

# Wound Recurrences Following Laparoscopic-Assisted Colectomy for Cancer

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**Objectives:** To determine the incidence and clinical relevance of wound recurrences (WRs) following laparoscopic-assisted colectomy for cancer; to analyze the most recent experimental studies examining possible pathogenic mechanisms; and to delineate possible prevention strategies.

**Data Sources:** A MEDLINE search was conducted using the words “colectomy,” “laparoscopy,” and “recurrence, local.” Additional articles were retrieved by cross-referencing.

**Study Selection:** All clinical and experimental studies retrieved were reviewed and subjectively selected according to their relevance for clinical practice.

**Data Extraction:** Clinical data from 1990 to 2000 with series analyzing 50 or more patients were preferentially considered. Experimental data were considered based on the most rigorous study designs and the

potential impact of experimental findings on clinical practice.

**Data Synthesis:** The incidence of WRs in large series and based on current techniques is comparable to what has been reported for WR following open colectomy. While the pathogenesis of early WR occurrences remains unclear, experience and appropriate training in laparoscopic-assisted colectomy are essential to minimize the incidence of WRs. Results from experimental studies are still controversial, and available data from prospective randomized clinical trials are still limited.

**Conclusions:** Results from prospective randomized trials are needed to provide definitive answers regarding the incidence and survival impact of WRs. Until then, WR may be considered a technical complication following laparoscopic-assisted colectomy.

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**T**HE ADVENT of laparoscopic cholecystectomy as a standard of care prompted the application of laparoscopic techniques in several surgical fields. Several series indicate that laparoscopic-assisted colectomy (LAC) is safe, technically feasible, and provides several patient-related benefits. Regarding benefits, specific parameters demonstrating advantages include decreased postoperative pain with reduction in narcotic usage, earlier ambulation, faster return to bowel function and oral intake, and earlier hospital dismissal. Potential additional advantages currently under scrutiny include reduction in overall costs and further improvements in the quality of life following hospital discharge.

Most benefits are modest but reproducible and, though not proven in prospective randomized trials, they have incited an increasing application of LAC

for benign conditions. Concerns regarding the oncologic adequacy of the procedure, in particular the reported occurrence of wound recurrences (WRs), have prevented a more widespread acceptance of LAC for cancer. Since the pathogenesis of this WR phenomenon remains obscure, the clinical application of the laparoscopic approach in the treatment of colon cancer remains a matter of controversy.

The following review analyzes LAC clinical experiences for cancer. Furthermore, it examines possible pathogenic factors for WR, describing experimental studies investigating possible mechanisms of WR, their implications for past reports of WRs, and more important, prevention strategies for the future.

Several studies of different size and design have described WR after LAC. The anxiety created by earlier reports has been partially tempered by results from larger series, which have suggested a relatively

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## METHODS

This review is based on articles retrieved through a MEDLINE search using the words “colectomy,” “laparoscopy,” and “recurrence, local.” Additional articles were identified using the references of the original MEDLINE articles. At the completion of the search, all available data on both clinical and experimental studies were reviewed. Only the most significant clinical experiences were considered, and preferentially, series including at least 50 patients were reported. However, important data based on smaller sample sizes were not necessarily discarded; the experimental studies were selected based on sample size, study design, and relevance for clinical practice.

infrequent occurrence of WR. In the meantime, studies on WRs following traditional open colectomy (OC) have indicated that this complication is not exclusive to the laparoscopic approach. However, it is now accepted that only prospective randomized trials can provide definite answers on the incidence and the impact on survival rates of patients with WR and other cancer concerns raised by LAC.

## RESULTS

### EARLY REPORTS

In the early 1990s, several isolated cases of WR following LAC for cancer were reported.<sup>1-8</sup> Data from these case reports were viewed as support for concerns regarding the adequacy of LAC to accomplish oncologically radical procedures. Perhaps the most alarming data were described in 1994 by Berendes et al<sup>9</sup> who reported 3 cases of abdominal wall metastases (21%) in a series of 14 LACs for colon carcinoma. Two aspects of these earlier reports on WR created particular anxiety regarding the applicability of LAC. First, WRs were detected in port sites remote from the incision used for tumor extraction<sup>5,6,9</sup>; second, that WRs occurred following removal of early-stage tumors.<sup>5,9,10</sup> It was therefore postulated that these unusual WR patterns could be attributed to pneumoperitoneum. Unfortunately, a sufficiently large denominator providing data on the actual incidence of WR was rarely reported at that time (**Table 1**).<sup>9,11-29</sup> Most early studies were anecdotal; finally, as experience increased, incidence studies were conducted. The preliminary report from the Laparoscopic Bowel Surgery Registry<sup>30</sup> in 1994 reported 3 cases of WR (1.4%) in patients undergoing 208 LACs in different centers. However, 2 WRs occurred in association with diffuse peritoneal carcinomatosis. Therefore, it was postulated that at least in some cases, WR might occur as a manifestation of a widespread disease rather than being a specific complication derived from the use of laparoscopic technique.<sup>30</sup>

