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SURGICAL ENDOSCOPY
and Other Interventional Techniques

Variables in the spread of tumor cells to trocars and port sites during operative laparoscopy

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Abstract
Background: Port-site recurrences have delayed the uptake of laparoscopic colectomy, but the etiology of these is incompletely understood. These studies were designed to investigate variables such as the size of the tumor inoculum and the volume and pressure of the insufflated gas during operative laparoscopy that might affect the deposition of these cells in relation to trocars and port sites.
Methods: Radiolabeled human colon cancer cells were injected into the peritoneal cavity of pigs. Three trocars were inserted, and the abdomen was insufflated with carbon dioxide. The movement of cells within the abdomen was traced on a gamma camera. After 2 h, the trocars were removed and the port sites excised. Two studies were performed. In the first study, tumor inocula were varied from 1.5×10^5 to 120×10^5. In the second study, insufflation pressure was varied, with pressures 0, 4, 8 and 12 mmHg were studied.
Results: When larger tumor inocula were injected, the contamination of both trocars ($p = 0.005$, Kendall's rank correlation) and trocar sites ($p = 0.04$, Kendall's rank correlation) increased.

The deposition of cells on a trocar site was linked to contamination of its trocar ($p = 0.03$, chi-square), but the contamination of trocars did not always result in trocar-site contamination ($p = 0.5$, chi-square). Increased volumes of gas insufflation caused increased intraabdominal movement of tumour cells ($p = 0.01$, Kendall's rank correlation), although this did not lead to greater contamination of trocars or port sites ($p = 0.82$, Kendall's rank correlation). Decreased insufflation pressures resulted in increased contamination of trocars and port sites ($p = 0.01$, Kendall's rank correlation).

Conclusions: If clinical situations parallel this study, strategies such as increasing insufflation pressure, reducing episodes of desufflation and gas leaks, and using frequent intraabdominal lavage may help to reduce the numbers of viable tumor cells displaced to port sites during laparoscopic surgery for intraabdominal malignancy. This may reduce the rate of port-site metastases.

Key words: Laparoscopy — Metastasis — Port site — Insufflation

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The success of laparoscopic cholecystectomy in the early 1980s with its benefits of reduced hospital stay, reduced postoperative pain, and improved cosmesis inevitably led to the trial of laparoscopic approaches for the resection of intraabdominal malignancies. However, it quickly became apparent in initial studies that a relatively high number of patients developed wound (port-site) metastases [5]. According some reports, port-site metastases followed procedures during which the primary tumor was not manipulated [15, 31].

The incidence of such port-site recurrences may now be decreasing as experience with laparoscopic resections increases. The wound recurrence rate reported by the American Society of Colon and Rectal Surgeons Laparoscopic Registry [29] in a series of 480 laparoscopic cases was 1.1%. This still exceeds the reported rates of 0.6% to 0.8% in large studies of open resections [12, 24], but matches rates observed after procedures for gynecologic malignancies [6].

Multiple studies in small animal models have suggested that the direct spread of viable intraabdominal tumor cells to trocar sites is an important factor in the etiology of port-site metastases. This also may represent the predominant etiologic mechanism in the development of port-site metastases in humans because free intraperi-

toneal tumor cells are found in 15% to 27% of patients undergoing open resection of colorectal malignancies [16, 26]. However small animal models may fail in accurately modeling the movement of tumor cells during laparoscopy in humans because of the inherent differences in size and anatomy. These differences are reduced in large animal models, in which the abdominal cavity and anatomy more closely match those of humans.

In a porcine model, Allardyce et al. [1] demonstrated that tumor cells are deposited on port sites during laparoscopic colorectal resections, and that this occurred to a greater degree on sites used by the operating surgeon than on those used by the assistant.

We have previously shown that tumor cells move within the abdomen during insufflation [11], but there is a scarcity of research evaluating factors that might alter the distribution of free intraperitoneal cells, and hence the contamination of port sites. The aim of these linked pilot studies was to investigate whether some of the common variables in laparoscopic surgery might effect tumor deposition on trocars and within trocar sites.

