Excisional surgery for cancer cure: therapy at a cost

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Excisional surgery is one of the primary treatment modalities for cancer. Minimal residual disease (MRD) is the occult neoplastic disease that remains in situ after curative surgery. There is increasing evidence that tumour removal alters the growth of MRD, leading to perioperative tumour growth. Because neoplasia is a systemic disease, this phenomenon may be relevant to all patients undergoing surgery for cancer. In this review we discuss the published work that addresses the effects of tumour removal on subsequent tumour growth and the mechanisms by which tumour excision may alter residual tumour growth. In addition, we describe therapeutic approaches that may protect patients against any oncologically adverse effects of tumour removal. On the basis of the evidence presented, we propose a novel therapeutic paradigm; that the postoperative period represents a window of opportunity during which the patient may be further protected against the oncological effects of tumour removal.

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"Does surgery accelerate or disseminate cancer cells?"
Michael Baum 1996[1]

Surgical excision is the mainstay treatment of solid tumours. Minimal residual disease (MRD) is the occult tumour that remains in situ after curative resection[2] in microscopic deposits in clearance margins and in micrometastases (stromal or haematogenous). There is increasing evidence that tumour excision may, in fact, adversely alter the natural history of MRD (figure 1).[1,3–6] This hypothesis led Baum and others to question the potential interaction between the process of tumour removal and the subsequent growth of MRD.[7] They suggest that cancer exists in a state of chaos that is further perturbed by the process of tumour removal. One of the effects of tumour removal is a disinhibition of angiogenesis during the postoperative period.[7] Such effects may account for the disappointingly modest survival benefits inherent in excisional surgery when used as a single treatment modality.

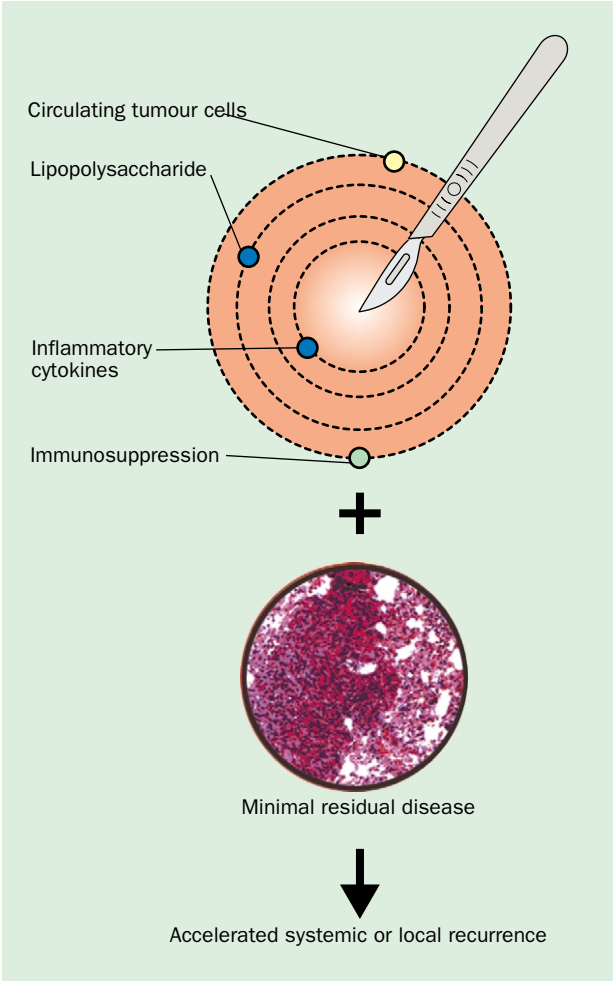

Figure 1. Some of the effects of tumour removal on subsequent recurrent tumour growth. These effects include factors that disseminate minimal residual disease (MRD, yellow dot) ,factors that facilitate MRD expansion in vivo (green dot), and factors that may accelerate MRD by altering neoplastic properties (blue dot). Although removal of a tumour produces multiple effects, the combination of any, or all, of these factors promote MRD leading to accelerated local and systemic recurrence.