A reappraisal of the incidence of abdominal wall WRs following OC has followed the surge of interest in LAC. Many authors have looked at these data as a standard against which WR should be compared. The incidence of abdominal WRs after OC ranges from 0.9% to 3.3% as given in **Table 2**, according to different diagnostic modalities, intensity of follow-up, and stage of disease.<sup>31-38</sup> Since these WRs are often asymptomatic, it is not surprising that surgical detection and results of autopsy studies reveal an increased rate of WR compared with findings from clinical examination.<sup>39</sup> It is therefore presumed that the real incidence of WR following OC is often underestimated. In addition, more rigorous follow-up probably increases the detection rate of WRs when patients are enrolled in clinical trials. Wound recurrences after OC also occur more frequently in patients with advanced primary disease at their first surgery or in association with peritoneal carcinomatosis. However, there is also evidence that WRs can complicate OC for early-stage tumors. In a series of 1603 patients, Hughes et al<sup>33</sup> reported 16 cases of WR. In 8 of 11 cases in which pathologic specimens were available, the primary tumor had been classified as Dukes stage B. Although this unusual pattern of WR remains unexplained, obviously no role is played by the pneumoperitoneum. It is therefore accepted that WRs, although rare, are not unique to LAC, and they do occur after OC.

### THE CLINICAL OUTCOME OF SURGICAL THERAPY STUDY GROUP

A surgical consortium referred to as the Clinical Outcome of Surgical Therapy Study group, the group performing the National Institutes of Health, Bethesda, Md, trial, has undertaken a retrospective study analyzing LAC performed prior to 1994 to evaluate cancer outcomes.<sup>14</sup> This study was performed in response to the high WR results reported to provide reassurance that it was appropriate to proceed with a large prospective randomized trial comparing LAC with OC in the treatment of right, left, and sigmoid colon cancer. Since one of the basic ethical requirements for the initiation of such a trial is to assume that the 2 treatments under investigation are similar, it was felt to be of paramount importance to assess the incidence of WR along with the oncologic outcomes for cancer patients already exposed to LAC. It was germane to the ethics of proceeding with the larger trial to assess the past WR incidence in patients of the surgeons embarking on the trial.

For 372 patients, the 3-year survival rates were comparable to those reported by large nationwide databases. In particular, only 4 cases (1.1%) of WR were recorded, 1 of which was associated with peritoneal carcinomatosis. The remaining 3 patients were further treated with WR resection and were apparently free of disease at their last follow-up visit. The retrospective design of the study could not allow a precise determination of the impact of WR on survival, for which prospective randomized trials are needed. However, these data suggest that WRs following LAC would not necessarily

**Table 1. Wound Recurrences in Clinical Experiences of Laparoscopic-Assisted Colectomy\***

Author	Year	No. of Patients	Length of Follow-up, Mean (mo)	WR With Other Recurrent Disease, No.	Overall WR, No. (%)
Guillou et al <sup>11</sup>	1993	57	NA	1	1 (1.8)
Berends et al <sup>9</sup>	1994	14	36	1	3 (21.0)
Drouard and Passone-Szerzyzna <sup>12</sup>	1995	507	NA	5	12 (2.4)
Boulez <sup>13</sup>	1996	117	18	0	3 (2.5)
Fleshman et al <sup>14</sup>	1996	372	23	1	4 (1.1)
Franklin et al <sup>15</sup>	1996	191	31-37†	0	0 (0)
Gellman et al <sup>16</sup>	1996	56	16	1	1 (1.8)
Hoffman et al <sup>17</sup>	1996	130	NA	1	1 (0.8)
Lacy et al <sup>18</sup>	1997	106	6‡	0	0 (0)
Larach et al <sup>19</sup>	1997	108	13	0	0 (0)
Vukasin et al <sup>20</sup>	1996	451	12‡	2	5 (1.1)
Fielding et al <sup>21</sup> §	1997	149	NA	2	2 (1.3)
Bouvet et al <sup>22</sup>	1998	91	26	0	0 (0)
Khalili et al <sup>23</sup>	1998	80	20	0	0 (0)
Bohm et al <sup>24</sup>	1999	63	27	0	0 (0)
Leung et al <sup>25</sup>	1999	154	20	1	1 (0.6)
Melotti et al <sup>26</sup> §	1999	163	>36	1	2 (1.2)
Pearlstone et al <sup>27</sup>	1999	93	13	0	0 (0)
Poulin et al <sup>28</sup>	1999	135	24 (9 for stage IV tumor)	0	0 (0)
Schiedeck et al <sup>29</sup> §	2000	399	30	0	1 (0.3)

\*WR indicates wound recurrence; NA, not available.

†Follow-up period was stratified for disease stage and reported as "medium."

‡Minimum follow-up.

§Includes anterior resections and abdominoperineal resections. Mean time of recurrence was 33 months.

||Median follow-up.