Methods

These experiments performed with pigs complied with the code of practice for the care and use of animals in research in Australia, as set forth by the National Health and Medical Research Council, 1997. The animal ethics committees of the Institute of Medical and Veterinary Science, the University of Adelaide, and the Queen Elizabeth Hospital approved the protocol.

Cell labeling

For these studies, LIM 1215 human colon cancer cells were grown in 75 cm^3 plastic flasks containing Dulbecco modified Eagle medium (DMEM; ICN Biomedicals, Costa Mesa, CA, USA). The cells were harvested when they were 80% to 90% confluent across the base of the culture flasks by washing with 20-ml phosphate buffered saline (PBS), and then by incubation of the cells for 5 min at 37°C with 0.05% trypsin solution (Gibco BRL, Gaithersburg, MD, USA). The free cells were suspended in 20 ml of Dulbecco modified Eagle medium and centrifuged at 400 g for 5 min. The supernatant was discarded, and the cells were resuspended in 20 ml of PBS. An aliquot of this solution was taken and examined in a hemocytometer to calculate cell numbers, and a further small aliquot was incubated for 3 min with 0.02% trypan blue solution (Flow Laboratories, New South Wales, Australia) to calculate cell viability. The cell inoculum then was adjusted as required by discarding a proportion of the total suspension.

The cells were radiolabeled by adding 1GBq of ^{99m}Tc exametazime (Ceretec; Amersham, Castle Hill, New South Wales, Australia) to the suspension, which was incubated for 15 min in a water bath maintained at 37°C. To ensure that no free Ceretec remained, the cells were washed in 50 ml of PBS and centrifuged at 400 g for 5 min, after which the supernatant was discarded. This process was then repeated for two more cycles before the radiolabeled cells finally were suspended in 10 ml of PBS. The radiochemical purity of exametazime labeling was checked according to a minicolumn method [23].

Cell movement

Female 30 kg domestic pigs were premedicated with intramuscular ketamine (300 mg; Troy Laboratories, New South Wales, Australia), and anesthesia was maintained by halothane (induction 3%, maintenance 1.5%; Zeneca, Macclesfield, England) via a cuffed endotracheal tube. The pigs were secured by Millipore tape to an operating table in a supine position.

A 12-mm umbilical trocar (Endopath; Johnson and Johnson Medical, New South Wales, Australia) was inserted using an open technique, and the abdomen was insufflated with carbon dioxide (CO_2) to a pressure of 12 mmHg. Additional 12-mm trocars were inserted in the left and right iliac fossae under direct vision. Finally, a gamma camera using a low-energy general purpose collimator (LEM; Searle Nucleonics, Chicago, IL, USA) connected to a computer (Microdelta) was positioned over the abdomen. The trocars were left with no further passage of instruments or manipulation for 2 h.

Radiolabeled LIM 1215 tumor cells in 10 ml of PBS then were injected through the abdominal wall using a 19-gauge needle into the pelvis of each pig. Serial gamma camera images were taken every 2 min by placing the collimator over the porcine abdomen.

At the end of a 2 h procedure, the pigs were killed by intravenous injection of 6.5 g Lethobarb (325 mg/ml pentobarbitone; Virbac Australia, New South Wales, Australia). The trocars then were removed and placed on the collimator of the gamma camera, and the quantitative images were acquired by the computer. The discs of the abdominal wall through which the trocars passed (port sites) also were excised with a 1-cm margin around the insertion site, and these were counted using the gamma camera. Images of background radiation also were created for each procedure and for the activity of each syringe of radiolabeled cells.

