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# The promotion of tumor metastasis by surgery and stress: Immunological basis and implications for psychoneuroimmunology

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**Abstract**

This mini-review emphasizes a psychoneuroimmunology (PNI) perspective of the hypothesis that stress and surgical excision of the primary tumor can promote tumor metastasis. It first establishes the empirical and theoretical basis for control of metastasis by cell-mediated immunity (CMI), as well as the interactive role of non-immunological risk factors. It then describes the various aspects of surgery that suppress CMI, and the neuroendocrine mechanisms mediating suppression by stress and surgery. Last, it briefly reviews the empirical evidence, from animal and human studies, for the promotion of metastasis by stress and surgery, with specific reference to the mediating role of CMI. It is concluded that: (a) Immunological mechanisms most likely play a role in limiting metastasis in patients with solid tumors. (b) Immunosuppression can be deleterious, especially when surgery is conducted early, before the tumor develops insurmountable mechanisms to escape immune destruction. (c) The most sensitive period for the establishment of metastases is the immediate aftermath of surgery. Interventions aiming at reducing stress and immunosuppression should thus strive to start beforehand. (d) 'Psychological and physiological insults activate similar neuroendocrine mechanisms of immunosuppression. Therefore, a multimodal therapeutic approach should be used to prevent tumor metastasis during the perioperative period. (e) Studies employing interventions aimed at reducing the surgical stress response should preferably assess immunological indices with an established clinical relevance, and follow up long-term recurrence provided sample size assure statistical power. (f) The progress toward earlier detection of cancer, and our growing understanding of immunosuppression, continuously improves the chances for successful PNI interventions.


*Keywords:* Cancer; Metastasis; Immunity; CMI; Stress; Surgery; PNI; Immunosurveillance

## 1. A role for the immune system in controlling tumor metastasis

Immunosuppression by stress or surgery can affect tumor metastasis only to the extent that the immune system controls cancer progression. While numerous studies have indicated that patients' immunocytes can recognize and often destroy autologous tumor cells (Uchida et al., 1990), there is still profound skepticism regarding the ability of the immune system to control cancer development. This skepticism stems mainly from the so far limited success of immunotherapy, and from the findings that immunosuppressed transplant patients do not exhibit significantly higher rates of the most prevalent types of cancer (Bodey, Bodey, Siegel, & Kaiser, 2000; Penn, 1999). However, the apparent inconsistency between the above observations is resolved by current theories of cancer immunology. These new perspectives maintain that the interaction between cell

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mediated immunity (CMI) and the malignant tissue is a microevolutionary process: at first, CMI is ignorant of the newly transformed tissue that resembles self. Gradually, the malignant tissue becomes more immunogenic, attracts more capillaries and immunocytes, and starts to emit danger signals (due to cellular stress resulting form hypoxia and genetic instability). At this stage, CMI recognizes and destroys many tumor cells, creating a selection pressure that favors mutated tumor cells capable of evading recognition or destruction by immunocytes. This process eventually leads to accumulation of tumor escape mechanisms that renders CMI ineffective, at least with respect to controlling the primary tumor (Hanahan & Weinberg, 2000; Pettit, Seymour, O'Flaherty, & Kirby, 2000).

The crucial question with respect to controlling metastasis, however, is whether CMI can limit the dissemination of tumor cells during this microevolutionary process, and whether it can eradicate residual disease after the surgical removal of the primary tumor. Residual disease consists of pre-established micrometastases, and single tumor cells in the lymphatics and circulation. Theoretically, CMI has a better chance of eradicating residual disease than primary disease: outside the protective microenvironment of the primary tumor, the concentration of immunosuppressive substances (released by the malignant tissue) is much lower; metastasizing tumor cells are outnumbered by various types of immunocytes and proliferate and mutate more slowly than cells of the primary tumor; and micrometastases do not have adequate blood supply for extended growth (Pantel, Cote, & Fodstad, 1999).