**Table 2. Abdominal Wall Recurrences Following Open Resection of Colorectal Cancer With Curative Intent**

Author	Year	Tumor Location	No. of Patients	Mean Length of Follow-up, mo	No. of Recurrences (%)
Gunderson and Sosin <sup>31</sup> *	1974	Rectum	74	6-12	1† (1.4)
Cass et al <sup>32</sup>	1976	Colon and rectum	280	12‡	7 (2.5)
Hughes et al <sup>33</sup>	1983	Colon and rectum	1603	24‡	16 (0.9)
Gunderson et al <sup>34</sup> *	1985	Colon	91	6-12	3 (3.3)
Reilly et al <sup>35</sup>	1996	Colon	1711	46§	26   (1.5)
Lacy et al <sup>36</sup>	1998	Colon	47	21	0 (0)
Milsom et al <sup>37</sup>	1998	Colon	38	20	2 (1.9)
Santoro et al <sup>38</sup>	1999	Colon	43	24-60	1 (2.3)

\*All patients underwent a planned or symptomatic second-look laparotomy approximately 6-12 months after the initial surgery.

†Wound implant as the only site of recurrence. Overall wound implant incidence 4 (5.4%) of 74.

‡Minimum follow-up.

§Median follow-up.

||Includes perineum. The number of documented wound recurrences was 11 (0.6%) of 1711.

portend a dismal prognosis. It was also critical reassurance that it was safe to proceed with the clinical trial.

### RECENT SERIES

Results from large series published in recent years are given in Table 1. The overview of recent series prompts considerations regarding the incidence of WR. First, multiple series confirm that the overall number of WRs often includes cases associated with disseminated peritoneal carcinomatosis or advanced metastatic disease. This is in keeping with what has also been demonstrated for other gastrointestinal malignant neoplasms.<sup>27,40</sup> The correlation between WR and advanced or disseminated disease is not surprising; hence, the clinical importance of

WR in these subsets of patients remains questionable. A second striking result is that the incidence of WR seems to have been variable during the last decade. While earlier, multicenter series typically report WR rates ranging between 1% and 21%, several single-institution experiences described in the last 2 to 3 years suggest that WR probably occurs in fewer than 1% of LAC cases. It is therefore reasonable to presume that the surgeon's experience might contribute to a decrease in the incidence of this complication. A recent multicenter survey conducted in Germany, Switzerland, and Austria on WR after laparoscopy for different neoplasms seems to confirm that limited LAC experience corresponds to an increased risk of WR. Sixteen (3.9%) of 412 patients who underwent laparoscopy for colorectal cancer had docu-

mented port-site and scar WRs. Only 10 of these cases occurred following LAC with curative intent. In addition, the operative specimens were retrieved on 5 occasions without using any protective measures, with the specimen opened to expose the tumor in 1 case. The number of surgeons performing LAC or individual surgeon experience in LAC was not reported. However, the overall number of contributors was 607, which suggests that many of the operating surgeons did not have a lot of experience performing LAC.<sup>41</sup> The discrepancy in individual surgeon outcomes also suggests that proper training and mentoring are essential to reduce the incidence of WR. It is increasingly acknowledged that only prospective randomized trials can provide accurate information on the risk of port-site WRs in clinical practice.

#### AVAILABLE RESULTS FROM PROSPECTIVE RANDOMIZED TRIALS

To our knowledge, there are 3 reported prospective randomized trials examining the incidence of WR following LAC vs OC for cancer. Stage et al<sup>42</sup> have followed up, for a median of 14 months, 18 patients who underwent LAC vs 16 who were treated with standard OC and found no incisional wound or port-site recurrences. Similarly, Lacy et al<sup>36</sup> reported no incisional wound or port-site recurrences after a mean follow-up period of 21 months in a randomized study on 91 segmental resections, 44 of which were performed laparoscopically. In a third randomized comparison, Milsom et al<sup>37</sup> reported 2 cases of abdominal wall WRs associated with widespread disease of 42 patients followed up for a median of 1.7 years after undergoing OC. Conversely, no WRs were found in any of 38 patients treated with LAC after a median follow-up period of 1.5 years. Although the small sample sizes limit the significance of results from these studies, it provides some measure of reassurance that acceptable oncologic results are feasible, and commitments to larger definitive studies should be made.

#### PATHOGENESIS

The pathogenesis of WR remains unclear. While some authors consider the unique conditions created by the pneumoperitoneum as essential for the promotion of WR, others point out the possible similarities between the pathogenesis of WR and that of abdominal wall WRs following OC.

It has been suggested that tumor cells exfoliated at the time of surgery might serve as the origin of tumor cell implantation on wound sites, perhaps for both OC and LAC. Experimental evidence demonstrates that tumor cells exfoliated from colorectal cancer tumors can be viable<sup>43,44</sup>; furthermore, their growth is enhanced at sites of wound healing, including colonic anastomoses and incisional wounds.<sup>45</sup> It has been repeatedly demonstrated that tumor cells can spill into the peritoneum before and during resection of cancerous bowel tumors. The incidence of positive findings for peritoneal tumor cells ranges between 0% and 42% according to the timing of retrieval during surgery (preresection or postresection), the tumor stage, and the sensitivity of the tech-

nique used to detect tumor cells.<sup>46-54</sup> However, there is no evidence suggesting any correlation between the presence of peritoneal tumor cells and the development of WR. Even if viable intra-abdominal exfoliated tumor cells are the source of tumor cell implantation on wound sites when WRs do occur, this alone does not explain why WRs by tumor cell implantation occur in some cases and not in others.

