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ORIGINAL RESEARCH

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Does gas insufflation during oncologic laparoscopic surgery cause dissemination of malignant cells?

Yossi Tzur[1,*], Ido Laskov[1], Asaf Aizic[2], Ziva Aharon[2], Avi Beri[3], Limor Gortzak-Uzan[1], Dan Grisaru[1], Nadav Michaan[1]

[1]Gynecologic Oncology Department, Lis Hospital for Women's Health, Tel Aviv Sourasky Medical Center, Affiliated to the Sackler Faculty of Medicine, Tel Aviv University, 6997801 Tel Aviv, Israel
[2]Department of Pathology, Tel Aviv Sourasky Medical Center, 6423906 Tel Aviv, Israel
[3]Urology Department, Tel Aviv Sourasky Medical Center, 6423906 Tel Aviv, Israel

***Correspondence**
yossitzur@gmail.com
(Yossi Tzur)

Abstract

To investigate whether benign or malignant cells are present in gas evacuated from the abdominal cavity during oncologic laparoscopic surgery. Thirty patients were included in this prospective observational study conducted at an academic, tertiary medical center. Fifteen patients underwent a laparoscopic staging procedure for high-grade uterine adenocarcinoma and 15 patients underwent laparoscopic nephrectomy for suspected renal cell carcinoma. The gas evacuated during laparoscopy was passed through a filter in order to capture any aerosolized cells formed during surgery. After surgery, the filter was rinsed backwards with 50 mL of saline, and the fluid was centrifuged and sent for cytological evaluation. The primary outcome was presence of benign or malignant cells in the rinsed fluid. Neither benign nor malignant cells were identified in evacuated gas in 29 cases (96.7%). In one endometrial cancer case, where macroscopic extra-uterine pelvic metastases were encountered intra-operatively, atypical epithelial cells were found in collected fluid of rinsed gas filter. Gas insufflation during laparoscopy for gynecologic and urologic malignancies apparently does not cause aerosolization and dissemination of malignant cells. However, laparoscopic surgery itself may cause cell spread possibly *via* surgical instruments when macroscopic, extra-organ tumor spread is encountered, the clinical significance of which remains undetermined.

Keywords

Minimal invasive surgery; Gynecologic oncology; Urologic oncology; Dissemination; Tumor cells; Safety

1. Introduction

Laparoscopic surgery has been routinely used for the surgical management of both gynecologic and urologic malignancies since the 1990's. Concerns about the effect of pneumoperitoneum on intra-abdominal aerosolized tumor cells spread have been reported in the past, with conflicting results. While some reports demonstrated the presence of tumor cells in evacuated gas during laparoscopy, others failed to do so [1–6]. During surgery for cervical cancer, intra-corporeal colpotomy in the presence of CO_2 pneumoperitoneum was shown to increase the risk of intra-abdominal tumor spread in patients with early stage cervical cancer when compared to vaginal colpotomy [7]. Furthermore, the Laparoscopic Approach to Cervical Cancer (LACC) trial, the first prospective randomized trial that examined the oncological safety of minimal invasive surgery (MIS) for cervical cancer compared to open surgery, demonstrated inferior oncological outcomes for the MIS approach [8]. Several theories have been proposed to explain the findings of the LACC trial, among them is the effect of CO_2 insufflation during laparoscopy on tumor-cell growth and spread [8]. The introduction of advanced laparoscopic instruments, such as the harmonic scalpel that uses ultrasonic vibrations to cauterize and cut tissue, may further increase the risk of aerosolized cells spread during laparoscopic surgery. The objective of our study was to investigate whether benign or malignant cells are present in the evacuated gas during laparoscopy for both gynecological and urological malignancies.

2. Materials and methods

Following the Reporting of Observational studies in Epidemiology (STORBE) guidelines, this was a prospective observational study. Patients undergoing conventional laparoscopy or robotic surgery for endometrial cancer were recruited. Patients with cervical cancer were not included in our study as following the publication of the LACC trial, the surgical approach for operable cervical cancer in our department is laparotomy. In order to increase the accuracy and generalization of our model, a second cohort of patients with suspected renal cell carcinoma (RCC) who underwent a laparoscopic nephrectomy was also recruited.