Indeed, various lines of evidence, shortly reviewed below, support the assertion that CMI interacts with the malignant tissue, restricts its metastatic growth, and plays a role in eradicating cancer after the primary tumor is removed. Studies in animals repeatedly implicated CMI in controlling tumor metastasis, specifically pointing at CTLs, NK cells, NKT cells, tissue macrophages (e.g., Kupfer cells), dendritic cells, and $T_H$ cells as key players (respectively, see Andreesen, Hennemann, & Krause, 1998; Brittenden, Heys, Ross, & Eremin, 1996; Fong & Engleman, 2000; Godfrey, Hammond, Poulton, Smyth, & Baxter, 2000; Svane, Boesen, & Engel, 1999; Toes, Ossendorp, Offringa, & Melief, 1999) (for review see Smyth, Godfrey, & Trapani, 2001). However, many animal studies, although methodologically sound, have been justly criticized for using tumor lines that are highly immunogenic, and for not modeling the natural microevolutionary course of human cancer and its metastatic progression (Hewitt, 1983; Killion, Radinsky, & Fidler, 1998). Thus, their findings can only be accepted if corroborated by studies in humans, which are described below.

Supporting the existence of anti-metastatic immunity in humans is the long-appreciated ability of immunocytes in some patients to identify and lyse autologous tumor cells in vitro. In recent years, molecular mechanisms underlying this capacity have been revealed for both the adaptive and innate arms of CMI (Moretta, Biassoni, Bottino, Mingari, & Moretta, 2000; Rosenberg, 2001). The extensive in vivo interaction between CMI and the evolving malignant tissue is attested by the growing numbers of escape mechanisms identified in human and in animal malignancies, and their scarcity in malignancies that have developed in immunodeficient strains (Pawelec et al., 2000). Additional evidence come from correlative clinical studies reporting that immune competence at the time of cancer treatment is an independent prognostic factor of recurrence-free survival. Immune indices identified as positive indicators include NK activity and specific CTLs response to the patient's tumor (McCoy, Rucker, & Petros, 2000; Taketomi et al., 1998). Infiltration of the primary tumor by NK, CTL, or dendritic cells, but not by macrophages, is also prognostic of metastasis-free survival (al-Sarireh & Eremin, 2000; Menard et al., 1997; Takanami, Takeuchi, & Giga, 2001). Additional support for immunological control of metastasis comes from immunosuppressed transplant patients: while immunosuppressive drugs do not seem to trigger de novo tumors (except for virally induced), they occasionally reactivate the disease in patients long-recovered from cancer, and markedly increase the rate of metastasis in patients carrying active disease (whether diagnosed before or after transplantation) (Detry, Honore, Meurisse, & Jacquet, 2000). Finally, novel techniques for identifying residual disease indicate that many patients that have residual disease following surgery do not proceed to develop metastases (Braun et al., 2000). Taken together, it could be suggested that complete remission following surgery often occurs not because all malignant tissue has been removed, but because residual disease is controlled by CMI (McCoy et al., 2000; Morton, Ollila, Hsueh, Essner, & Gupta, 1999).

In sum, although in cancer patients CMI has clearly failed to prevent the development of the primary tumor, its potential role in restricting metastasis should not be overlooked. If the primary tumor is removed early, before intractable escape mechanisms or sizeable metastases develop, immunity may have a significant clinical role in preventing recurrence. Suppression of CMI under these conditions may increase recurrence rates, and should be prevented.

## 2. Risk factors for progression of metastasis during the perioperative period

In addition to immunosuppression, several non-immunological risk factors might promote metastasis immediately after surgery. First, the malignant tissue is notoriously non-cohesive and tumor cells are often

embedded in its blood vessels. The surgical procedure almost always disrupts the neoplasm or its vascularization, leading to the release of tumor cells into the circulation (Eschwege et al., 1995; Yamaguchi, Takagi, Aoki, Futamura, & Saji, 2000). Second, the presence of the primary tumor is believed to induce the release of factors that limit angiogenesis (e.g., angiostatin, endostatin), thus preventing micrometastases from growing beyond a critical size. As was shown by some animal studies, the removal of the primary tumor discontinues this inhibition and facilitates the development of metastases (Folkman, 1990; Zetter, 1998). Third, following surgery there is ample release of growth factors that promote the healing of damaged tissue. These factors are suspected to promote the development of metastasis in local and remote sites (Abramovitch, Marikovsky, Meir, & Neeman, 1999; Hofer et al., 1999).