The pathogenesis of WRs is probably multifactorial. Although the possibility of a lymphatic or hematogenous spreading from the primary tumor has been suggested, no experimental or clinical data have substantiated this hypothesis. Alternatively, it has been postulated that carbon dioxide (CO<sub>2</sub>) might chemically stimulate tumor growth, regardless of any contribution deriving from the intra-abdominal pressure. However, there are 2 main theories currently discussed: (1) indirect contamination caused by the pneumoperitoneum vs (2) direct wound contamination via the resected specimen or the surgical instruments used during the procedure.

Indirect contamination might derive from tumor cell dispersion as a result of the pneumoperitoneal gas, a phenomenon referred to as *aerosolization*, or by the formation of tumor droplets. Another possibility is that the pressure effect of the pneumoperitoneum may create a unique distribution of tumor cells. A focused mass of viable tumor cells may be critical to the development of tumors at the sites of cannulas where leaks may occur. No matter the mechanism, it has been emphasized that inadvertent intraoperative desufflation of the pneumoperitoneum or evacuation of the intra-abdominal gas at the completion of the laparoscopic procedure could expose the patient to a particularly increased risk of contamination. These episodes could enhance passage of the pneumoperitoneum gas through the port-site incisions, a mechanism referred to as *chimney effect*.<sup>55</sup> However, it has also been surmised that immunologic alterations caused by the pneumoperitoneum might affect the tumor immune response and create a more favorable environment for tumor growth within trocar wounds.

An alternative explanation might be proposed for tumor cell implantations occurring at the small incision sites used for LAC procedures. Specifically, direct contamination by exfoliated tumor cells might occur during the specimen extraction. Although this mechanism is generally accepted, it does not explain the incidence of port-site WRs in trocar wounds located remote from the extraction site. Alternatively, direct contamination might be caused by tumor cells contaminating the instruments and/or trocars in which tumor cells would be carried to the port-site wounds by tumor manipulation and exchange of the instruments during the laparoscopic procedure. The increased frequency of port-site WRs in the trocars used by the operating surgeon seems to support this theory.

#### EXPERIMENTAL STUDIES

Several animal studies have been conducted in the attempt to experimentally examine the various theo-

**Table 3. Experimental Studies Demonstrating a Favorable Effect (Less Tumor Growth) Following Laparoscopic Procedures\***

Author	Year	Animal Model	Technique of Tumor Establishment	Group Size, Laparoscopic/Open	Procedure(s) Performed	Tumor Assessment
Allendorf et al <sup>56</sup>	1995	Mouse	Dorsal skin inoculation	15/15†	Pneumoperitoneum, sham laparotomy	Tumor presence and weight
Allendorf et al <sup>57</sup>	1995	Mouse	Dorsal skin inoculation	47/48†	Pneumoperitoneum, sham laparotomy	Tumor presence, weight, and volume
Bouvy et al <sup>58</sup>	1996	Rat	Solid tumor introduction	8/8‡	Tumor extraction	Peritoneal tumor size (semiquantitative score)
			Intraperitoneal injection	12/12‡	Pneumoperitoneum, sham laparotomy	
Bouvy et al <sup>59</sup>	1996	Rat	Intraperitoneal injection following procedures	11/11	Small-bowel resection	Peritoneal tumor size (semiquantitative score)
				6/6	Laparoscopy, anesthesia only	
Bouvy et al <sup>60</sup>	1997	Rat	Intraperitoneal injection	13/13	Small-bowel resection	Peritoneal tumor size (semiquantitative score)
			Subcapsular renal implantation	8/8		Subrenal tumor weight
Southall et al <sup>61</sup>	1998	Mouse	Dorsal skin inoculation	119/109	Pneumoperitoneum, sham laparotomy	Tumor weight
Pauwels et al <sup>62</sup>	1999	Rat	Intracolonic enema, colon transection, and reanastomosis	10/10	Pneumoperitoneum, sham laparotomy	Tumor weight and volume
Allendorf et al <sup>63</sup>	1999	Mouse	Dorsal skin inoculation	17/13§	Pneumoperitoneum, sham laparotomy	Tumor weight
Gutt et al <sup>64</sup>	1999	Rat	Transanal injection	11/11	Colonic resection	Peritoneal tumor size (semiquantitative score)
Mutter et al <sup>65</sup>	1999	Rat	Intrapancreatic inoculation	12/12	Observation or tumor manipulation	Tumor weight and volume

\*Control groups are not reported unless otherwise specified. WAG/Rij, Sprague-Dawley, BD IX, and Lewis rats and BALB/c, C57 BL/6, and C3H/He mice were used as experimental models.

†Includes mice injected with different cell lines and preparations.

‡The study also included a third equivalent group undergoing gasless laparoscopy.

§Immunocompetent mice only.

||Each group was further subdivided into tumor manipulation and no tumor manipulation.

ries proposed for the pathogenesis of WR. It is difficult to assess the degree of significance of these studies, since it is unclear how closely the experimental conditions approximate clinical and human conditions. Besides in vitro studies, a variety of animal models have been used. Small animals, such as mice, rats, and hamsters, have been the basis of the models favored by investigators. Less often, large animals such as pigs have been used. While small animals are more readily available to perform larger studies with increased statistical power, large animals more precisely approximate the human setting. A few human experimental studies have also been reported.

