ANNALS OF SURGERY
Vol. 227, No. 2, 242–248

Reduction of Peritoneal Trauma By Using Nonsurgical Gauze Leads to Less Implantation Metastasis of Spilled Tumor Cells

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Objectives
To evaluate whether infliction of peritoneal trauma would promote tumor cell adherence to damaged peritoneal surfaces; to investigate whether peritoneal damage could promote tumor growth of extraperitoneal tumors; and to evaluate whether the amount of trauma correlated with the degree of tumor cell adherence and local and distant tumor growth.

Background Data
After potentially curative resection of colorectal carcinoma, the most common site for recurrence is locoregional. We previously demonstrated that surgical trauma induces a cascade of events leading to adhesion formation. The same mechanisms may be responsible for improved tumor cell adherence and growth facilitation in early local recurrence.

Methods
A reproducible rat model was used in which peritoneal damage was inflicted by standardized rubbing of the peritoneum with surgical gauzes of different texture. In the first experiment, tumor cell adherence and growth at traumatized and nontraumatized peritoneal sites were assessed semiquantitatively 3 weeks after perioperative intra-abdominal injection of CC-531 tumor cells. In the second experiment, the effect of peritoneal trauma on ectopic tumor growth was investigated (CC-531 implanted under the renal capsule). In the final experiment, we evaluated how soon after peritoneal traumatization tumor cell adhesion and growth-promoting factors were active and whether they could be passively transferred to naïve nontraumatized abdominal cavities.

Results
A significant correlation between the amount of peritoneal trauma and the degree of tumor take at damaged peritoneal surfaces was found ($p \leq 0.018$). Tumor take at remote peritoneal sites not directly traumatized was also significantly higher after severe trauma than after moderate trauma of the peritoneum ($p \leq 0.005$). In addition, a significant correlation between the degree of peritoneal trauma and the growth of ectopic tumors under the renal capsule was observed ($p \leq 0.009$). The final experiment demonstrated that

within a few hours after infliction of peritoneal trauma, tumor growth-promoting effects could be passively transferred to naïve recipients.

Conclusions

Surgical trauma is an important factor in the promotion of local recurrence. The enhancing effect of trauma is not restricted to the inflicted site but rather has a generalized character. Avoidance of unnecessary surgical trauma by using gentle techniques and materials is therefore indicated.

Locoregional recurrence of colorectal adenocarcinoma remains an important complication after potentially curative surgical resection. Its incidence varies from 0% to 45%.[1-4] Ways to prevent these locoregional recurrences are the subject of various clinical and experimental studies.[5-9] The most common site for colorectal adenocarcinoma to recur is the site of the primary tumor; the second is the peritoneal surface.[2,6,10,11] The tumor cell entrapment hypothesis might explain this pattern of surgical treatment failure resulting in locoregional recurrence. When a tumor is removed, tumor cells can leak from transected lymphatics into the abdominal cavity.[10] Experimental studies have shown that the proliferative and metastatic potentials of these spilled cells are very well preserved. Consequently, exfoliated carcinoma cells may undergo further division and give rise to implantation of metastases.[12,13] However, implantation of spilled tumor cells on surfaces with intact basement membranes is an inefficient process, whereas implantation on damaged surfaces, resulting from intra-abdominal manipulation, is very efficient.[10,14] The dynamic process of peritoneal healing after ischemic damage of the peritoneal surfaces, sometimes leading to adhesion formation, also seems to be important in the process of adhesion and growth of spilled tumor cells on the peritoneum.[15] In clinical situations, it appears that peritoneal tumor implants may recur within a fibrous adhesion resulting from surgical trauma.[10]

In a rat model, we recently showed that surgical trauma evoked by standard surgical gauze led to marked adhesion formation, which could significantly be reduced by using a nonabrasive textile.[16] The present study was undertaken to evaluate whether the intra-abdominal use of this less traumatic nonsurgical textile would also lead to less intraperitoneal tumor cell adhesion and tumor growth of spilled carcinoma cells. In addition, experiments were performed to evaluate whether the relation between degree of trauma and tumor growth was merely a local phenomenon, or whether systemic effects might also be involved.