Tumour removal adversely alters residual neoplastic disease

Clinical evidence

To definitively characterise the oncological effects of tumour excision, studies comparing outcome after expectant management with that after surgical management should be evaluated. However, because solid neoplasms have long been regarded as treatable diseases, there is a lack of such comparative studies.[6] We identified two studies comparing

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Table 1: Tumour removal adversely alters residual neoplastic disease: clinical evidence

Study	No of patients	Tumour type	Outcome	Ref
Prospective cohort study	1173	Mammary adenocarcinoma	Early first peak in hazard rate for death after mastectomy	6
Randomised controlled trial	111	Prostatic adenocarcinoma	No benefit in survival after radical prostatectomy for late-stage disease	8
Prospective cohort study	1547	Mammary adenocarcinoma	Early first peak in hazard rate for death after mastectomy	10
Retrospective cohort study	8	Testicular carcinoma	Accelerated tumour regrowth after cytoreductive surgery	11
Retrospective cohort Study	197	NSCLC	Models of recurrence generated from observed patterns of rapid recurrence—escape from dormancy after resection	18
Retrospective cohort study	120	NSCLC	Rapid local recurrence within 6 months in 13 patients	19
Prospective randomised controlled trial	219	Colorectal adenocarcinoma	Survival outcome after laparoscopic-assisted colectomy is better than after open colectomy	22
Prospective randomised controlled trial	507	Mammary adenocarcinoma	Survival improved with immediate postoperative chemotherapy	26
Prospective randomised controlled trial	2795	Mammary adenocarcinoma	Improved survival after one course of perioperative chemotherapy in early breast cancer	29
Prospective cohort study	1175	Mammary adenocarcinoma	Worse prognosis for patients operated on during follicular phase of menstrual cycle	60

NSCLC, non-small-cell lung cancer.

long-term outcome after surgery with expectant treatment.[6,8] Iversen and colleagues found no survival benefit with radical prostatectomy over expectant management, for adenocarcinoma of the prostate.[8] This randomised study followed 111 patients for 23 years. Demicheli and colleagues examined the death-specific hazard rates in patients with breast cancer.[6] They compared these parameters in patients that underwent mastectomy alone with those of an accepted historical database of untreated patients. In patients managed expectantly they showed a single peak around the fourth and fifth years in the hazard rate for death.[9] By contrast, a two peak pattern was observed in patients who underwent mastectomy. The first peak occurred at the earlier point of the third and fourth years after surgery followed by a second peak at the eighth year. Similar patterns of recurrence and cancer-related mortality after mastectomy were observed by other investigators.[10] These findings strongly indicate that the natural history of breast cancer is in some way adversely altered by tumour removal. A selection of clinical trials that point to the phenomenon of altered residual tumour growth after primary tumour removal is summarised in table 1.

It has not been possible to definitively show that tumour removal alters the growth properties of MRD so we must rely on anecdotal evidence to evaluate the relation between excisional surgery and subsequent changes in MRD. Lange reported a study of eight patients who underwent cytoreductive surgery for testicular cancer.[11] In each patient, tumour cytoreduction led to the accelerated growth of residual disease.[11] Similar findings led Moore and others to urge caution with respect to cytoreductive surgery.[12,13] There is increasing experimental evidence that tumour cytoreduction leads to the rapid acceleration of residual neoplastic disease. We have recently shown accelerated recurrent tumour growth after total or subtotal xenograft excision in various solid tumour cell lines.[14] The effects of tumour excision are not confined to local recurrence. Several studies have shown increased metastatic growth after primary tumour removal.[15] These studies are substantiated by a large body of experimental data showing increased metastasis after surgery.[16,17] Mitsudomi and colleagues examined the pattern of recurrence of lung cancer after primary tumour excision.[18] They developed a kinetic model of recurrence that was primarily based on the accelerated growth of dormant metastases after excisional surgery. Demicheli and colleagues examined the rates of local and systemic recurrence after mastectomy and developed a similar model, again based on the acceleration of dormant neoplastic disease.[5] Maniwa and co-workers examined the pattern of pulmonary metastatic recurrence after curative metastasis resection.[19] In their series, all patients had primary tumours excised several months before undergoing pulmonary metastasectomy. They identified a cohort of patients (n=27) who, after apparently curative surgery, rapidly developed metastatic recurrence. Indeed, 13 of the 27 patients developed recurrence within 6 months of apparently curative metastasectomy. Reports are accumulating that indicate that relatively minor surgical processes such as wound biopsy or gamma knife irradiation are associated with tumour progression.[20,21] Clinical reports such as these provide further evidence that the process of tumour removal adversely alters MRD, locally and systemically.

The surgical techniques by which tumours are removed have recently been shown to influence outcome when this is evaluated in terms of disease-free interval and time to recurrence. Lacy and colleagues recently showed that open resection of colorectal cancer was associated with shorter disease-free interval and time to recurrence compared with laparoscopic resection.[22] Extensive experimental data corroborates these findings that laparoscopy and laparotomy differentially alter the natural history of tumour growth.[23–25] The finding that different surgical approaches influence oncological outcome is strong evidence that tumour removal, and the

techniques by which this is achieved, differentially influence the subsequent growth of residual neoplastic disease.