### Limitations of Experimental Studies

In this field of investigation, study diversity has been the norm. Perhaps this yields a high degree of informative data, but it renders a summary of common themes and recurring study limitations difficult. Studies differ greatly by study design, animal and tumor cell type used, methods of tumor establishment, tumor dose inocula, number of ports used per animal, pressure and duration of pneumoperitoneum, length of the surgical incision(s), methods used to assess tumor growth or tumor cell implantation on wound sites, and the time between tumor

inoculation and animal sacrifice. It is therefore not surprising that current study results are still controversial regarding the effects of laparoscopy. While some studies suggest a beneficial effect of pneumoperitoneum in reducing tumor growth (**Table 3**), others suggest that pneumoperitoneum favors tumor cell implantation and growth (**Table 4**).<sup>56-73</sup>

Most of the experimental studies examine the impact of specific factors on tumor growth or tumor cell implantation on wound sites. However, all of the variables mentioned hamper the accurate reproduction of the clinical circumstances in experimental settings. Critical variables such as the tumor load and the biologic behavior of tumor cells remain difficult to analyze. For example, different studies using the same hamster model reveal that decreasing tumor inocula can annul differences in tumor cell implantation rates on wound sites following laparoscopy vs laparotomy.<sup>66,71,74</sup> On the other hand, while it is well known that many circulating tumor cells do not metastasize,<sup>75</sup> few studies examine the viability of malignant cells dispersed intraperitoneally and the wound environmental conditions favoring tumor attachment and growth.

An accurate pneumoperitoneal pressure is also difficult to reproduce in the experimental models. While different pressures might affect tumor growth,<sup>76</sup> exces-

**Table 4. Experimental Studies Demonstrating Adverse Effects (Enhanced Tumor Growth) Following Laparoscopic Procedures\***

Author	Year	Animal Model	Technique of Tumor Establishment	Group Size, Laparoscopic/Open	Procedure(s) Performed	Tumor Assessment
Jones et al <sup>66</sup>	1995	Hamster	Intraperitoneal suspension via laparotomy	50/41	Pneumoperitoneum, anesthesia only	Tumor presence at various sites
Mathew et al <sup>67</sup>	1996	Rat	Intraperitoneal injection	12/12	Pneumoperitoneum, sham laparotomy	Tumor size
				6/6	Tumor laceration at laparotomy vs laparoscopy	
Mathew et al <sup>68</sup>	1997	Rat	Intraperitoneal injection	12/12†	Pneumoperitoneum, sham laparotomy	Density of tumor implantation (semiquantitative score)
Jacobi et al <sup>69</sup>	1997	Rat	Intraperitoneal and subcutaneous injection	20/20†	Pneumoperitoneum, sham laparotomy	Tumor weight
Jacobi et al <sup>70</sup>	1997	Rat	Intraperitoneal and subcutaneous injection	25/25†	Pneumoperitoneum, sham laparotomy	Tumor weight
Wu et al <sup>71</sup>	1997	Hamster	Intraperitoneal suspension via laparotomy	62/60	Pneumoperitoneum, anesthesia only	Tumor weight and presence at various sites
Dorrance et al <sup>72</sup>	1999	Rat	Intraperitoneal injection	20/20† 10/10	Pneumoperitoneum, sham laparotomy	Tumor weight and number of nodules
Volz et al <sup>73</sup>	1999	Mouse	Malignant melanoma intraperitoneal injection	36/36	Pneumoperitoneum, anesthesia only	Electronic microscopy examination

\*Control groups not reported unless otherwise specified. Golden Syrian hamsters; BD IX, Fischer, and Dark Agouti rats; and C57 black mice were used as experimental models.

†Additional groups were analyzed for room air pneumoperitoneum, helium pneumoperitoneum, and carbon dioxide pneumoperitoneum followed by laparotomy.

sive pressure may result in a continuous gas leakage through the ports. At least 1 study indicates that the tumor deposit weight at trocar sites where gas leaking was intentionally induced was significantly increased compared with control sites.<sup>77</sup>

### The Role of CO<sub>2</sub>

**In Vitro Studies.** In vitro and in vivo studies have examined changes in tumor growth associated with a CO<sub>2</sub>-rich environment. Although it has been postulated that the CO<sub>2</sub> may promote tumor cell growth, in vitro studies demonstrate no such effect and rather suggest that CO<sub>2</sub> has a toxic effect on tumor cells,<sup>78</sup> at least at 10 mm Hg and 15 mm Hg.<sup>76</sup>

A second postulate considers that CO<sub>2</sub> may promote WR by tumor cell aerosolization. Whelan et al<sup>79</sup> examined aerosols of tumor cell cultures in a high-pressure CO<sub>2</sub> environment undergoing a subsequent 2-week incubation. Tumor growth could not be demonstrated in 124 test dishes analyzing aerosols from 2 different cell lines. When tumor cells underwent rapid desufflation following insertion into a balloon, tumor cell transport through the desufflation gas could be demonstrated only when the balloon surface had been entirely coated with tumor cells before the desufflation actually occurred.<sup>79</sup> Similarly, Thomas et al<sup>80</sup> have not identified any malignant cell in CO<sub>2</sub> exhaust examined using filter systems, although instruments and ports were contaminated. Therefore, no experimental evidence supports that any chemical characteristics of CO<sub>2</sub> might contribute to WR.