The data were first converted to an interfile 3.3 format. The resulting images then were analyzed with a proprietary written program on a Macintosh personal computer. The detected counts within a user-defined area were determined. By subtracting the observed background activity and correcting for radioactive decay, the true count caused by the trocar or port site was calculated. The number of cells present on each sample was obtained by multiplying the derived number of counts on the sample by the number of cells present per count in the original syringe. The software also enabled "stitching" of all the images acquired together to form a QuickTime movie of the resulting cell movement over the 2-h period.

Study 1

Using the aforementioned protocol, 17 female 30-kg pigs were studied. The tumor inocula were varied as 12×10^6, 6×10^6, 2.5×10^6, 1.25×10^6, 0.75×10^6, 0.3×10^6, or 0.15×10^6 cells. The insufflation pressure was maintained at 12 mmHg, and the amount of CO_2 gas used was recorded for each procedure. The abdomen was desufflated with the trocars still *in situ* at the end of the procedure. Pigs were randomly assigned to tumor inoculum groups.

Study 2

Using the aforementioned protocol, 8 female 30-kg pigs were studied. Insufflation pressure was varied as 0, 4, 8, or 12 mmHg. The injected tumor inoculum consisted of 6×10^6 cells. In this study, the trocars were removed from the abdomen before it was desufflated. The pigs were randomly assigned to insufflation pressure groups.

Statistical analysis

Statistical analysis was performed with the assistance of the Statistical Consulting Service at the University of South Australia. Because data were so clearly nonnormal in nature, a nonparametric analysis was chosen using Kendall's rank correlation, and contingency tables were analyzed using a chi-square test with probability values less than 0.05 regarded as significant. Calculation was performed using StatsDirect 1.612 (Ashwell, Hertfordshire, England).

Results

Cell viability was greater than 95%, and Ceretec labeling efficiency was greater than 85% for all the experiments. Cell resolution was calculated assuming a Poisson dis-

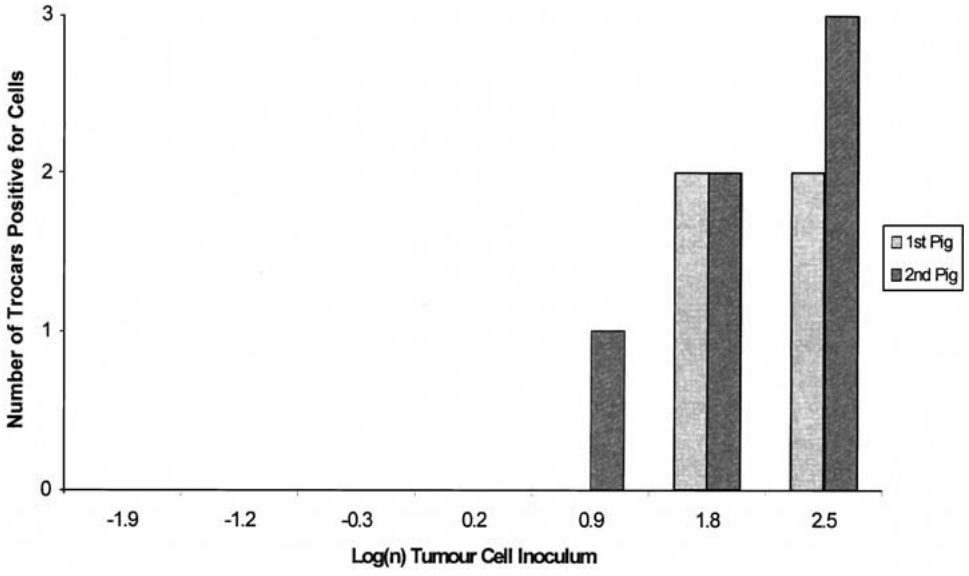

Fig. 1. Number of trocars contaminated with tumor cells for each of the two pigs compared with number of cells injected ($p = 0.005$, Kendall's rank correlation).