Further evidence that tumour excision may alter tumour growth comes from studies examining outcome after perioperative chemotherapy with that after conventional chemotherapy. Nissen-Meyer and colleagues compared the effects of single-dose perioperative cyclophosphamide with the same regimen given 3 weeks after surgery.[26] This was a randomised prospective trial of 507 patients with breast cancer over 10 years. Recurrence and death rates were significantly lower in patients who received perioperative cyclophosphamide ($p<0·001$ and $p<0·01$, respectively).[25] The differential benefits of perioperative chemotherapy, in terms of recurrence rates, increased to a peak difference of 10·7% at 4 years. However, a large trial that also evaluated the potential benefits of postoperative cyclophosphamide failed to show any differences.[27] Interestingly, an overview analysis showed a significant increase ($p<0·001$) in time to first event in patients who received postoperative cyclophosphamide.[28] Similar findings to those of Nissen-Meyer, with respect to perioperative chemotherapy, have been reported by others indicating that perioperative chemotherapy may benefit patients in a way yet to be characterised.[29,30] The potential beneficial effects of perioperative chemotherapy indicate that factors present during surgery alter the subsequent growth of residual neoplastic disease. Moreover, perioperative chemotherapy may protect against these factors.[26,29,30]

It is particularly interesting that the benefits of perioperative chemotherapy, in terms of rates of recurrence, reached a maximum after 4 years.[26] This figure is almost synchronous with the additional peak in the hazard rate for death described by Demicheli.[6] If we assume that surgery does alter tumour growth in an adverse manner, according to the Demicheli model this effect is greatest 4 years after mastectomy. If perioperative chemotherapy were to protect against the oncological effects of tumour removal one could predict that this benefit would be greatest after 4 years. According to the findings of Nissen-Meyer this seems to be the case when perioperative chemotherapy is given to patients undergoing mastectomy. Thus, it is feasible that the benefits of perioperative chemotherapy relate to the attenuation of the effects of tumour excision on MRD.

Experimental evidence

> "Dormancy of micrometastases: balanced proliferation and apoptosis in the presence of angiogenesis suppression"
> Holmgren and colleagues 1995.[61]

A selection of experimental trials that point to the phenomenon of altered residual tumour growth after removal of primary tumour is summarised in table 2. Several investigators have used experimental systems to show increased metastatic growth after surgical procedures such as laparotomy, laparoscopy, and primary tumour removal.[14–17,22–25,31–36] Li and colleagues showed increased primary and metastatic tumour growth after tumour excision.[34] They indicate that this relates to reduced concentrations of circulating angiostatin. With similar models, we and other investigators have shown that pulmonary metastatic tumour burden is increased after laparotomy compared with anaesthetised controls.[16,17] Some researchers suggest that primary tumour excision is a prerequisite for this effect. Investigators have shown increased recurrent tumour growth after partial tumour excision in rats and mice.[37] Near total (or total) mouse xenograft excision can be followed by local recurrences that rapidly exceed the initial tumour in volume.[14] This effect is mirrored by accelerated local recurrence and early patient mortality after cytoreductive surgery.[11] Survival after removal of the primary tumour is reduced when tumours exceed a certain volume.[35] Hence, there is extensive experimental evidence that points to the acceleration of local and systemic recurrence after tumour excision.

Much of the experimental evidence that excisional surgery alters residual tumour growth comes from studies that focus on the differential effects of laparoscopy and laparotomy.[36,38,39] Dacosta showed in mice that laparoscopy increased extraperitoneal tumour growth relative to anaesthesia-only controls and that this increase correlated with impaired cellular immunity.[23] In addition, the cancer-spreading effects of laparotomy seem to be greater in

Table 2. Tumour removal adversely alters residual neoplastic disease: experimental evidence

Study type	Animal	Tumour type	Outcome	Ref
In vivo, blinded	BALB/c	4T1 mammary adenocarcinoma	Accelerated metastasis growth after laparotomy	16
In vivo trial of laparoscopy and laparotomy	C57BL/6	B16 murine melanoma/ YAC1 lymphoma	Increased flank tumour growth and greater immunological impairment after laparotomy	24
In vivo	C57BL/6	3LL Lewis lung	Tumour resection accelerates the growth of other tumours	34
In vivo	Nude	LS174T human colorectal adenocarcinoma	Accelerated local tumour re-growth after cytoreductive surgery	35
In vivo trial	C57BL/6	3LL Lewis lung	Reduced life-expectancy after tumour removal	36
In vivo trial of laparoscopy and laparotomy	BALB/c	B16 murine melanoma/ Colon-26	Accelerated xenograft growth after laparotomy compared with laparoscopy	37
In vivo study	..	Mouse carcinoma	Increased localisation of metastases to points of injury	40
In vivo study	Lister rat	MC28 sarcoma/OES5 mammary adenocarcinoma	Increased growth of tumour cells at colonic anastomoses	42
In vivo trial	Nude	C6 glioma spheroids	Stimulated wound growth by wound-derived growth factors	44