Importantly, these processes accompany immunosuppression during the postoperative period, and may act in synergy to render the patient vulnerable to metastases that could have been kept under control otherwise. For example, reduced levels of angiogenesis-inhibitors combined with high levels of growth factors may promote the development of micrometastases into sizable metastases; the shedding of tumor cells into the circulation accompanied by systemic suppression of CMI may promote implantation of malignant cells in remote organs.

## 3. Mechanisms of immunosuppression by surgery and stress

Major surgeries dramatically suppress CMI in animals and humans, and the degree and duration of immunosuppression are correlated with the degree of tissue damage inflicted (Sietses, Beelen, Meijer, & Cuesta, 1999). Immunosuppression is an acknowledged postoperative complication that is believed to underlie the outbreak of life-threatening infections such as pneumonia and sepsis (Weighardt et al., 2000). Several aspects of surgery were implicated in immunosuppression, including anesthetic and analgesic drugs, hypothermia, tissue damage, blood loss and transfusion, nociception, pain, and perioperative anxiety and stress (see Section 4). Immunosuppression is caused by an intricate array of local and systemic physiological responses; as described below, many of these responses involve a CNS-mediated neuroendocrine feedback. Generally, whereas in the vicinity of the wound the predominant response is pro-inflammatory, in the periphery, where the fate of metastases is determined, an opposite picture emerges: there is a drastic reduction in pro-cellular $T_{H1}$ type responses and suppression of CMI, with minor perturbation to humoral immunity. These effects include marked reductions in cell numbers, cytokine levels, cytotoxic and secretory activity, and in vivo functions.

### 3.1. Local factors and cytokine responses

The response to tissue damage is initiated by local products of cell lysis, humoral factors released by macrophages and other resident cells, and by local neurogenic inflammatory agents. Prominent among these factors are prostaglandins (e.g., $PGE_2$), which are potent in vitro suppressors of CMI and are known to be involved in the initiation of the cytokine response (Faist, Schinkel, & Zimmer, 1996). In humans, cyclooxygenase inhibitors blunted the cytokine responses (Chambrier et al., 1996) and the suppression of CMI following surgery (Faist et al., 1990; Markewitz et al., 1996), and in rats they were also shown to reduce the promotion of metastasis by surgery (Colacchio, Yeager, & Hildebrandt, 1994; Rosenne, Melamed, Abudarham, & Ben-Eliyahu, 2001). The local neurogenic pro-inflammatory response is initiated by nociceptive afferents. It involves local and spinal reflexes, and promotes erythema and edema around the surgical wound by releasing numerous compounds, including substance P (Schaffer, Beiter, Becker, & Hunt, 1998; Rameshwar, 1997). The cytokine response to major surgery includes an immediate surge in systemic levels of pro-inflammatory cytokines (e.g., IL-6 and IL-8), and an increase in plasma levels of type 2 cytokines and other factors that interfere with CMI (e.g., IL-10, IL-1rA, sTNF-αr, and sIL-2r) (Faist et al., 1996; Lin, Calvano, & Lowry, 2000). Additionally, in vitro studies indicated a marked decrease in the production of pro-CMI cytokines (such as IL-2, IL-12, IFN-γ, TNF-α, and IL-1β) by monocytes and $T_{H1}$ cells, and an increase in the production of factors that interferes with CMI, such as IL-10 and IL-1rA (Munford & Pugin, 2001). The cytokine response to surgery is intertwined with the neuroendocrine response described below. For example, IL-1 and IL-6 are critical for initiating the HPA response to surgery, while sympathetic activity was shown to trigger IL-10 release following surgery (Woiciechowsky et al., 1998; Woiciechowsky, Schoning, Lanksch, Volk, & Docke, 1999).