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MATERIALS AND METHODS

Animals

Female inbred WAG rats of reproductive age weighing 115 to 170 g (Harlan-CPB, Austerlitz, The Netherlands) were used. They were bred under specific pathogen-free conditions, kept under standard laboratory conditions (temperature 20–24 C, relative humidity 50%–60%, 12 hours light/12 hours dark), and fed with standard rat food and water *ad libitum*. The experimental protocol adhered to rules laid down by the Dutch Animal Experimentation Act and was approved by the Committee on Animal Research of Erasmus University, Rotterdam, The Netherlands. Before performing any new experiments, we made sure that the model used in our adhesion studies,[16] executed on Wistar rats, was also valid in WAG rats.

Gauzes

The gauzes used were surgical Medipres gauze, consisting of 100% cotton, commonly used in abdominal surgery (van Heek Medical, Losser, The Netherlands), and nonsurgical Fastsorb clean-room wiper, used in the electronics industry on abrasion-sensitive surfaces (Berkshire Corp., Great Barrington, MA). Fastsorb is a rayon–polyester blend with strength, softness, and a high absorbing capacity. In previous experiments, we demonstrated that nonsurgical Fastsorb textile was less traumatic for the peritoneum and caused less adhesion formation after intra-abdominal manipulation than surgical Medipres gauze.[16]

Tumor

Tumor CC-531 is a moderately differentiated, weakly immunogenic colonic adenocarcinoma induced in WAG rats by 1,2-dimethylhydrazine.[17] It is transplantable in syngeneic WAG rats. The tumor is maintained as a cell culture in RPMI 1640 medium (Gibco, Paisley, UK) supplemented with 5% fetal calf serum (virus- and *Mycoplasma*-screened), 1% penicillin (5000 U/mL), 1% streptomycin (5000 U/mL), and 1% L-glutamine (200 mM). Before use *in vivo* tumor cells were harvested from stationary cultures by gentle trypsinization (5 minutes, 37

C), centrifugation (5 minutes, 700 g), and resuspension in RPMI 1640, providing cell suspensions with a viability greater than 95%. CC-531 is relatively insensitive to chemotherapy but is sensitive to the effects of biologic response modifiers. To grow solid tumor, 1×10^8 tumor cells were injected into the right flank of a syngeneic WAG rat. After 6 weeks, a tumor mass with a volume of 2.5 cm^3 had grown and could be aseptically isolated from the outer membrane of the main lesion with a scalpel. The harvested tumor was cut into 1-mm^3 cubes (weighing 5.8–7.2 mg) and immersed in a culture solution stored at 4 C. Within 1 to 4 hours after collection of the solid CC-531 tumor, the cubes were implanted subrenally in syngeneic WAG rats.

Operative Procedures

Under ether anesthesia, the abdomen was shaved and cleansed with alcohol 70%. Laparotomy was performed using a lower midline incision of 5 cm. Both horns of the uterus were exposed, rubbed with either severely traumatizing surgical gauze or less traumatizing nonsurgical Fastsorb textile, or not manipulated at all by any gauze. Rubbing took place using a device enabling the application of a constant pressure of 120 g/cm^2.[16] The uterus horn was rubbed 10 times over its total length. Thus, three different peritoneal traumas could be inflicted. After performing one of these 3 procedures, the uterus horn was subsequently sutured to the lateral peritoneum, both proximally and distally, using single Surgilene 6-0 sutures (B Braun, Melsungen AG, Germany). The abdomen was closed in 2 layers with Dexon 5-0 and silk 2-0 sutures (B Braun).