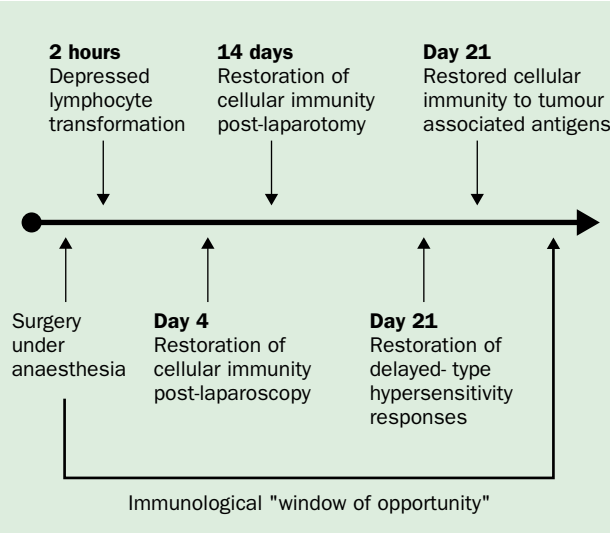

Figure 2: The immunological events after cancer surgeryunder general anaesthesia. Most parameters have been restored by the fourth week after surgery. The first three weeks are characterised by altered parameters that indicate an immunological window of opportunity for minimal residual disease. This may also represent a therapeutic window of opportunity during which patients may be further protected against accelerations in tumour growth.

magnitude than those of laparoscopy.[23–25,36,38,39] There is increasing experimental data showing accelerated extraperitoneal and intraperitoneal tumour growth after laparotomy and laparoscopy. These experimental data provide strong support for the recent clinical findings of Lacy and colleagues that the technique by which a tumour is removed influences outcome.[22] Hence, evidence is accumulating that shows that surgical techniques adversely influence subsequent tumour recurrence and that the oncological effects of laparotomy-based procedures may be greater in magnitude than laparoscopy-based procedures.[22–25,36,38,39]

It is well established that neoplastic cells have an affinity with sites of tissue trauma. As early as the turn of the 20th Century, Rous and Tyzzer began to question the preferential feeding of neoplastic cells in wound sites of various organs.[40,41] Subsequently, several investigators showed that neoplastic cells preferentially grow in areas of trauma. Skipper and colleagues reported the same phenomenon in colonic anastomoses and laparotomy wound sites.[42] Similar patterns have been reported by other investigators who propose a role for wound-related growth factors.[43,44] Tissue trauma is an unavoidable facet of surgery. Oncological surgery frequently requires major procedures that necessitate extensive dissection and organ removal. Hence the surgical process, as it crucially depends on wound formation, may be said to be inherently tumorigenic.

Wounds represent an environment that favours tumour growth.[40–42,44] This experimental finding is mirrored by the similar incidence of port-site and laparotomy metastases, in the clinical setting.[45] Although the factors responsible for the affinity of neoplastic cells to sites of tissue trauma are unknown, there is strong evidence that inflammation itself is protumorigenic.[46–48] More than a century ago, Virchow proposed that a complementary relationship existed for neoplastic and inflammatory processes.[46] This concept was further developed by Dvorak who described tumours as wounds that failed to heal.[47] Other studies have shown the inherent tumorigenicity of proinflammatory mediators such as interleukin 6 and tumour necrosis factor α (TNFα).[48] Thus, there are strong theoretical links between tissue trauma, wound formation, inflammation, and subsequent tumour growth.[40, 42–50]

Mechanisms for changes in tumour growth after surgery

Several mechanisms have been proposed by which surgery may alter the subsequent growth of MRD. These may be broadly classified as mechanisms that disseminate, facilitate, or accelerate expansion of tumour cells after removal of the primary tumour. The combination of any, or all, of these is also possible (figure 1). We propose that, according to this definition, four hypotheses may explain altered growth of MRD after tumour removal. First, tumour manipulation leads to the dissemination of tumour cells, eg, circulating tumour cells. These may contribute to MRD by adding to overall tumour burden. Second, the effects of surgical intervention generate a window of opportunity during which the patient is more susceptible to tumorigenesis. During this phase of wound healing, postoperative immunosuppression may facilitate MRD expansion by promoting immune escape. Third, tumour removal may alter biological properties of neoplastic cells and lead to increased cellular proliferation and reduced cell death. These circumstances would offer increased opportunity for tumorigenicity and thereby accelerate MRD expansion. The fourth hypothesis is that a combination of any of these mechanisms may be involved. For example, circulting tumour cells disseminated during surgery may be more tumorigenic because of mutations arising from genetic instability. In addition, the window of opportunity created after surgery may facilitate their escape from immunity thereby permitting MRD expansion.