**In Vivo Models.** Several models have been investigated. The intraperitoneal injection of a tumor cell suspension

has been reported often and is probably the most easily reproducible. Alternatively, a procedure referred to as *tumor laceration technique*<sup>67</sup> has been used to better approximate the pathophysiology of human colon cancer. In this model, the injection of a tumor cell suspension into the flank of the animal is followed 1 week later by intentional laceration of the resulting tumor from within the abdomen, either via a laparotomy or laparoscopically. More recently, a colon anastomosis carcinoma model has been developed in which transanal injection of tumor cells is followed by colon transection and reanastomosis.<sup>62</sup>

**Human Experimental Studies.** The few experimental human studies conducted have mostly focused on the examination of the pneumoperitoneum gas for the presence of cells, either benign or malignant. Only sporadically has tumor cell implantation been encountered on the camera and port-site wounds at the time of LAC for cancer.<sup>81</sup> On the other hand, benign cells have been demonstrated as aerosolized particles retrievable in the smoke generated during LAC.<sup>82</sup>

When CO<sub>2</sub> effluent was examined in 35 patients, including 20 benign cases and 5 cases of peritoneal carcinomatosis out of 15 noncolorectal malignant neoplasms, malignant cells were found in only 2 patients with peritoneal carcinomatosis, and benign mesothelial cells were encountered in 2 patients with no cases of aerosolized tumor cells identified.<sup>83</sup> Similarly, a small study strictly focused on 12 patients with pancreatic cancer staged with laparoscopy failed to demonstrate any aerosolized cells. No free-floating tumor cells could be demonstrated in the CO<sub>2</sub> despite using several testing techniques. Cells were, however, retrieved on several of the instruments used.<sup>84</sup>

## DIRECT PORT-SITE CONTAMINATION

Although contamination of the wound from specimen extraction is recognized as a possible pathogenic mechanism, most experimental studies have analyzed the effects of tumor manipulation and the contamination of the instruments used during laparoscopic procedures to explain WRs.

### Tumor Manipulation

Studies suggesting a beneficial immune effect of pneumoperitoneum in reducing tumor growth have also attempted to substantiate the direct tumor cell implantation theory as the most important pathogenic mechanism for port-site WRs. Allendorf et al<sup>85</sup> studied a murine model in which tumor cells were inoculated intradermally in the dorsal skin. In this model, the use of pneumoperitoneum decreased tumor establishment and growth compared with laparotomy using different cell lines.<sup>57,61</sup> A rat model in which animals received a single-site intrapancreatic inoculation of tumor cells confirmed the reduction in tumor growth when tumor manipulation was accomplished during laparoscopy with CO<sub>2</sub> pneumoperitoneum vs laparotomy. Conversely, no difference was demonstrated between the 2 techniques when the tumor was not manipulated.<sup>65</sup> The same group of investigators performed a series of studies evaluating a murine model consisting of intrasplenic tumor injection via a left flank incision followed by splenectomy. Abdominal tumor cell implantation was significantly more likely to occur when the established tumor was intentionally crushed with a clamp at the time of splenectomy, regardless of the use of a 20-minute CO<sub>2</sub> pneumoperitoneum following the procedure.<sup>86</sup> When laparoscopic procedures were tested in a subsequent study, splenectomy following laparoscopic mobilization with CO<sub>2</sub> pneumoperitoneum was significantly more likely to result in tumor cell implantation on wound sites than laparotomy.<sup>87</sup> However, using the same model, the incidence of WR after open surgery remained constant, and the incidence of port-site tumor cell implantation decreased significantly in the laparoscopy group as a result of experience and eventually became comparable to the open technique.<sup>88</sup> Overall, results from studies performed using these models suggest that WRs are more likely a consequence of tumor manipulation rather than of CO<sub>2</sub> pneumoperitoneum; furthermore, this difference can be substantially reduced with experience.

### Instrument Contamination—Large Animal Studies

The number of large animal studies has been limited, and to our knowledge, only porcine models have been tested. Porcine models are less practical and provide a smaller sample size compared with rodent models. However, it has been argued that the animal's larger size simulates experimental conditions more similar to humans. Most studies are based on intraperitoneal tumor injection, and no model in which tumor attachment was induced prior to the experimental study has been investigated. Unlike

smaller animal models, data from large animal studies more consistently suggest that the use of pneumoperitoneum is not associated with an increased rate of tumor cell implantation on wound sites.