Table 1. Number of cells detected on trocars compared with number of cells injected

	Number of cells detected		
No. of cells	Umbilical trocar	RIF trocar	LIF trocar
12,000,000	3657	—	3,039
	28191	2,039	1,712
6,000,000	—	11,944	28,081
	—	1,940	1,131
2,500,000	—	1,375	—
	—		—
1,250,000	—	—	—
	—	—	—
750,000	—	—	—
	—	—	—
300,000	—	—	—
	—	—	—
150,000	—	—	—
	—	—	—

Table 2. Number of cells detected on port sites compared with number of cells injected ($p = 0.04$, Kendall's rank correlation)

	Number of cells detected		
No. of cells	Umbilical port site	RIF port site	LIF port site
12,000,000	—	—	91,034
	—	717	—
6,000,000	1,851	40,244	16,394
	—	4,868	—
2,500,000	—	—	—
	—	—	—
1,250,000	—	—	—
	—	—	—
750,000	—	—	—
	—	—	—
300,000	—	—	—
	—	—	—
150,000	—	—	—
	—	—	—

tribution of radioactivity. Therefore, a significant change in radioactivity was calculated as greater or equal to background activity + ($3 \times \sqrt{\text{background activity}}$). It was further assumed that this change would be observable on image analysis, giving an average theoretical minimum cell resolution of 45 cells (range, 12–200) for both studies.

Study 1

Three pigs in experienced malignant hyperthermia during the laparoscopic procedure and were excluded from analysis. There was no further operative mortality or morbidity in the remaining 14 pigs. The median quantity of CO_2 used for each 2-h procedure was 13 l (interquartile range, 10–19 l).

Trocar and port-site contamination. Detectable contamination of both trocars (Table 1) and port sites (Table 2) occurred when a tumor inoculum of more than 2.5×10^6 cells was injected into the abdomen. Overall, the number of contaminated trocars, (Fig. 1; $p = 0.005$, Kendall's rank correlation) and ports sites (Fig. 2; $p = 0.04$, Kendall's rank correlation) increased as tumor inoculum increased. Altogether, significant numbers of tumor cells were detected on 10 of a possible 42 trocars and 6 of 42 port sites (Table 3). Only one port site was contaminated, whereas no cells were detected on the corresponding trocar ($p = 0.03$, chi-square).

Study 2

In all, eight pigs were studied. There was no operative mortality or morbidity in any of these animals.

Trocar and port-site contamination. The data for trocar (Table 4) and port sites (Table 5) were concatenated because fewer animals were studied in this group. The numbers of both contaminated trocars and port sites increased as insufflation pressure decreased (Fig. 3; $p = 0.01$, Kendall's rank correlation).

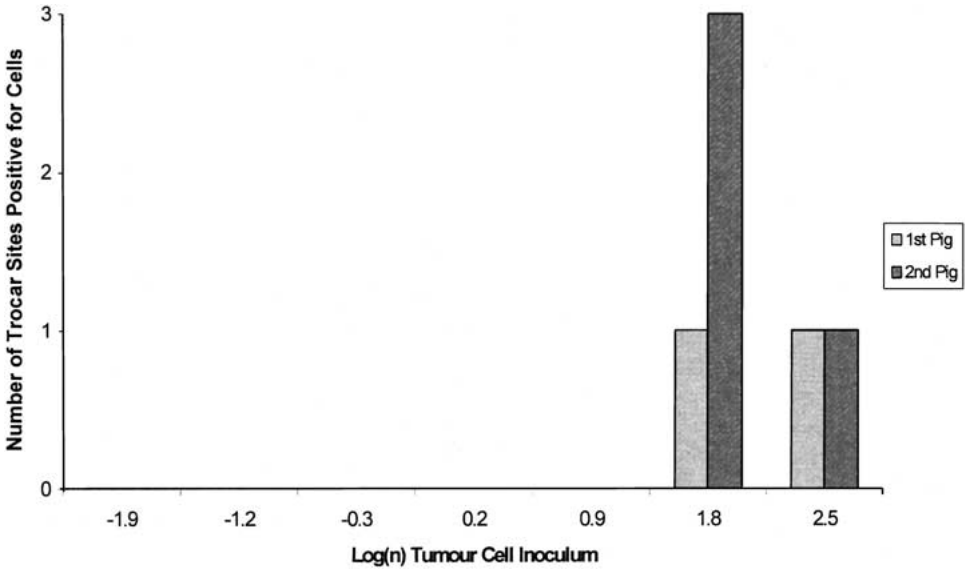

Fig. 2. Number of port sites contaminated with tumor cells for each of the two pigs compared with number of cells injected.