### 3.2. Neuroendocrine responses

#### 3.2.1. The sympathetic nervous system (SNS)

The SNS innervates lymphoid organs and most leukocytes express adrenergic receptors (Elenkov, Wilder, Chrousos, & Vizi, 2000). During the perioperative period and following psychological stress, catecholamines are released systemically, as well as locally by nerve endings that are believed to form "synapses" with leukocytes (Elenkov et al., 2000). In vitro studies have indicated that catecholamines can act directly to suppress many aspects of CMI, including NK, CTL, and macrophage activity (Elenkov et al., 2000). Catecholamines can also act indirectly to suppress CMI by reducing

macrophages and $T_H$ production of type 1 cytokines (e.g., IL-12, TNF-α, and IFN-γ), and by stimulating the release of immunosuppressive factors including IL-10 and TGF-β (Platzer, Docke, Volk, & Prosch, 2000; Woiciechowsky et al., 1999).

The ex vivo study of SNS effects on immunity is hindered by two factors. First, activation of the SNS causes massive redistribution of leukocyte subpopulations, which often ends shortly after catecholamines levels drop (Schedlowski et al., 1996). However, following harvesting of leukocytes into the test tube, the momentary profile of leukocyte subpopulations is fixed. This may yield ex-vivo findings of limited biological (in vivo) significance. Second, some of the effects of catecholamines on functions of CMI are transitory and depend on the presence of catecholamines (Hellstrand, Hermodsson, & Strannegard, 1985). Thus, effects of catecholamines that do occur in vivo may not be preserved and depicted in ex-vivo studies in which the humoral in vivo milieu is replaced by an artificial in vitro medium. These two factors probably explain several examples where ex-vivo findings are inconsistent with in vivo and in vitro findings (Shakhar & Ben-Eliyahu, 1998).

Nevertheless, several groups provided compelling evidence that in vivo blockade of the SNS could attenuate the immunosuppressive effects of surgery and stress. Suppression of lymphocyte proliferation following laparotomy was attenuated by a β-adrenergic antagonist (Nelson & Lysle, 1998), as was the increase in IL-10 plasma levels after brain surgery (Woiciechowsky et al., 1998). Stress and activation of the SNS were shown to suppress various aspects of CMI, including macrophage and NK activity, and these effects were attenuated by sympathetic blockade (Broug-Holub, Persoons, Schornagel, Mastbergen, & Kraal, 1998; Hodgson, Yirmiya, Chiappelli, & Taylor, 1999; Shimizu, Kaizuka, Hori, & Nakane, 1996). In our studies, abdominal surgery, anesthesia, hypothermia, social confrontation, and swim stress all suppressed NK activity (per NK cell) and promoted experimental metastasis. Furthermore, we were able to attenuate these effects by employing β-blockers, adrenal demedullation, or a ganglionic blocker (Ben-Eliyahu, Page, Yirmiya, & Shakhar, 1999a; Ben-Eliyahu, Shakhar, Page, Stefanski, & Shakhar, 2000; Melamed, Bar-Yosef, Rosenne, Weisman, & Ben-Eliyahu, 2001; Rosenne et al., 2001; Stefanski & Ben Eliyahu, 1996). Taken together, in vitro, ex vivo, and in vivo findings strongly suggest that the SNS is involved in the suppression of CMI by surgery and stress (Elenkov et al., 2000; Woiciechowsky et al., 1999).

*3.2.2. The hypothalmo-pituitary–adrenal (HPA) axis*

Surgery activates the HPA axis via a spinal pathway, as well as through the release of IL-1 and IL-6 (Mastorakos, Chrousos, & Weber, 1993). Increased levels of corticosteroids following surgery lasts for days and correlates with the severity of surgery and the degree of immunosuppression (Tashiro et al., 1999). Activation of the HPA axis was once thought to be the most prominent mediator of immunosuppression following stress or surgery as corticosteroids are established in vitro immunosuppressors, and, when administered in pharmacological doses, are potent immunosuppressive drugs. Indeed, the use of synthesis inhibitors or competitive antagonists of corticosteroids reduced T-cell apoptosis and metastasis following surgery in rats (Deguchi, Isobe, Matsukawa, Yamaguchi, & Nakagawara, 1998), and attenuated the suppression of monocyte activity in injured mice (Cech, Shou, Gallagher, & Daly, 1994). In addition, stress was shown to suppress various aspects of CMI and promote infection via activation of the HPA axis (Sheridan, Dobbs, Brown, & Zwilling, 1994).

