these differences did not remain after the adjustment for multiple comparisons in peer-to-peer comparisons. There were no differences between changes in concentrations in the time intervals for the anesthetist-3- site (P = 0.094). At the injector-4- site, a statistically significant difference (P < 0.001) was detected for intervals 0–2 in relation to intervals 2–5 (P = 0.002) and 5–15 (P = 0.008). With regard to the changes in concentrations at the air outlet and outside the operating room, there were no statistically significant differences (P = 0.097 and P = 0.124 respectively). The time assessment between 30–35 exposure showed a median of 0.

# 4. Discussion

The use of intraperitoneal chemotherapy has gained increasing importance in tackling metastases, mainly with the increased use of hyperthermic chemotherapy associated with surgical cytoreduction. That way, different chemotherapeutic agents are being used more in surgical centers around the world. The advent of PIPAC, which turns liquid chemotherapy into an aerosol, has brought new challenges regarding safety in the handling of these substances in clinical practice. By creating a therapeutic mist, this procedure raised extra concerns regarding the safety of healthcare professionals and the workplace. Methods of continuous assessment of contamination of the operating room for 60 minutes during the application of PIPAC procedure with 3-level safety mechanisms (closed abdomen, laminar flow room/protective cover, isolated operating room)[7] proved to be safe for the members of the assistant team taking part in the procedure.[8][9] Unlike previous studies, the purpose is to assess whether or not there is a pattern of aerosol contamination inside the operating room during a failure in the abdominal wall sealing mechanisms and in the total absence of any safety barrier. During the validation of the best model, the observations made as project's pilots, even with the video laparoscopy insufflator turned on and the trocar's luer lock opened, were not sufficient to detect residues in the analyzed samples. (Figure-1) A second pilot model with the acrylic box lid open showed the same difficulty in detecting the substance used (caffeine) at the different collection points .(Figura-1). The first study to assess contamination of the surgical environment was presented by Sollas in 2013 during the first PIPAC applications to determine the safety standards of the procedure.[10] A system leak simulation was carried out with the opening of the trocar's luer lock, keeping the "pneumoperitoneum" active during aerosolization in a model with an acrylic box. However, only the aerosol's behavior was described. The degree of contamination at different sites in the operating room or the behavior of the therapeutic mist was not measured. The first group assessed mathematical models that indicate the maximum dose inhaled in the event of a failure in the PIPAC procedure. The possible contamination identified is between 1:100 000 and 1:1 000 000 of the total dose used during the 30 minutes of the procedure.[11] Subsequent analyses were carried out to identify the sites in the surgical environment that were most exposed to the therapeutic mist. During the procedures, traces of cisplatin were not detected in the surgeon and anesthetist sites[10], but there were no flaws or leakages in these procedures. This meets the levels of contamination measured during the PIPAC procedure without signs of leakages in the operating room. Doxorubicin levels below 0.00002 ng/m3 were observed during the entire procedure, which represents only 1% of the maximum allowed

dose of exposure to healthcare professionals.[12] Graversen analyzed the presence of particles in both the anesthetist and surgeon sites, and he found no trace of contamination by a chemotherapeutic agent in the volume of air analyzed during two consecutive procedures.[13] Wouter Willaert et al assessed contamination on PIPAC applications and identified which preventive measures are effective in reducing contamination in the surgical environment during PIPAC [14]. This data demonstrates the safety of the procedure but does not determine the behavior of the aerosol in the event of a failure in the process of applying aerosolized chemotherapy.