Dissemination of tumour cells

Tumour cells may be inadvertently spread by several mechanisms during surgical procedures.[49,50] These include the grasping of lymph nodes with forceps, the local injection of analgesic agents, and the insertion of an arterial clip into the tumour to control bleeding.[50] Furthermore, intraoperative tumour manipulation may promote metastatic embolisation. Port and wound–site recurrences are a major concern after laparoscopic procedures. Contamination of port and instrument sites, increased cellular exfoliation, and trapping of intraperitoneal tumour cells may cause metastases to arise after laparoscopy.[45,51] Each of these suggestions may explain how the process of tumour removal is associated with the inadvertent dissemination of viable neoplastic cells that in turn contribute to recurrent tumour growth.

Circulating tumour cells are a souce of haematological dissemination. Despite intensive investigation, the tumorigenic significance of circulating tumour cells is undefined. Although most patients have circulating tumour

cells before surgery, most patients do not develop recurrence.[52] By use of RT-PCR-based detection techniques, several investigators have repeatedly shown that the presence of circulating tumour cells after surgery is not commensurate with overall survival. The low viability of such cells (<0·01%) may explain the lack of correlation between number of cells and disease outcome when evaluated in terms of survival and metastatic recurrence.[53,54] However, increased dissemination of circulating tumour cells during surgery does not adequately explain the findings of Maniwa.[19] These authors described the recurrence of overt pulmonary metastases within 6 months of curative metastatic resection. In their studies, primary tumours had been excised before metastasectomy. Resection of all lesions identified was guided by preoperative imaging and intraoperative palpation. Nevertheless, 27 patients developed metastatic recurrences after apparently curative metastasis excision, and 13 of these patients developed recurrence within 6 months. These authors suggest that such recurrences were unlikely to be due to intraoperative dissemination of tumour cells. Although it is possible that circulating tumour cells arose from the metastases excised, such cells would have had to develop at an accelerated rate to generate overt metastases in such a short time. The functional significance of cells disseminated during tumour removal, and in particular, their relation to alterations in MRD growth, are not yet clear.[19,52–54]

An immunological window of opportunity

The second mechanism whereby tumour excision may alter subsequent tumour growth is that surgery generates an immunological window of opportunity during which the patient may be more susceptible to tumorigenesis. During postoperative immunosuppression the host environment may promote immune escape and thereby facilitate MRD expansion. Historically, primary tumour excision was regarded as immunologically beneficial as it restored antitumour immune responses by abolishing tumour-dependent immunosuppression.[55,56] However, there is accumulating evidence to support a causative role for the immune response in the potentiation of MRD after tumour removal.

Immunosuppression is a feature of the postoperative stress response and is associated with anaesthesia, blood transfusion, and the release of acute-phase proteins.[57] Natural killer (NK) and lymphocyte activated killer (LAK) cells form an integral component in immune antitumour surveillance. Experimental and clinical data show that antitumoral activities of NK and LAK cells are reduced immediately after surgery.[23,24] This reduction is greater after laparotomy than after laparoscopy.[23,24] Antitumour activities of NK and LAK cells are also impaired after surgery for breast and oesophageal cancers. Activity of NK cells is already impaired in patients with an underlying malignant disease so the additive effects of surgery may be sufficient to improve the ability of circulating cancer cells or stromal tumour cells to evade the immune response long enough for metastases to develop. Additional changes in cellular immunity occur after tumour removal. Concentrations of dendritic cells increase transiently but then decrease significantly on the second day after surgery.[58] Similarly, cell-mediated immunity is markedly altered with prominent Th2 polarisation during the postoperative period.[59] Also of note, activity of NK cells changes during the course of the menstrual cycle. This difference may explain the earlier pattern of disease recurrence in premenopausal women who undergo excisional surgery during the follicular phase of the menstrual cycle.[60] Overall, these findings point to a critical role for NK antitumour surveillance during the postoperative period. However, the oncological significance of postoperative changes in activities and numbers of NK, LAK, and dendritic cells are yet to be confirmed definitively.