During surgery, pneumoperitoneum was established using a Veress needle, after which laparoscopic trocars were placed. A gas evacuation system, which enables enhanced visualization

during tissue cauterization, was connected to a 5 mm trocar with a gas filter connected to the efferent end of the evacuation system. All gas evacuated during surgery passed through the filter in order to capture any aerosolized cells formed during surgery.

For the endometrial cancer cases, a laparoscopic staging procedure that included total hysterectomy, bilateral salpingo-oophorectomy and sentinel lymph node biopsy/full pelvic lymph node dissection was performed. A uterine manipulator was used in all cases. In order to increase the likelihood of the presence of extrauterine disease and possible aerosolization of malignant cells, only cases with high-grade histology (grade 2/3 endometrioid, serous, clear cell or carcinosarcoma histologies) were included. Harmonic scalpel (Harmonic ACE® +7, Ethicon, Johnson & Johnson) as well as mono/bi-polar energy were used for tissue dissection and cauterization.

A transperitoneal laparoscopic approach was used for renal masses suspected for RCC. Patients underwent partial or radical nephrectomy according to the preoperative radiologic evaluation and intra-operative findings. A harmonic scalpel (Harmonic ACE® +7, Ethicon, Johnson & Johnson) or Thunderbeat Olympus® system was used for tissue dissection and cauterization.

Following the surgical procedure, the filter was disconnected and rinsed backwards with 50 mL of normal saline. The collected fluid was centrifuged and sent for a cytological evaluation at our pathology laboratory. The presence of benign or malignant cells in the centrifuged fluid, benign or malignant was recorded.

Before patient recruitment, the ability of the filter to capture malignant cells was confirmed by filtering malignant ascites fluid from an ovarian cancer patient and rinsing it backwards with saline as described above. The centrifuged saline was positive for malignant adenocarcinoma cells, thus establishing the efficacy of the filtration and rinsing technique used. Cases needing conversion to laparotomy for any reason were excluded from the study.

3. Results

A total of 15 patients with high-grade endometrial carcinoma and 15 patients with suspected RCC who were scheduled for a laparoscopic surgery were recruited between June 2020 and May 2021. The demographic data and tumor characteristics for the gynecologic and urologic tumors are described in Tables 1 and 2, respectively. No benign or malignant cells were found in the fluid collected from the gas filters after the laparoscopic staging procedure in all but one of the endometrial cancer cases. A minute amount of atypical, epithelial cells was identified in the cytology examination of the collected fluid in the latter case (Fig. 1). In this case, clear macroscopic extra-uterine disease spread was identified protruding from the uterus along the left sacrouterine ligament during surgery. Due to the scant amount of cells identified no further pathologic testing could be done to clarify the nature these cells. There were no cases of iatrogenic intraoperative perforation of the uterus with the uterine manipulator. Neither benign nor malignant cells were identified in the fluid collected from rinsed gas filters in any of the suspected RCC cases.

TABLE 1. Demographic characteristics: endometrial cancer patients.

	N = 15 (%)
Age (yr ± SD)	71.2 ± 9.8
BMI	30.1 ± 8.7
Endometrial cancer histology	
Endometrioid	11 (73)
Serous	4 (27)
Carcinosarcoma	1 (1)
Tumor grade	
1	0
2	6 (40)
3	9 (60)
Tumor stage	
1	13 (87)
2	0
3	2 (13)
4	0
Energy Type	
Harmonic®	15 (100%)
Surgery length (min)	139 ± 40

BMI, body mass index; SD, standard deviation.

TABLE 2. Demographic characteristics: urologic malignancies.

	N = 15 (%)
Age (yr ± SD)	62.1 ± 9.5
Male	9 (60)
Female	6 (40)
BMI (±SD)	28.5 ± 4.4
RCC subtype	
Clear cell	12 (80)
Papillary	2 (13)
Chromophobe	1 (7)
Extra organ spread	0
Approach	All trans-peritoneal
Type of Nephrectomy	
Partial	13 (87)
Radical	2 (13)
Final stage	
1	9 (60)
2	4 (27)
3	2 (13)
4	0
Energy Type	
Harmonic®	12 (80)
Thunderbeat®	3 (20)
Surgery length (min)	104 ± 27

BMI, body mass index; RCC, renal cell carcinoma; SD, standard deviation.