The contamination pattern does not seem to have a normal curve. However, the data collected pointed out some critical sites when using PIPAC. Our samples showed that the patient site is the most exposed during inadvertent aerosolization. This leads us to discuss the use of impermeable and disposable fields as the only measure to reduce the risk of aerosol contact with the patient’s skin. The unprotected surgical site becomes an important exposure point and should be a concern that justifies the use of skin protection films. The surgeon and the anesthetist sites and the area under the injector are critical during inadvertent aerosolization, which supports Sollas' initial concern. Ndau et al assessed the presence of platinum after PIPAC after detecting contamination two meters from the operating table and on the injector. However, there was substantially lower 3 meters from the operating table.[15] Our observations support this idea. The first 5 minutes seem to be the most critical period for contamination of the surgical environment. The anesthetist site, despite showing a variation in the 75% percentile up to 5 minutes (0 to 2.91), still shows a lower value than the surgeon site. However, it seems to be within the critical exposure range of less than 3 meters suggested by Ndaw et al.[15] Also the first 2 minutes of the injector shows a significant differents The first 2 minutes on the injector showed a significant difference, pointing to corroborating the idea that this location, even though it is farther from the centre of the aerosolization, there is a possible contamination site mainly during the injection.Aerosolization occurs mostly up to 5 minutes – in our study, no aerosolization exceeded 6 minutes. At this point, the injection pressure and the therapeutic mist turbulence are at their highest, as pointed out in the video (video-1),treaching the highest levels of contamination. The simulation of two leakage scenarios during the procedure evaluated by Dr. Reymond's team showed an insignificant substance concentration in the environment after 12–15 minutes.[12][11] Our samples present a median of 0 in the difference in contamination corrected by the exposure time in all 6 sites evaluated in this study after 15 minutes. This tendency continues in the 30–35 exposure period. In any sample, all sites showed an occasional presence of caffeine. Even though they may be related to some bias and having the limitation of being an analysis of the surfaces contaminated by the substance under analysis, this trend leads us to believe that after 15 minutes there is no more dispersion of therapeutic cloud, having all of them already condensed in the environment. In any sample, all sites showed an occasional presence of caffeine. Even though there may be some bias and due to the limitation of being an analysis of the surfaces contaminated with the substance under analysis, we believe this tendency indicates that after 15 minutes, the therapeutic mist is no longer dispersed and it has already condensed. This idea is supported by the tendency of negativity in the assessment of the 75th percentiles corrected by the exposure time in the different sites analyzed after 15 minutes. This analysis must be carefully extrapolated to the closed therapeutic pneumoperitoneum system since the

therapeutic mist faces other challenges in the closed abdomen environment and must have a different distribution behavior. However, we must point out the need to assess the impact of this finding in the ultimate objective of the treatment of peritoneal metastases through PIPAC. In this laparoscopic environment with reduced space and under 12 mmHG, this build-up tendency should be more dramatic and possibly below 15 minutes.

## 5. Conclusions

The moment of major contamination risk identified in the samples analyzed in the surgical environment occurs in the first 15 minutes in different sites: patient, surgeon, anesthetist, and injector. The patient and surgeon sites and the area near the injector showed the highest levels of contamination. The anesthetist site tends to get contaminated.

## Declarations

# a. Ethics approval:

the research was submitted and approved by the research ethics committee of the Santa Casa de Misericordia of Porto Alegre with the number-17506919.0.0000.5335

# b. Availability of data and materials:

All data generated or analysed during this study are included in this published article with supplementary material (raw data HSRcontaminacao fev20.xlsx)

# c. Competing interests:

I would like inform that Rafael Seitenfus, Eduardo Dipp de Barros and Paulo Roberto Walter Ferreira have a part of the patent device. (Br-1020180757415, Br-3020180557379)

# d. Funding Source:

The company Bhiosupply financed 32 aerosolizers and all the necessary inputs for data collection (cellulose membranes). None of the authors received any personal funding or even sponsored by Bhiosupply.

# e. Authors' contributions:

i. Study concepts:... Rafael Seitenfus/ V1viane de Moura Linck/ Paulo Roberto Walter Ferreira/ Eduardo Dipp de Barros/Marcelo Outra Arbo

ii. Study design: ... Rafael Seitenfus/ Viviane de Moura Linck/ Paulo Roberto Walter Ferreira/ Eduardo Dipp de BaiTos/Marcelo Outra Arbo

iii. Data acquisition: ..... Rafael Seitenfus/Cassio Bona Alves/ Gustavo Andreazza Laporte/ Thaís Spohr Christ/Tiago Franco de Oliveira/ Marcelo Outra Arbo

iv. Quality control of data and algorithrns: ..... Rafael Seitenfus/ Cassio Bona Alves/ Viviane de Moura Linck/ Paulo Roberto Walter Ferreira/ Gustavo Andreazza Laporte/ Thaís Spohr Christ /Tiago Franco de Oliveira/ Marcelo Outra Arbo

v. Data analysis and interpretation: ..... Rafael Seitenfus/ Cassio Bona Alves/ Viviane de Moura Linck/ Paulo Roberto Walter Ferreira/Marcelo Dutra Arbo

vi. Manuscript editing: ..... Rafael Seitenfus/ Viviane de Moura Linck/Marcelo Dutra Arbo
..... .