Experimental Design

Effect of Uteral Horn Manipulation on Intraperitoneal Tumor Growth

Ten rats (group I) underwent an operation in which one uteral horn was rubbed with surgical gauze and the other was not manipulated. In 10 rats (group II), one uteral horn was rubbed with nonsurgical textile and the other was not touched. In 9 rats (group III), one uteral horn was rubbed with surgical gauze and the other with nonsurgical textile (Table 1). Directly after manipulation of the peritoneum, and before closing the abdomen, 0.5×10^6 CC-531 tumor cells, in 1 mL RPMI 1640, were injected intraperitoneally (0.5 mL along the left and 0.5 mL along the right abdominal wall). Three weeks after surgery, the rats were killed and intraperitoneal tumor take was scored semiquantitatively at the following sites: subcutaneously (at the site of the operative scar), right uteral horn, left uteral horn, parietal peritoneum, retroperitoneum, kidney, liver, and omentum. The scoring was performed by 2 independent observers and ranged from 0 to 5 per site according to the peritoneal cancer index described by Steller.[18] A score of 0 meant there was no tumor growth, a score of 1 indicated an estimated tumor diameter less than 0.5 cm, a score of 2 a tumor diameter between 0.5 and 1 cm, a score of 3 a tumor diameter between 1 and 2 cm, a score of 4 a tumor diameter between 2 and 3 cm, and a score of 5 a tumor diameter of more than 3 cm.

Table 1. MEDIAN TUMOR TAKE (RANGE) AT UTERUS HORNS SEVERELY TRAUMATIZED BY RUBBING WITH SURGICAL GAUZE (GROUPS I AND III), UTERUS HORNS MILDLY TRAUMATIZED BY RUBBING WITH NONSURGICAL TEXTILE (GROUPS II AND III), AND NOT DIRECTLY TRAUMATIZED UTERUS HORNS (GROUPS I AND II)

Uterus horns	N	Median Tumor Take	Range
I. No touch	10	0.0	0–2
I. Medipres manipulation	10	4.5	3–5
p			0.005
II. No touch	10	0.0	0–2
II. Fastsorb manipulation	10	2.0	0–3
p			0.018
III. Medipres manipulation	9	5.0	4–5
III. Fastsorb manipulation	9	1.0	0–3
p			0.008

N = amount of uterus horns assessed.
Statistics: Wilcoxon matched pairs test.

Effect of Uteral Horn Manipulation on Established Ectopic Tumor Growth

On day 1, 30 rats underwent a laparotomy using a midline incision of 2.5 cm. A solid cube of CC-531 colon tumor weighing about 6 mg was placed under the capsule of both exposed kidneys under microscopic vision. Thereafter, the abdomen was closed in one layer. On day 3, all 30 rats were operated on again. Both uteral horns and 5 cm of the small bowel were rubbed, in 10 rats (group IV) with surgical gauze and in 10 rats (group V) with nonsurgical textile. Group VI (n = 10) underwent a laparotomy only; neither the left nor the right uteral horn nor the small bowel was touched. Ten days after tumor implantation, the rats were killed and the growth of the subcapsular tumors was measured by weighing the 60 enucleated lumps (for each rat, the 2 individual data were averaged; 10 data per group were used for statistical analysis).

Passive Transfer Experiments

To evaluate whether the tumor-promoting effect of surgical trauma of the peritoneum could be passively transferred to naïve nontraumatized rats, the following procedure was employed. Three rats were operated on. Two animals underwent a laparotomy, during which both uteral horns and a 5-cm-long part of the small intestine were rubbed with either surgical gauze (rat 1) or nonsurgical textile (rat 2). Rat 3 had only a laparotomy. The abdomen was closed in one layer. After 5 hours, these rats underwent a second laparotomy, during which the abdominal cavity was rinsed 5 times per rat with 5 mL RPMI 1640. Each time, 1 mL of the injected irrigant was collected.