The suppressive immunological changes that follow surgical stress occur along a temporal pattern (figure 2). Depression of lymphocyte transformation is detectable 2 h after induction of anaesthesia and is generally restored to normal after 1 week.[57] Depression of cellular immunity to tumour-associated antigen and depression of delayed-type hypersensitivity, are present for up to 3 weeks after surgery. The immunosuppressive effects of laparoscopy and laparotomy last up to 4 and 14 days, respectively.[23,24] Total concentrations of dendritic cells are lowest during the third day after surgery.[58] A peak in immunosupression is said to occur at day three. Hence, it can be suggested that the early postoperative period represents an immunological window of opportunity during which the extracellular millieu may be increasingly permissive to MRD growth and spread.

Accelerated residual tumour growth

Altered neoplastic properties within residual cancer cells

The process of tumour removal alters the biological properties (ie, proliferation, apoptosis, and metastatic properties) of neoplastic cells. These changes lead to improved tumorigenicity, promoting accelerated expansion of MRD in vivo. The evidence that surgery may lead to changes in the cellular properties of MRD comes from observations of reduced apoptosis and increased proliferation after primary tumour removal.[16,17,43,61] Other investigators have shown increased DNA synthesis within primary and metastatic tumour cells after primary tumour removal. A recent report described malignant transformation within a vestibular schwannoma in a patient who underwent gamma knife irradiation.[20] It has been suggested that multiple wounds from breast biopsy may have a similar effect.[21]

Several of the blood-borne factors that are increased after surgery (ie, interleukin 6, TNFα, vascular endothelial growth factor [VEGF], and lipolysaccharide) have been shown to potentiate tumour growth.[48] For example, VEGF increases resistance to apoptosis in vitro by a BCL2-related mechanism.[62] Bacteria and their products deserve separate attention in this regard (figure 3). Increasing evidence supports a role for bacterial cell-wall components, such as lipopolysaccharide in perioperative tumour growth.[16,63,64] This hypothesis stems from observations that laparotomy and laparoscopy differentially stimulate intraperitoneal and extraperitoneal tumour growth.[23,24,36,38,39] It has been speculated that lipopolysaccharide, an airborne constituent, was partly responsible for differences seen between laparoscopy and laparotomy.[65] In 1995, Watson and colleagues showed

differential increases in gut-derived lipopolysaccaride after laparotomy and laparoscopy.[65] This difference was related to the translocation of enteric bacteria. More recently, we showed that the beneficial effect of probiotics given during surgery was associated with an attenuation of surgically induced endotoxaemia.[17] Overall, these findings point to a major role for gut-derived lipopolysaccaride in altering residual tumour growth after excisional surgery.

Although the above data implicates lipopolysaccharide in perioperative tumour growth, the underlying mechanisms have not been fully characterised. It is known however, that lipopolysaccharide is proangiogenic.[66] Moreover, it is a potent proinflammatory mediator that stimulates release of interleukin 6, TNFα, and VEGF from various cellular sources. Wang and co-workers showed how lipopolysaccharide promotes adhesion of tumour cells through a ß1-integrin-mediated mechanism. This effect is related to NFκB activation because the effects were lost in cells transfected with a dominant-negative form of IκB.[67]

Further evidence that surgery alters the neoplastic properties of cancer cells comes from studies that indicate the activation of dormant micrometastases after tumour removal. Tumour dormancy is defined as an equilibrium state which if disrupted leads to tumour resurgence.[68] Disruptions in this equilibrium may result from surgery.[61,69] Verani and colleagues showed an increase in the activation of dormant micrometastases after surgery.[69] On the basis of patterns of local and systemic recurrence, several authors suggest that these result from the surgical activation of dormant micrometastases.[5,6,18,19,61] Although the determinants of tumour dormancy are not known, the transition to an active metastasis has been attributed to reduced apoptosis after release from angiogenic restraints. In mice with suppressed angiogenesis, Holmgren and colleagues showed that release of antiangiogenic constraints led to rapid growth.[61] They suggest that metastases remain dormant when cell proliferation is balanced by equivalent apoptosis and that an indirect relationship exists between antiangiogenic restraints (ie, angiostatin, endostatin, and thrombospondin) and increased apoptosis of tumour cells.[61]