Table 3. Number of port sites contaminated with tumor cells when the corresponding trocar also was contaminated ($p = 0.03$, chi-square)

	Trocar positive	Trocar negative
Port site positive	5	1
Port site negative	5	31

Table 4. Number of cells detected on trocars compared with insufflation pressure

Insufflation pressure (mmHg)	Umbilical trocar	RIF trocar	LIF trocar
0	—	4,920	12,312
	21,887	32,567	2,785
4	3,744	5,380	6,163
	—	633	981
8	—	—	12,187
	—	—	—
12	—	—	—
	—	—	—

Table 5. Number of cells detected on port sites compared with insufflation pressure

Insufflation pressure	Umbilical port site	RIF port site	LIF port site
0 mmHg	931	1,049	13,038
	484	1,946	4,606
4 mmHg	—	847	7,729
	—	—	238
8 mmHg	—	—	4,145
	—	9,662	—
12 mmHg	—	—	1,034
	—	13,110	54,371

Cell movement

Cell movement within each of the six regions was derived by calculating the maximal number of cells displaced out of each region. Assuming that cell movement would normally follow a random walk distribution, this value was standardized by dividing it by the variation present in each region. The sum value for all six regions (Z value) was calculated and compared with the volume of insufflated gas (Table 6). The median quantity of insufflated CO_2 for all the animals was 15.5 l (interquartile range, 10–19 l). Cell movement increased as larger insufflation volumes were used (Fig. 4, $p = 0.01$, Kendall's rank correlation). No correlation existed between the number of trocars and the port sites contaminated and the volume of insufflated gas either on analysis of all animals ($p = 0.82$, Kendall's rank correlation) or on separate analysis of inoculum ($p = 0.45$, Kendall's rank correlation) or insufflation groups ($p = 0.11$, Kendall's rank correlation).

Discussion

Evidence exists to show that laparoscopic procedures may reduce postoperative pain, improve cosmesis, and lead to a faster return to normality [19]. As such, most patients seem to perceive laparoscopic techniques as preferable to an open procedure. This has resulted in considerable patient and surgical interest in the evaluation of laparoscopic resections for malignancy, which may be of additional benefit because immune function may be better maintained after laparoscopic [3, 4, 20, 27].

However, a number of early trials and case reports suggested that, compared with open surgery, these procedures might increase the risk of a wound (port-site) metastasis developing [32]. The relative risk of developing such a metastasis currently is under investigation in several multicenter trials, but before these procedures are more widely adopted, it should be demonstrably no higher than after open resection.

It is likely that most port metastases occur as a result of viable tumor cells contaminating the wound after direct spread from free intraabdominal cells [25, 30] or