Subsequently, 15 naïve rats were treated. In 5 rats (group VII), 1 mL of irrigant collected from rat 1 (peritoneal manipulation with surgical gauze) and 0.5×10^6 CC-531 tumor cells in 1 mL RPMI 1640 were injected intraperitoneally along the inner left and right abdominal walls. In 5 rats (group VIII), the same procedure was performed with the irrigants collected from rat 2 (peritoneal manipulation with nonsurgical textile). In the last group (group IX), irrigants collected from rat 3 (no peritoneal manipulation) were used.

To ensure that all fluids were injected intraperitoneally, the drop test was performed. In this test, a drop of saline solution is placed within the open lumen of the injecting needle, from which it should disappear as soon as the needle enters the peritoneal cavity because of its relative negative pressure.

After 3 weeks, the rats were killed and tumor take and growth were scored semiquantitatively at the sites depicted in Table 4.

Statistical Analysis

The median and range of intraperitoneal tumor load and the means and standard deviations of the subrenal tumor weights were calculated. Statistical analysis was performed using the Wilcoxon matched pairs test if two groups were compared and the nonparametric Kruskal-Wallis test if three groups were compared. If the latter overall test indicated significance, comparisons were made using the Mann-Whitney U test. Statistical significance was defined as $p < 0.05$.

RESULTS

Effect of Uteral Horn Manipulation on Intraperitoneal Tumor Growth

Table 1 summarizes the results observed at the site of the uteral horns. In three different experiments, a significant correlation was found between tumor take and the degree of peritoneal trauma imposed by rubbing. Rubbing with severely traumatizing surgical gauze produced the highest tumor take, whereas no rubbing resulted in the lowest (group I; $p = 0.005$). Rubbing with mildly traumatizing nonsurgical textile evoked a low degree of tumor take, but it was still significantly more than when no rubbing had taken place (group II; $p = 0.018$). At the site of the uteral horns, the tumors were often located in adhesions. Table 2 shows the tumor take at the nonmanip-

Table 2. MEDIAN TUMOR TAKE (RANGE) AT DIFFERENT NOT DIRECTLY TRAUMATIZED PERITONEAL SITES IN RATS HAVING BEEN INTRA-ABDOMINALLY MANIPULATED BY SEVERELY TRAUMATIZING SURGICAL GAUZE (GROUP I), MILDLY TRAUMATIZING NONSURGICAL TEXTILE (GROUP II), OR A COMBINATION OF BOTH MATERIALS (GROUP III)

	Median Tumor Take			
Site	I Medipres (n = 10)	II Fastsorb (n = 10)	III Medipres and Fastsorb (n = 10)	Significance
Subcutis	0 (1–3)	2 (0–3)	1 (0–4)	–
Parietal peritoneum	0 (0–2)	0 (0–1)	0 (0–1)	–
Kidney	1 (0–2)	1 (0–2)	1 (0–2)	–
Liver	2 (0–3)	1 (0–2)	2 (1–3)	–
Retroperitoneum	2 (1–3)	1 (0–2)	2 (1–3)	+
Omentum	2 (0–3)	1 (0–1)	2 (2–4)	+
Total	1.5 (0–3)	1 (0–3)	1.5 (0–4)	+

N = amount of treated rats.
Statistics: Kruskal-Wallis test, with a Mann-Whitney U post hoc test (retroperitoneum I *vs.* II: $p = 0.007$; I *vs.* III: $p = 0.84$; II *vs.* III: $p = 0.01$; omentum I *vs.* II: $p = 0.01$; I *vs.* III: $p = 0.16$; II *vs.* III: $p < 0.0001$; total tumor take I *vs.* II: $p = 0.005$; I *vs.* III: $p = 0.31$; II *vs.* III: $p = 0.001$).