However, a closer look reveals that surgeries that increase corticosteroids levels to a similar degree can cause different levels of immunosuppression (Redmond et al., 1994), and that physiological levels of corticosteroids do not suppress some immune functions in vivo (Bodner, Ho, & Kreek, 1998). Additionally, various neuroendocrine interventions that do not affect corticosteroids levels (e.g., the blockade of the SNS) can abolish some immunosuppressive and metastasis-promoting effects of surgery or stress (Ben-Eliyahu et al., 2000; Rosenne et al., 2001). Thus, other neuroendocrine responses must also play a key role in mediating immunosuppression.

*3.2.3. Opioids*

Following surgery and stress opioids are released from the pituitary, adrenal medulla, and from various lymphocytes (Kavelaars, Ballieux, & Heijnen, 1990). It has long been acknowledged that exogenous opiates, administered centrally or systemically, can suppress CMI (Carr & Serou, 1995). Among endogenous opiates, β-endorphin is most recognized for such in vitro and in vivo effects (Carr & Serou, 1995). Indeed, the opioid antagonist naltrexone attenuated the reduction in NK cytotoxicity, lymphocyte proliferation, and IFN-γ production caused by laparotomy (Nelson, Carrigan, & Lysle, 2000). Naltrexone also attenuated immunological perturbations caused by various types of stressors (Panerai & Sacerdote, 1997; Shavit, Lewis, Terman, Gale, & Liebeskind, 1984).

## 4. Empirical evidence that suppression of CMI by surgery or stress can promote metastasis

A large number of studies in animals, employing various tumor models, have convincingly demonstrated that surgery and stress can promote metastasis. Many of these studies have further shown that surgery and stress

also suppress various immune indices, suggesting a possible mediating role for CMI (e.g., Colacchio et al., 1994; Da Costa, Redmond, & Bouchier-Hayes, 1998; Shiromizu et al., 2000). Few studies have attempted to provide more causative evidence that CMI indeed mediates these effects. For example, others and we reported increased metastasis in immunocompetent animals, but not in immunodeficient ones (Allendorf et al., 1999; Ben-Eliyahu et al., 1999a). We further found that the periods of NK suppression following surgery or stress coincide with the periods of compromised in vivo resistance to metastasis of the NK-sensitive MADB106 syngeneic line (Ben-Eliyahu, Shakhar, Rosenne, Levinson, & Beilin, 1999b). Finally, when we examined host resistance to lung metastasis of this tumor, and its relation to the ex vivo cytotoxicity of pulmonary immunocytes against this tumor, both functions were compromised by laparotomy, and the same treatment (NSAID + β-blocker) efficiently reversed both inhibitions (Rosenne et al., 2001).

Because animal models of cancer do not always simulate the human disease faithfully (Hewitt, 1983; Killion et al., 1998), it is important to focus in this mini-review on empirical evidence from clinical studies. Given the methodological limitations of human studies, especially the lack of a non-operated control group, no direct evidence that surgery or stress promote metastasis can be expected. Nevertheless, while surgery itself cannot be withheld from patients, some of its immunosuppressive aspects have been modified. Employing different procedures have caused different levels of immunosuppression, resulting, at times, in parallel effects on rates of tumor recurrence. Described below are such concordant effects in cancer patients. Taken into consideration together with homologous well-controlled studies in animals, they support the suggestion that surgery can promote metastasis in cancer patients by suppressing CMI.

First, general anesthesia was shown to suppress several aspects of human CMI, including lymphocyte numbers and blastogenic response, NK activity, and $T_{H1}$ to $T_{H2}$ ratios (Galley, DiMatteo, & Webster, 2000). Local or regional anesthesia, on the other hand, is not immunosuppressive, and when given to supplement general anesthesia during surgery, was shown to attenuate the suppression of CMI (Koltun et al., 1996; Rem, Brandt, & Kehlet, 1980). These benefits are attributable to the blunting of the sympathetic and the HPA surgical stress response (Koltun et al., 1996; Pflug & Halter, 1981), which are achieved by the blockade of both ascending (mainly nociceptive) and descending (mainly sympathetic) fibers. Most importantly, the use of local anesthesia instead of general anesthesia was recently identified as an independent positive predictor of recurrence-free survival, in a large-scale clinical trial in melanoma patients (Schlagenhauff et al., 2000). Animal studies indicated that various anesthetics can suppress CMI and promote metastasis (Melamed et al., 2001), and our recent studies demonstrated that the addition of spinal block to rats operated under general anesthesia reduced the promotion of metastasis by surgery (Bar-Yosef et al., 2001; Page, Blakely, & Ben-Eliyahu, 2001).