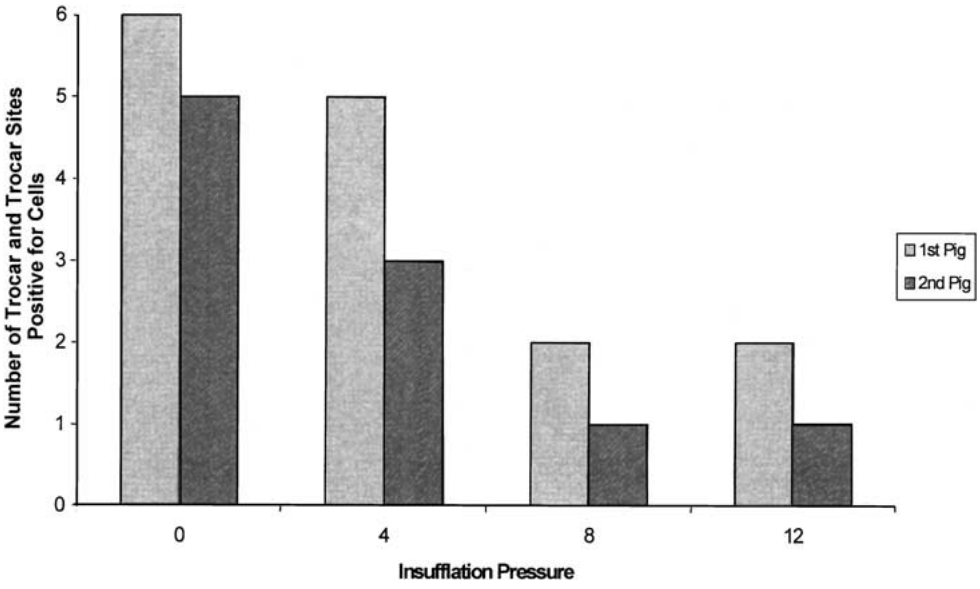

Fig. 3. Number of trocars and port sites contaminated with tumor cells for each pig compared with insufflation pressure ($p = 0.01$).

Table 6. Cell movement in all regions compared with volume of insufflated gas

Pig	*Z* value	Insufflated CO_2	No. of positive sites
Inoculum study group (no. of cells)			
12,000,000	3.161	37	3
	2.910	18	4
6,000,000	2.260	7	4
	2.746	20	3
2,500,000	2.411	19	0
	2.959	17	1
1, 250,000	1.901	8	0
	1.815	11	0
750,000	2.505	24	0
	2.322	11	0
300,000	3.341	10	0
	2.627	14	0
1 50,000	2.358	12	0
	2.168	10	0
Pressure study group (mm Hg)			
12	3.957	17	1
	2.362	19	2
8	2.731	21	2
	1.983	16	1
4	3.162	15	5
	3.777	18	3
0	1.924	0	5
	2.138	0	6

from tumor cells liberated by tumor handling [17]. This study demonstrated several factors that may increase the contamination of such port sites.

First, the contamination of port sites is linked to the contamination of trocars. Trocar lavage should reduce the number of cells on trocars, thereby reducing port-site contamination. Such port-site lavage (with 5-fluorouracil) has been shown to reduce the incidence of port-site metastasis significantly in a rat model [7]. Franklin et al. [18] suggested that the routine use of trocar lavage contributed to the 0% port-site metastasis rate in a study of 191 patients undergoing a laparoscopic colorectal resection.

Second, increased numbers of free intraabdominal cells increased the contamination risk for both trocars and port sites. No contamination of these occurred if fewer than 2.5×10^6 cells were present in the peritoneal cavity, although this also may reflect the limit of cell resolution with small tumor inocula. This is an area of concern because Hansen et al. [10] have demonstrated that up to 10×10^6 cells may be shed during open resection of solid tumors, approaching the number of cells used in this study in an abdominal cavity of comparable size. Previous animal studies have demonstrated that reduced numbers of intraperitoneal cells reduce the incidence of port-site metastases [33] or lead to reduced tumor growth [20]. Additionally, traumatic handling, which may be expected to increase dissemination of tumor cells into peritoneal cavity also increased the rate of port-site metastases [18]. Peritoneal lavage with cytotoxic solutions or heparin reduced port-site metastases in several animal model [13, 21, 22] or reduced the contamination of port sites [2]. All this evidence suggests that port-site metastases in such models are related to the number of viable tumor cells remaining in the abdomen.