Table 3. MEAN TUMOR WEIGHT (STANDARD DEVIATION) OF THE SUBRENAL TUMORS AFTER INTRA-ABDOMINAL RUBBING WITH SEVERELY TRAUMATIZING SURGICAL GAUZE (GROUP IV), WITH MILDLY TRAUMATIZING NONSURGICAL TEXTILE (GROUP V), OR AFTER NO RUBBING OF THE PERITONEUM AT ALL (GROUP VI)

Mean Tumor Weight (mg)			
IV Medipres (n = 10)	V Fastsorb (n = 10)	VI No Touch (n = 10)	Significance
34.14 (7.2)	28.01 (6.5)	17.80 (6.1)	†

N = amount of operated rats, per rat the mean of two subrenal tumors were assessed and used for analysis.
Statistics: Kruskal-Wallis test, with a Mann-Whitney post-hoc test (IV *vs.* V: $p = 0.009$; V *vs.* VI: $p < 0.0001$; IV *vs.* VI: $p = 0.002$).

ulated remote peritoneal sites in groups I, II, and III. It shows significant differences in tumor take at 2 abdominal sites (the retroperitoneum [$p \leq 0.01$] and the omentum [$p \leq 0.01$]) between group II (nonsurgical textile) and groups I and III (surgical gauze). A significant difference in total tumor take between the same groups (II *vs.* I and II *vs.* III) was found ($p \leq 0.005$). Differences in tumor take at the other three peritoneal sites were not significant.

Effect of Uteral Horn Manipulation on Established Ectopic Tumor Growth

The mean weight of the subrenal tumors was measured 10 days after tumor implantation, 7 days after manipulation with surgical gauze and nonsurgical textile. Significant differences in mean tumor weight between the 3 groups were found (Table 3). Again, a significant correlation between the degree of peritoneal trauma and tumor growth was observed: the mean weight of the ectopic tumor was the highest in rats rubbed with surgical gauze (IV) and significantly lower in rats rubbed with nonsurgical textile (V) ($p = 0.009$). When the peritoneum was not touched (VI), the lowest mean tumor weight was found, significantly lower than after rubbing with nonsurgical textile ($p = 0.002$) or surgical gauze ($p < 0.0001$).

Passive Transfer Experiments

The median total peritoneal tumor take in rats injected with irrigants collected from abdominal cavities, manipulated with surgical gauze or nonsurgical textile or not, differed significantly from each other (see Table 4; $p \leq 0.016$). These differences were mainly due to differences at the site of the omentum and the kidney. As in the previous experiments, a decreasing gradient of tumor take was found, from surgical (VII) to nonsurgical (VIII) to nontraumatized abdominal cavities (IX).

DISCUSSION

Experimental and clinical studies suggest that surgical trauma promotes tumor cell adherence and tumor growth.[15,19–22] The mechanism by which surgical trauma promotes these processes is not completely understood but is probably multifactorial, because tumor cell adherence as well as local and regional tumor growth can be enhanced. It seems that trauma leads to a process producing locally and regionally active tumor-promoting agents.[15,19] We recently demonstrated that surgical Medipres gauze was more traumatizing to the peritoneum than nonsurgical Fastsorb textile, leading to significantly more adhesion formation.[16] Our current data suggest that the factors responsible for the formation of postsurgical adhesions also play a role in the adhesion and growth of tumor cells at the peritoneum. The most impressive tumor growth was observed at sites where abrasion of the mesothelium was most severe. The degree of tumor growth at traumatized sites was highly correlated with the degree of trauma: abrasion with surgical gauze produced the highest tumor take, whereas untouched peritoneum showed the lowest tumor burden, and surfaces traumatized by nonsurgical textile presented intermediate tumor growth. The finding that traumatized surfaces are privileged sites for tumor cells has been demonstrated before.[15,23,24]

It is conceivable that the process of enhanced tumor growth in traumatized tissue is biphasic. First, trauma of the peritoneum and the ensuing inflammatory response leads to upregulation of adhesion molecules, thus promoting the anchoring of tumor cells. Second, the subsequent healing of the peritoneum leads to growth promotion of the adhered tumor cells through the action of locally produced growth factors.