Second, blood transfusion was shown to suppress CMI in patients, causing perturbations in cytokine levels and suppression of NK cytotoxicity and T-cell blastogenesis (Shao, Edelman, Sullivan, Nelson, & Shelby, 1998) (for review see Klein, 1999). Blood transfusion is a well-documented risk factor for recurrence. Importantly, more than 30 clinical studies (approximately half of those conducted) were also able to show that the negative prognostic value of blood transfusion is independent of other complications and risk factors associated with it (Klein, 1999). Animal studies clearly indicate that transfusion per se suppresses CMI and promotes metastasis, and provide more direct evidence for the mediating role of CMI (Blajchman, Bardossy, Carmen, Sastry, & Singal, 1993; Clarke, Burton, & Wood, 1993).

Third, to remove colon tumors, two successive surgeries rather than a single operation were used in the past. This staged procedure resulted in increased rates of metastasis and long-term mortality (Fielding & Wells, 1974), as was also shown by animal studies (Weese, Ottery, & Emoto, 1986).

Fourth, minimally invasive surgeries (MIS) in patients (e.g., laparoscopy) have been shown to be less immunosuppressive than standard procedures (e.g., laparotomy) (Vittimberga, Foley, Meyers, & Callery, 1998). Animal studies have shown that the use of MIS also reduces the promotion of metastasis (Mutter et al., 1999), presumably by decreasing immunosuppression (Allendorf et al., 1999; Da Costa et al., 1998). In cancer patients, studies have provided initial evidence that MIS reduces recurrence rates in surgeries that are markedly traumatic (e.g., thoracotomy for removing early-stage lung carcinoma—Kaseda, Aoki, Hangai, & Shimizu, 2000; Lewis, Caccavale, Bocage, & Widmann, 1999; Sugi, Kaneda, & Esato, 2000), but apparently not in less immunosuppressive operations (e.g., excision of colorectal tumors—Hartley, Mehigan, MacDonald, Lee, & Monson, 2000). Substituting these traumatic surgeries with MIS reduced sympathetic activation (Tschernko, Hofer, Bieglmayer, Wisser, & Haider, 1996), cytokine responses (Yim, Wan, Lee, & Arifi, 2000), and lymphopenia (Leaver, Craig, Yap, & Walker, 2000), but did not reduce the release of tumor cells into the circulation (Yamashita, Kurusu, Fujino, Saisyoji, & Ogawa, 2000). These findings suggest that reduced immunosuppression is a mediating beneficial aspect of MIS, which may be attributed to a reduction in tissue damage, bleeding, neuroendocrine responses, and pain.

In sum, the findings from animal studies clearly indicate that it is feasible for surgery to promote metas-

tasis in cancer patients by suppressing CMI. However, for methodological reasons, the evidence in humans is no more than correlative. It seems that only clinical trials aimed specifically at preventing perioperative immunosuppression could provide direct evidence and clarify the circumstances in which the hypothesis holds true in humans.

## 5. The critical perioperative period and implications for psychoneuroimmunology-based clinical interventions

Surgical excision of the primary tumor presents an opportunity to eradicate cancer because it removes the major source of metastasizing cells, limits the potential for further immuno-resistant mutations, and reduces systemic levels of tumor-derived immunosuppressive substances. However, in the short run, the surgery itself is believed to increase the risk of metastases. As reviewed above, surgery can do so by: (a) releasing tumor cells into the circulation, (b) reducing anti-angiogenic factors, (c) increasing growth factors, and (d) causing immunosuppression that results from the medical procedures and from perioperative stress and anxiety. These deleterious consequences of surgery favor the survival and implantation of newly-released tumor cells, and promote the development of preexisting micrometastases. The postoperative window of opportunity to eradicate cancer will close once residual tumor cells develop into large metastases that can grow and escape immune control, as did the primary tumor. Because most of the above postoperative risk factors are transitory, lasting days or weeks, and because the fate of residual disease (to expand or to be eradicated) is probably decided within days (especially for circulating cells—Yamashita et al., 2000), the immediate postoperative period seems to have a disproportional weight in determining long-term recurrence.