Allardyce et al<sup>89,90</sup> used a porcine model in which laparoscopic vs OC procedures were performed after the intraperitoneal introduction of suspended <sup>51</sup>chromium-labeled tumor cells. Preferential contamination of the instruments and ports used by the operating surgeon was noted, regardless of the use of pneumoperitoneum or gasless abdominal lifting. When LAC was compared with OC in the same model, more tumor cells were found deposited in open wounds than trocar sites.<sup>91</sup>

Porcine models have also examined the intraperitoneal movement of malignant cells following intraperitoneal injection, analyzing the CO<sub>2</sub> expelled from the peritoneal cavity with a polycarbonate filter system<sup>80,92</sup> or detecting radio-labeled tumor cell movement with a gamma camera.<sup>93</sup> Using both techniques, there was only 1 occurrence of malignant cells identified in 1 filter examining exhaust CO<sub>2</sub>. Conversely, tumor cells were frequently found in washings from laparoscopic ports or on laparoscopic instruments, especially after an extended contact of the trocars with the peritoneum. Importantly, the presence of intraperitoneal blood affected tumor contamination of the trocars and trocar sites.

### IMPACT OF LAPAROSCOPY ON IMMUNE FUNCTION

Experimental studies on immune function and laparoscopy have been conducted to investigate potential alterations in tumor responses that could affect cancer outcomes. As such, observations on experimental tumor cell implantation on wound sites and tumor growth remote from wounds have been examined as a testing of a generalized immune response to tumors rather than focusing specifically on WR.

While some studies reveal a depressed local inflammatory response following laparoscopy,<sup>94,95</sup> others have suggested a direct correlation between the enhanced preservation of immune response and reduction in tumor growth and/or tumor cell implantation following laparoscopy.<sup>96-98</sup> Several investigations demonstrate a better preservation of the delayed-type hypersensitivity response following laparoscopy, suggesting a mediator role for the cell-mediated immune response.<sup>96,99</sup> This result is in accordance with other study results that confirm the effects of laparotomy on creating relative T-cell immune suppression: laparoscopic approaches better preserve T-cell function.<sup>63</sup> Thus, although laparoscopy tends not to generate as much immunosuppression as laparotomy, results from experimental studies examining the contribution of the immune response to WR are still inconclusive.

### PREVENTION

One perceived advantage of using animal models and studies to complement human investigations is the possibility of testing preventive measures. Combining ob-

servations from the human experience with those gleaned from animal studies has allowed opportunities to consider corrective actions.

### Experimental Studies on Preventive Measures

Some experimental studies on laparoscopic surgery have examined the effect of a modified physical environment in reducing tumor growth. The use of heated and humidified CO<sub>2</sub> has significantly reduced trocar contamination in an experimental model.<sup>100</sup> However, there is no further evidence that these modifications might affect tumor cell aerosolization compared with dry CO<sub>2</sub> in humans. Alternative pneumoperitoneal gases have also been tested without any proven advantages. While some experimental models indicate less tumor growth using helium and room air,<sup>101</sup> others demonstrate no difference,<sup>72</sup> and some reveal a decrease in tumor growth using CO<sub>2</sub> rather than air or nitrogen dioxide.<sup>102</sup>

Similarly, some studies demonstrate a reduction in tumor cell implantation on wound sites following gasless laparoscopic technique vs CO<sub>2</sub> pneumoperitoneum,<sup>58,103</sup> while others have offered opposite results.<sup>104</sup> This discrepancy and the proven occurrence of WR following thoracoscopy, which does not require establishment of pneumoperitoneum,<sup>105</sup> have prevented a widespread acceptance of gasless laparoscopy in humans, despite its technical feasibility.<sup>106</sup>

A different approach to reduce tumor cell implantation consists in the use of tumoricidal agents, chemotherapeutics, and disinfectants. Heparin and taurolidine cause maximum inhibition of tumor growth and tumor cell implantation when used simultaneously compared with using single agents in an experimental study.<sup>107</sup> The use of intraperitoneal chemotherapy at the time of LAC or in the early postoperative period has also been suggested.<sup>108</sup> The rationale for this therapeutic approach is that isolated intraperitoneal-spilled tumor cells would be the ideal targets for locoregional chemotherapy, which would be directed at a minimal, local tumor burden prior to the onset of postoperative adhesions.<sup>109</sup> Both modalities are still investigational and not accepted in the clinical setting.

Conversely, investigations on disinfectants more closely reflect daily laparoscopic practices. The intraperitoneal instillation of a povidone-iodine solution in a rat model prevents WR compared with instillation of isotonic sodium chloride solution, methotrexate, aqueous chlorhexidine acetate, and intramuscular injection of methotrexate. Based on their experimental results, Neuhaus et al<sup>110</sup> have recommended routine peritoneal washings with diluted povidone-iodine solution during LAC for cancer. A similar study reveals greater efficacy with 5-fluorouracil vs water, isotonic sodium chloride solution, and heparin.<sup>111</sup> Intraperitoneal sodium hypochlorite also is a poor cytotoxic agent.<sup>72</sup> Other studies have focused on the local treatment of trocar wounds such as the application of povidone-iodine solution or silver sulfadiazine prior to pneumoperitoneum with moderate reduction of the tumor cell implantation rate

in a hamster model.<sup>112</sup> In another study, the more drastic excision of laparoscopic abdominal wound sites significantly reduced the incidence of tumor cell implantation on wound sites.<sup>113</sup> However, the clinical use of the latter measure is impractical and remains unproved.