The angiogenic switch

Several investigators have speculated that primary tumours secrete factors which circulate and inhibit the growth of metastases.[70,71] Two such antoangiogenic factors, endostatin and angiostatin, are not detectable in serum shortly after tumour excision.[34,61,71] Tumour removal may facilitate tumour growth by reducing concentrations of anti-angiogenic agents, thereby causing an angiogenic switch that promotes angiogenesis. Further evidence of an angiogenic switch comes from Baum and colleagues who used chaos theory to explain hazard rates for survival after tumour removal.[7] In their model, removal of primary tumour disinhibits angiogenesis and thereby "kick-starts" the process of metastasis.[7] To further explain the mechanism by which disinhibited angiogenesis may promote tumour growth, Li and co-workers speculated that apoptotic rates within tumour masses are altered by nutritional supply and that a good nutritional supply promotes increased proliferation.[34,72] After tumour removal a switch in the angiogenic phenotype seems to occur and microvessel density increases in metastases. This could provide sufficient nutritonal impetus for increased proliferation of tumour cells, reduced apoptosis, and improved survival after excisional surgery.

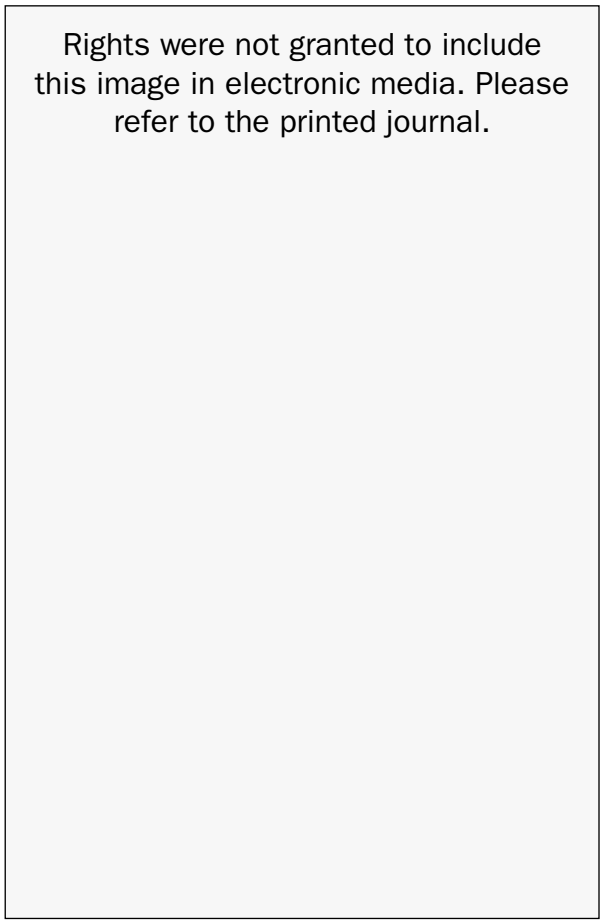

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Figure 3. The role of lipopolysaccharide in accelerated tumour growth after surgery. Endotoxin is derived from enteric bacteria, through the process of translocation. This promotes angiogenesis, decreases apoptosis, and accelerates metastatic formation. Antiendotoxin strategies such as probiotics and taurolidine, may act by altering bacterial translocation.

A combination of factors

The fourth hypothesis is that any of the above three mechanisms may be involved in the changes in tumour growth after tumour excision. For example, tumour removal leads to the dissemination of circulating tumour cells, postoperative immunosuppression, and the increased translocation of enterally derived lipopolysaccharide, which stimulates a potent proinflammatory response generating increased circulating concentrations of interleukin 6, VEGF, and TNFα. Synchronously, lipopolysaccharide promotes the survival capacity and metastatic properties of circulating tumour cells. In these circumstances, tumour removal may be said to have disseminated tumour cells, facilitated their survival (immune evasion), and accelerated the growth

of MRD (lipopolysaccharide, inflammation, changes in apoptosis, and metastasis).

Therapeutic options after tumour removal

Perioperative chemotherapy

The clinical trials of Nissen-Meyer and others provide strong evidence that perioperative chemotherapy protects against the effects of tumour removal on the growth of MRD.[26,29,30] Epidemiological studies such as those of Demicheli and others, support the use of tamoxifen and anti-VEGF therapies during the perioperative period.[5,6,19] When a mastectomy is done during the follicular phase of the menstrual cycle unopposed oestrogen may increase tumour growth. Theoretically, perioperative tamoxifen could protect against this effect. Angiogenesis has been implicated in the activation of dormant micrometastases after surgery. Hence, antiangiogenesis therapies (endostatin, angiostatin, anti-VEGF, and monoclonal antibodies) may be protective during the postoperative period.[15,19,61,71]