Using the same tumor model as in the present study, we recently demonstrated that the phenomenon of enhanced tumor growth as it relates to trauma and healing also occurs in other experimental settings. It was found that laparoscopic removal of a bowel segment led to less adherence of intraperitoneal tumor cells than when conventional surgery was performed, again indicating that the degree of surgical trauma was proportional to the extent of tumor growth.[22] In addition, we observed that the growth of a regenerating liver after partial hepatectomy led to a marked propagation of intrahepatic tumor growth.[25,26]

Interestingly, our present results indicate that the sequelae of peritoneal trauma with regard to tumor growth

Table 4. MEDIAN TUMOR TAKE (RANGE) AT DIFFERENT PERITONEAL SITES IN RATS INTRA-ABDOMINALLY INJECTED WITH IRRIGANT OBTAINED FROM RATS THAT UNDERWENT RUBBING OF THEIR PERITONEUM WITH SEVERELY TRAUMATIZING SURGICAL GAUZE (GROUP VII), MILDLY TRAUMATIZING NONSURGICAL TEXTILE (GROUP VIII), OR NO RUBBING AT ALL (GROUP IX)

Site	Median Tumor Take			Significance
	VII Medipres (n = 5)	VIII Fastsorb (n = 5)	IX No Touch (n = 5)	
Uterus A	0	0	0	–
Uterus B	0	0	0	–
Subcutis	0	0	0	–
Parietal peritoneum	0	0	0	–
Kidney	2 (0–3)	1 (0–2)	0	+
Liver	2 (1–3)	1 (0–2)	0 (0–2)	–
Retroperitoneum	1 (0–3)	1 (0–2)	1 (0–2)	–
Omentum	3 (2–5)	1 (0–3)	0 (0–2)	+
Total	0 (0–5)	0 (0–3)	0 (0–2)	+

Statistics: Kruskal-Wallis test, with a Mann-Whitney U post hoc test (kidney VII *vs.* VIII: p = 0.22; VII *vs.* IX: p = 0.031; VIII *vs.* IX: p = 0.032; omentum VII *vs.* VIII: p = 0.032; VII *vs.* IX: p = 0.008; VIII *vs.* IX: p = 0.31; total tumor take VII *vs.* VIII: p = 0.016; VII *vs.* IX: p = 0.008; VIII *vs.* IX: p = 0.0015).

are not confined to the inflicted site itself, but appear to have a generalized character. We showed that trauma led to more tumor at the traumatized site and also at nontraumatized peritoneum. Again, the amount of tumor at these locoregional sites correlated with the severity of the inflicted trauma. This clear correlation was also found in the experiment in which we studied the effect of peritoneal trauma on tumor growth under the renal capsule. Even in this ectopic tumor model, the consequences of the intra-abdominal trauma were demonstrable. Because promotion of adherence was irrelevant in this model, this experiment also revealed that trauma could evoke enhancement of the growth of an established tumor. Gutman et al.[27] made comparable observations, finding that a regenerating liver induced enhanced tumor growth not only in the liver but also at distant sites.

Our final experiment, in which we demonstrated that within a few hours after infliction of peritoneal trauma, the effects on tumor growth could be passively transferred to naïve recipients, supports the notion that trauma *per se* has a marked effect, most likely on tumor cell adherence.

Taken together, the current experiments suggest that both tumor cell adherence and tumor growth are modified by surgical trauma. It is clear that the present model provides unique possibilities to unravel further the similarities and differences between the processes of adhesion formation and tumor cell adhesion and tumor growth. Variables such as kinetics of adhesion molecule expression with regard to inflammatory cytokines and growth factors and the role of mesothelial hyaluronic acid and CD44 are currently being investigated. These studies may lead to sophisticated tools to prevent the unwanted side effects of surgery. On the other hand, the present study clearly indicates that these unwanted side effects already can partly be omitted by the use of delicate surgery and nonabrasive gauze material.

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