Third, insufflation pressure had an inverse relation to trocar and port-site contamination, with lower insufflation pressures resulting in more contamination. This may be explained by the decreased distance between the anterior abdominal wall and free tumor cells in the peritoneal cavity. If this explanation is correct, it also would suggest that any period of desufflation with trocars remaining *in situ* would tend to increase tumor cell deposition in port sites. Jacobi et al. [14] provided some evidence to suggest that higher insufflation pressures might yet prove to be of oncologic benefit by demonstrating that in a rat model, the rate of port-site metastases decreased when insufflation pressure was increased from 10 to 15 mmHg. Not all work has supported this. Gutt et al. [9] concluded that insufflation with CO_2 at 12 mmHg stimulated *in vitro* tumor cell growth better than at lower pressures. Additionally in this study, although the absolute number of trocars and port sites contaminated by tumor cells was reduced by

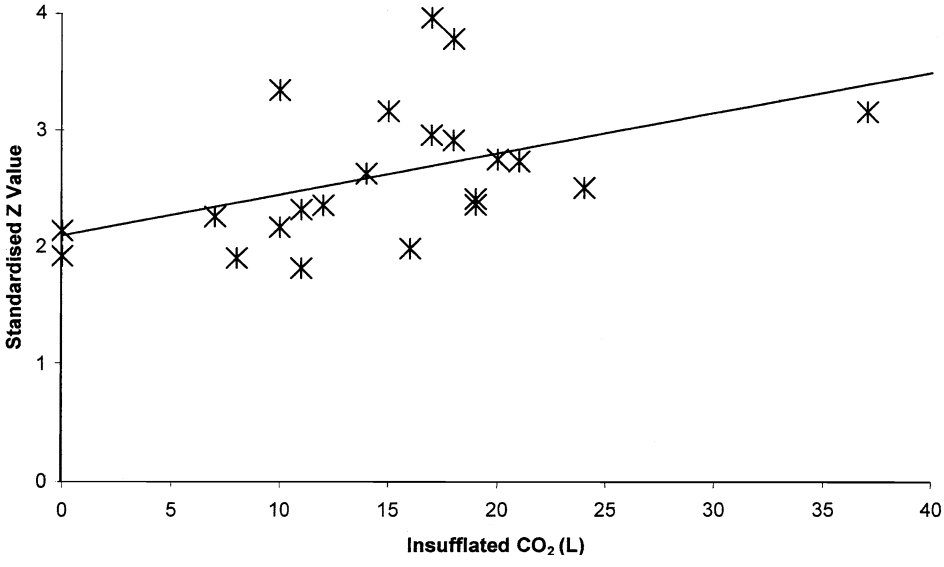

Fig. 4. Cell movement in all regions compared with volume of insufflated gas ($p = 0.01$).

increasing the insufflation pressure, the number of cells on the contaminated port sites was greater at higher insufflation pressures, an effect not observed with the trocars.

Finally, the movement of cells was related to the volume of the insufflated gas. No correlation existed, however, between increased cell movement and deposition of tumor cells on trocars or port sites. This reinforces the most commonly held belief that most contamination of trocars and/or port sites occurs after direct contact of cells with either the trocar or instruments, which then transfer the cells to the trocar after manipulation. Tseng et al. [28] demonstrated with comparatively high leak rates in rats that "leaking" port sites enhanced tumor growth. However, this may reflect the small distance that cells are required to move before reaching the port site in rat models. It is our belief that even a large volume of insufflating gas would produce a negligible effect in a larger abdominal cavity.

The results from this study suggest that the porcine model described may be helpful in the investigation of port-site metastases because a more clinically relevant tumor inoculum can be studied, particularly in comparison with the reported small animal models. Additionally, the early results suggest that certain strategies might decrease port-site contamination with tumor cells. These strategies include the use of trocar lavage, frequent intraabdominal lavage, insufflation pressures as high as physiologically well tolerated, and removal of trocars before desufflation. Further research may help refine surgical techniques to reduce the incidence of port-site recurrences, which may permit a more wide scale adoption of these procedures outside controlled trials.

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