Antiendotoxin agents

The association between lipopolysaccharide and perioperative tumour growth has led to the investigation of anti-lipopolysaccharide agents in this setting.[16,17,32,64,65] Taurolidine, a potent antioxidant and antiendotoxin agent, has been shown to reduce spontaneous and perioperative tumour growth.[32] Probiotics have been shown to reduce perioperative metastatic tumour growth.[17]

Immunotherapy

The additive effects of surgery and malignant disease on early postoperative immunosuppression support attempts at therapeutic immunomodulation during this period. Several immunomodulatory approaches have shown promise during the perioperative period, including interferon γ, subcutaneous interleukin 2, and the transfer of interleukin 2 generated LAK cells whose cytotoxic repertoire is greater than that of NK cells.[73,74]

Biomodulation

Cao and colleagues showed that the expression of angiostatin cDNA in a mouse fibrosarcoma suppresses tumour growth and induces long-term dormancy of micrometastases after removal of the primary tumour.[75] These findings indicate that by combining excision of the primary tumour and forcing micrometastases into dormancy, long-term survival may be considerably improved. This treatment is an example of biomodulation, whereby the micrometastases are not eradicated but are stabilised.[76] Tumour vaccines are an alternative strategy for the stabilisation of micrometases during the perioperative period.[77] Dendritic-cell vaccines are currently under investigation for this purpose.

Future Directions

The protection of patients against perioperative tumour growth is not, as yet, an accepted therapeutic paradigm. With the exception of the investigations of Nissen-Meyer and colleagues, no trials have been done to evaluate the long-term effects of the agents described above, when administered during the perioperative period. Given that the accumulating data points to the phenomenon of tumour growth after surgery, further trials need to be done.

The major issues that are still to be addressed include the significance of the circulating tumour cells (in particular that of circulating tumour cells disseminated during tumour removal), the determination of the true biological effects of tumour removal on residual neoplastic disease, and the contribution of wound healing and inflammation to perioperative tumour growth. Recently, Klein and colleagues isolated circulating tumour cells and found pronounced genetic heterogeneity. Similar approaches may now be applied to characterise changes in circulating tumour cells during surgery. Tumour removal accelerates the activation of dormant micrometastases. With the advent of high-throughput techniques such as gene microarray and proteomics, future studies may unravel the molecular basis of tumour dormancy as well as the effects of surgery.

Several investigators have reported increased cellular proliferation and reduced apoptosis within metastases after tumour excision or laparotomy. These findings strongly point to intrinsic changes in the biological properties of tumour cells. To date however, there are no data that characterise the molecular pathways that underpin these changes. Similarly, little data is available regarding the biological activity of tumour cells before and after surgical injury, because of the absolute lack of studies that have harvested and compared tumour cells in these settings.

The role of postoperative inflammatory phenomenae is remarkably underinvestigated. Proinflammatory cytokines such as interleukin 6 activate NFκB, a family of transcription factors that inhibit apoptosis and promote cellular proliferation and survival. However, the role of interleukin 6, other cytokines, transcription factors, and hormonal mediators during perioperative tumour growth remain to be determined.

Conclusion

There is emerging evidence that tumour removal adversely alters the subsequent resurgence of MRD. The principle underlying mechanisms involve intraoperative tumour cell dissemination, the generation of a permissive environment for tumour growth, and the direct alteration of neoplastic properties leading to accelerated tumour growth. Because the patient seems to be at maximum risk during the immediate postoperative period this may represent a therapeutic window of opportunity during which novel paradigms aimed at reducing perioperative tumour growth may be used. These may include antiendotoxin-based strategies, strategies aimed at bolstering the immune response, and therapies aimed at stabilising dormancy within micrometastases.

Little is known about the direct effects of tumour removal on neoplastic cells and even less is known about the molecular mechanisms behind these effects. Novel experimental techniques that enable the purification of viable tumour cells will facilitate parallel molecular and functional studies. It is envisaged that these studies will

Search and strategy selection criteria

Referenced papers were identified by searches of PubMed and OVID with the search terms "perioperative AND tumour AND growth", "tumour AND recurrence", "perioperative AND chemotherapy", and "postoperative AND tumour AND growth". Only papers published in English after 1960 were included. Additional papers were identified from the reference lists of retrieved papers. Other papers of relevance were identified from the personal collections of the authors. Only published abstracts presented at recent international oncology forums such as the Society of Surgical Oncology, were included. Papers were included on the basis of available evidence for each specific point.

identify the cellular and corresponding molecular mechanisms that underpin perioperative tumour growth. In turn, this evidence may lead to novel, focused therapeutic paradigms aimed at protecting patients during the postoperative window of opportunity.

Conflict of interest

None declared.

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