vii. Manuscript review: ..... Rafael Seitenfus/ Cassio Bona Alves/ Viviane de Moura Linck/ Paulo Roberto Walter Ferreira/ Eduardo Dipp de Barros/Marcelo Dutra Arbo

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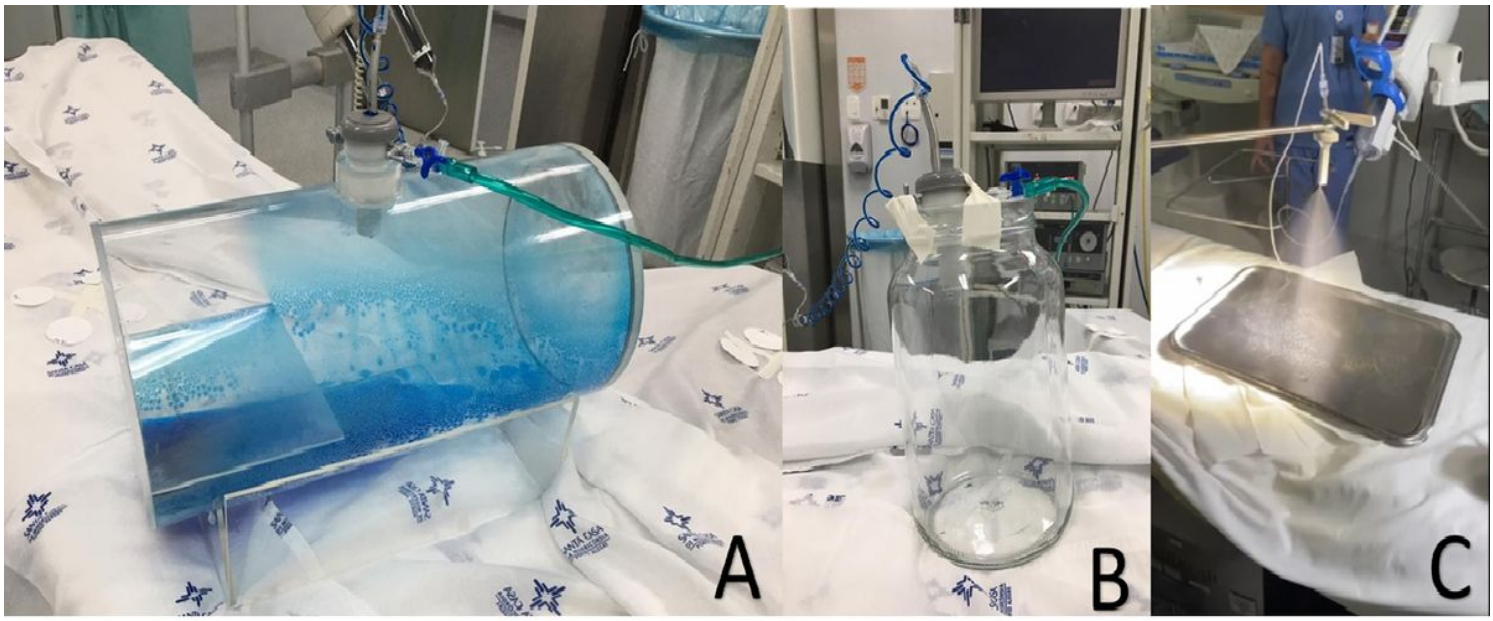
# Table

Due to technical limitations, table 1 is only available as a download in the Supplemental Files section.