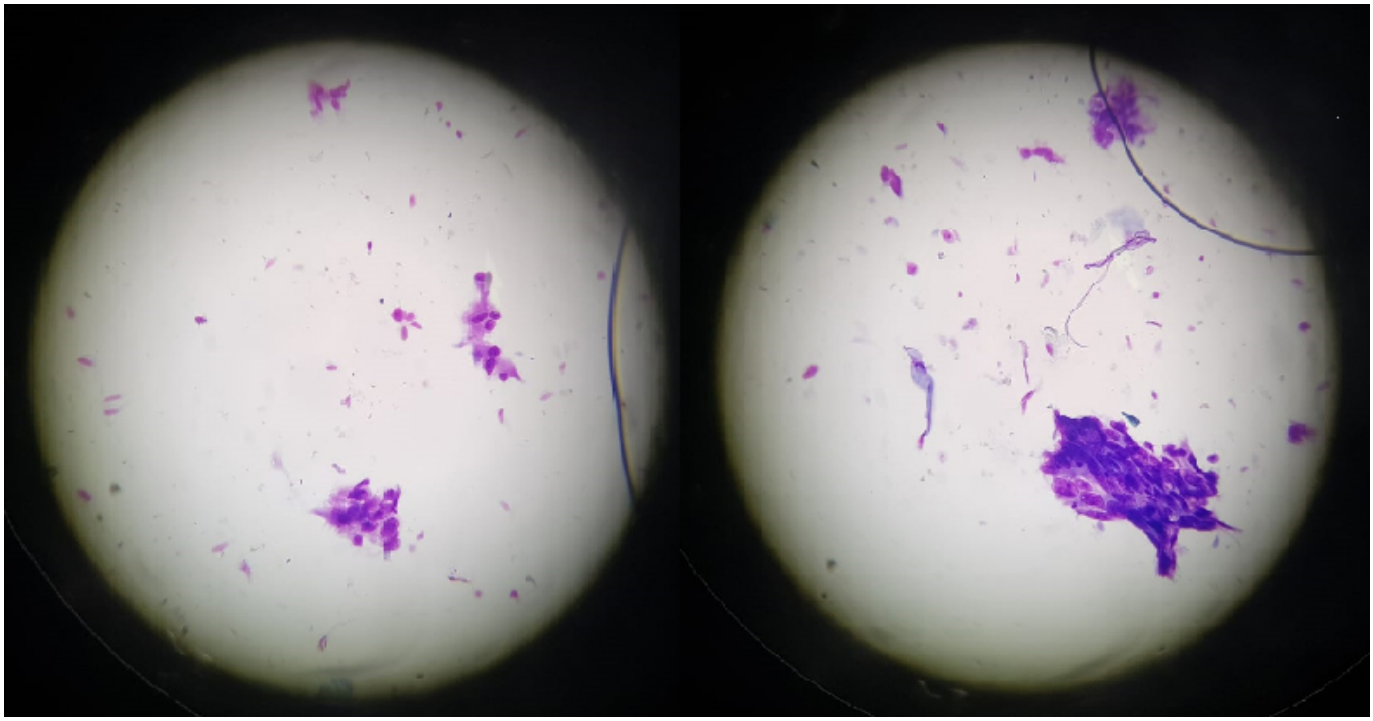

FIGURE 1. Microscopic view of filtered cells captured from evacuated gas during laparoscopic staging for advanced stage endometrial cancer case (×40).

4. Discussion

Concerns regarding malignant cells aerosolization and potential tumor spread during laparoscopic surgery have been raised in the past. Moreover, the introduction of advanced tissue dissection and cauterization instruments might further increase the risk of cell detachment and spread. The results of our study revealed no evidence of cell spread through the gas evacuated from the abdominal cavity during laparoscopy in 29 of the 30-patient cohort. The single exception was a patient with overt, macroscopic extrauterine tumor spread that was encountered during surgery, where atypical epithelial cells were identified in the evacuated gas filter. While the spread of cells in that case might have been due to aerosolization of cells during tissue dissection, we consider that a more plausible explanation would be adherence of tumor cells to the surgical instruments that handled the malignant tissue. These instruments are passed in and out of the trocar port through which gas was evacuated during surgery. Adherent cells could have been suctioned and ultimately captured in our filter.