All considered, it seems critical to prevent immunosuppression during the perioperative period. Psychoneuroimmunological interventions should ideally start before surgery, covering this critical period, and continue for as long as psychological distress persists.

Importantly, surgery and stress activate overlapping neuroendocrine immunosuppressive responses, including catecholamine, corticosteroid, and opioid secretion. Psychological or psychopharmacological interventions may have no beneficial effects immediately after surgery because the responses they aim to reduce are activated in parallel by physiological aspects of surgery (e.g., tissue damage and pain). This consideration suggests that multimodal interventions should be considered perioperatively. Noteworthy, although psychological distress may induce smaller neuroendocrinological responses than the physiological insult, it starts well before surgery and continues long after the physiological effects of surgery have subsided. Therefore, attending psychological distress may be critical, as was suggested by selected studies reporting that psychological interventions prolong survival time or reduce recurrence rates (e.g., Fawzy et al., 1993).

Because the most important clinical endpoints are recurrence and survival rates, they must also be studied. These studies, however, should only be initiated if enough participants can be recruited to demonstrate a significant improvement given the expected potency of a psychoneuroimmunological intervention. For example, if one expects to reduce the mortality rate from 30 to 25%, more than 1000 patients should be recruited to each arm to ensure an 80% chance of reaching statistical significance (i.e., having a power of 80%, using $\alpha = 0.05$). On the other hand, if one expects a reduction from 40 to 20%, only 74 patients per arm are needed (see Table 1 for a complete array of probabilities, and statistical considerations). Studies that use samples that are a priori too small may be detrimental to the field because

Table 1
The number of patients required in each arm in order to have 80% chance (power of 80%) of showing a statistically significant difference in mortality rates between two conditions

| | Probability of mortality in the treated population ($P_1$) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | .05 | .1 | .15 | .2 | .25 | .3 | .35 | .4 | .45 |
| $P_0 = .1$ | 385 | | | | | | | | |
| $P_0 = .15$ | 131 | 585 | | | | | | | |
| $P_0 = .2$ | 72 | 178 | 760 | | | | | | |
| $P_0 = .25$ | 48 | 92 | 218 | 910 | | | | | |
| $P_0 = .3$ | 35 | 58 | 109 | 253 | 1035 | | | | |
| $P_0 = .35$ | 27 | 41 | 67 | 123 | 281 | 1135 | | | |
| $P_0 = .4$ | 22 | 31 | 46 | 74 | 134 | 303 | 1210 | | |
| $P_0 = .45$ | 18 | 25 | 34 | 50 | 80 | 142 | 319 | 1260 | |
| $P_0 = .5$ | 15 | 20 | 27 | 37 | 54 | 84 | 148 | 328 | 1286 |

Calculations are based on one-tailed test comparing two *unknown* proportions, with $\alpha = 0.05$. $P_0$ and $P_1$ are the assumed probability in the non-treated and treated populations, respectively (Campbell, Julious, & Altman, 1995).

they risk being erroneously interpreted as solid evidence against the efficacy of psychoneuroimmunological interventions. In reality, such studies are non-informative.

Finally, screening programs and novel methods of cancer detection bring patients to surgery at earlier stages of cancer development. Consequently, the chances that the patient's immune system is still capable of preventing metastasis and eradicating residual disease are continuously improving, and so does the clinical potential for interventions aimed at preventing immunosuppression or boosting CMI during the perioperative period. Additionally, our emerging understanding of mechanisms that mediate immunosuppression by stress and surgery fosters better interventions. It seems that the broad array of medical considerations in treating cancer patients should now incorporate the impact of psychological and physiological factors on immune-mediated resistance to tumor metastasis.

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