# Figures




## Figure 1

a) aerosolization with open Luer lock b) superior container open C) free

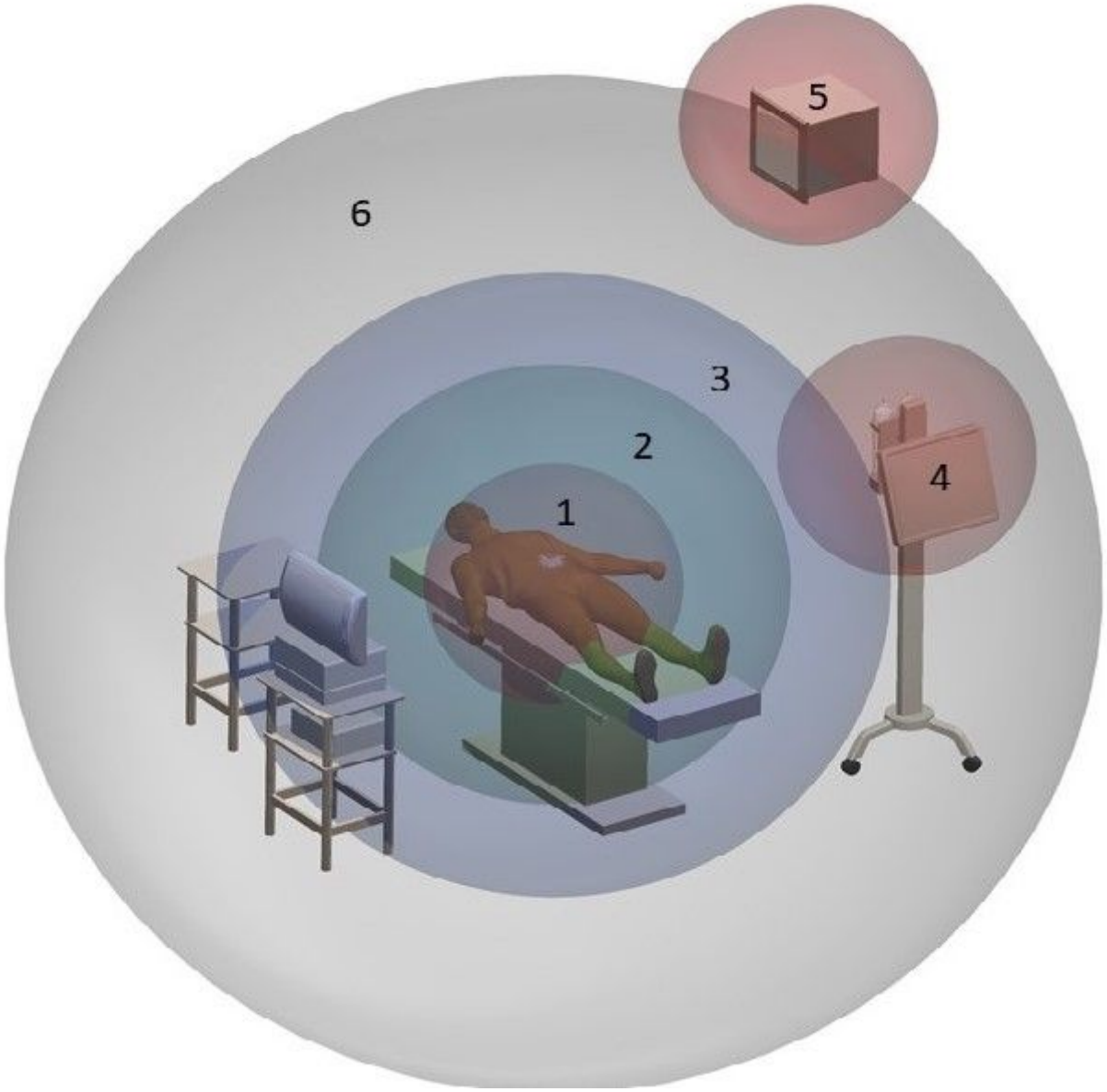



**Figure 2**

(1) patient, (2) surgeon site, (3) anesthetist site, (4) below the injection site near the injector, (5) at the airflow outlet (which remained turned off during the procedure) and (6) under the operating room door frame.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- rawdataHSRcontaminacaofev20.xlsx
- Table1.docx