Our findings highlight several important points. When a solid tumor is confined to its organ, such as early-stage endometrial cancer, limited to the uterus, laparoscopic resection of the uterus seems safe, and the risk of malignant cell aerosolization and spread appears to be remote. Alternatively, when the tumor has extended beyond its anatomical barriers and spread within the peritoneal cavity, tumor cell aerosolization or spread through laparoscopic instruments is possible. This finding could explain why no cells were found in evacuated gas in all but one cases in which macroscopic tumor was found in the pelvis. This finding could also explain the occasional port site metastases that are seen in some patients following laparoscopic surgery, as well as partly explain the differences between the safety of laparoscopic surgery for endometrial cancer and that of cervical cancer. Laparoscopic surgery for endometrial cancer has been proven oncologically safe in prospective randomized trials [9, 10]. In contrast to endometrial cancer, both retrospective data as well as prospective randomized data from the LACC trial show inferior oncological outcome for MIS in cervical cancer [8, 11–13]. The tumor is concealed within the uterus in most cases of endometrial cancer. Intra-operative laparoscopic colpotomy does not breach this anatomical barrier and the tumor is usually not exposed to either peritoneal gas circulation or surgical instruments. Such is not the case with cervical cancer, especially squamous cells carcinomas, where the peritoneal cavity is exposed to the tumor as soon as colpotomy is carried out during laparoscopy, thereby risking tumor spread through gas circulation, surgical instruments or uterine manipulators. Two patients in our study had endometrial cancer with lymph node metastases. Even though the tumor had spread beyond the uterus, it was concealed within lymph vessels and lymph nodes and not exposed to the peritoneal cavity. Similarly, two of the RCC patients had stage 3b disease due to renal vein involvement and, despite the advanced stage, the gas evacuated from their peritoneal cavity was negative for both benign and malignant cells.

Our work has several drawbacks. The limited sample size may prevent generalization of our conclusions. This work was originally planned as a proof of concept study. After our observation that no cells were collected in evacuated gas in all but one case, we decided to halt patient recruitment. Had we found aerosolized cells within evacuated gas in additional cases, recruitment would have continued to refine the understanding of the nature of cell spread during laparoscopy. Even though we had found atypical cells in the evacuated gas in that

single case with macroscopic, peritoneal tumor involvement, the clinical significance of this finding remains unclear for several reasons. Firstly, we were unable to diagnose the exact nature of the scant amount of cells that were identified. Secondly, the tumor had already spread beyond the uterus prior to surgery (it seems unlikely that cell aerosolization, even if it had occurred, would have changed the prognosis of this patient). Finally, even though a small amount of atypical cells were identified in collected fluid, cell spread during surgery does not necessarily mean that detached cells have the biologic ability to attach to any other tissue surface and proliferate.

The strengths of our work includes the novel methodology to collect and filter the evacuated gas circulating during laparoscopic surgery, in an *in-vivo* model that employed the most up-to-date surgical instruments. In order to increase the chances of finding circulating tumor cell in evacuated gas, we enrolled only those endometrial cancer cases that had high-grade histology only. In these cases, extra-uterine tumor spread would be more common. Finally, a second group of patients diagnosed with RCC was also recruited in order to increase the accuracy and generalization of our model.

5. Conclusions

In conclusion, we found no evidence of aerosolization of malignant cells during laparoscopic surgery for both endometrial and renal cell malignancies. While malignant cell spread *via* laparoscopic instruments is conceivably possible in cases of overt, macroscopic preoperative tumor spread, the clinical significance of which is unclear. Future studies are needed to validate the lack of tumor cell aerosolization in the setting of minimally invasive procedures for cervical cancer.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

YT—Involved in project administration, data curation and analysis, writing and reviewing the manuscript. IL—Involved in conceptualization, investigation and supervision. AA and ZA—Involved in data curation and cytological analysis. AB—Involved in methodology, project administration and data curation. LGU—Involved in conceptualization, methodology, supervision and reviewing. DG—Involved in conceptualization, methodology, project administration, investigation, data curation and analysis, supervision, writing—original draft and reviewing. NM—Involved in conceptualization, methodology, project administration, investigation, data analysis, supervision, writing of original draft, reviewing and editing. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was performed in line with the principles of the Declaration of Helsinki and approval was granted by The Tel-Aviv Medical Center Institutional Review Board, approval #0204-20-TLV. Informed consent was obtained from all individual participants included in the study. The authors affirm that all participants provided informed consent for publication.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Dan Grisaru is serving as one of the Editorial Board members of this journal. We declare that Dan Grisaru had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to EH.

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