More importantly, the effect of technical precautions to reduce WR has been recently examined in a porcine model. Nine pigs received an intraperitoneal injection of tumor cells followed by a laparoscopic sigmoid resection with protective measures and were compared with 9 pigs undergoing surgery without any precautions. The systematic adoption of trocar fixation, prevention of gas leak, instrument rinsing, wound protection, and irrigation with betadine prior to closure significantly reduced the incidence of WR.<sup>114</sup> Although several specific modalities deserve further study before clinical use is warranted, experimental studies offer support to several practical measures useful to prevent WR in clinical practice.

### Preventive Measures in Clinical Practice

While experimental studies might herald technical innovations in LAC or disclose the unclear role of the pneumoperitoneum in promoting port-site WRs, it is probably best at present to focus on surgical techniques. Most of the principles are directly derived from the tenets of a correct traditional open colonic resection as they are aimed at preventing tumor rupture and spillage. Every effort should be made to avoid tumor manipulation. The mobilization of the segment to be resected should be accomplished along anatomical bloodless planes when feasible, limiting the potential for the blood to function as a tumor cell reservoir. Meticulous care should be taken when delivering the specimen through the minilaparotomy to avoid any direct contact between the tumor and the wound. The use of wound protection is appropriate in this setting. Although it is still not established whether a gas leakage actually increases the risk of port-site WRs, pneumoperitoneal leaks should be minimized by the appropriate fixation of ports to the abdominal wall. Gas leaks during the procedure should be immediately corrected, and massive leaks should be avoided whenever possible. At the end of the procedure, cannulas should be removed after the pneumoperitoneum has been evacuated through the ports. Some authors also recommend irrigation of instruments and ports before removal and frequent irrigation and suctioning of the peritoneal cavity.<sup>115</sup> At a minimum, trocar and minilaparotomy wounds should be generously irrigated prior to closure. Although we use physiologic saline, others have proposed diluted betadine.<sup>116</sup> The actual impact of these specific measures in the reduction of WR is uncertain. Although there is not uniform agreement on which specific recommendations should be adopted, there is unanimous consensus that oncologic principles must be rigidly followed. Furthermore, experience with benign cases should precede attempts at resection for cancer cases, preferably after a credentialing process, and should be limited to controlled trial evaluations.

## FUTURE ISSUES

It is important to approach LAC for cancer only when adequate clinical experience has been obtained, treating benign cases or cancer cases with palliative intent. Stoma construction or laparoscopic procedures of a lesser magnitude should be approached first, followed by more complex operations. Ideally, one should start LAC under the mentorship of a more experienced surgeon. The ongoing National Institutes of Health–sponsored clinical trial on LAC vs OC requires participating surgeons to submit a video-recorded procedure with demonstration of oncologic techniques and evidence documenting experience with at least 20 LACs (typically benign).

The ongoing National Cancer Institute–sponsored US trial on LAC vs OC for cancer will accrue and follow 1200 patients randomized to either technique.<sup>117</sup> Similar prospective randomized trials are underway in Europe, Australia, and South America.<sup>118</sup> The Colon Cancer Laparoscopic or Open Resection Trial, currently under way in Europe, is also examining the impact of LAC on several immunologic parameters. All of these trials should provide a definitive answer to concerns regarding port-site WRs as well as overall survival data.

Wound recurrences are a known complication of laparoscopic surgery for cancer, including colonic resection. Alarming reports in the early 1990s prompted concern over the feasibility of LAC for cancer, alluding that the incidence might be unacceptably high, contraindicating the acceptance of laparoscopic techniques into routine practice. Results from experimental studies are still controversial and do not effectively address concerns regarding the adequacy of laparoscopic colonic resection. Although recent clinical series suggest that the incidence of WR in clinical practice may be minimal, only large prospective randomized clinical trials can provide definitive answers regarding the actual incidence of WRs and their impact on cancer outcomes. Until such trials are completed, this procedure for cancer must be considered controversial.

## KEY POINTS

## Animal Studies

- Several variables hamper comparisons among experimental studies.
- Small animals are more readily available and allow a larger sample size for study.
- Large animals are less practical but probably better approximate the human setting.
- Results on the contributions of the pneumoperitoneum to wound recurrence are controversial.
- Several studies have supported the role of tumor manipulation and instrument contamination.
- Human experimental studies do not suggest a role for pneumoperitoneum.
- Studies on the relationship between immunologic alterations and wound recurrence are inconclusive.

- Current experimental studies do not resolve concerns regarding wound recurrence.

## Human Studies

- Initial anecdotal case reports created anxiety regarding the oncologic safety of laparoscopic-assisted colectomy.
- Early series suggested an incidence of wound recurrence following laparoscopic-assisted colectomy of 1% to 3% and up to 21% in one series.
- Recent retrospective laparoscopic-assisted colectomy series have generally indicated an incidence of wound recurrence of 0% to 1%.
- The wound recurrence incidence in multicenter studies tends to be higher, probably owing to a learning curve.
- The incidence of clinically detected wound recurrence after open colectomy is approximately 1%.
- Only prospective randomized trials truly provide answers on the incidence and impact of wound recurrence.
- Large prospective randomized trials are under way in several countries.

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