

Surgical Oncotaxis –Excessive Surgical Stress and Postoperative Complications Contribute to Enhancing Tumor Metastasis, Resulting in a Poor Prognosis for Cancer Patients–

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We investigated the relationship between surgical stress and tumor metastasis. The excessive surgical stress of a thoracotomy enhanced tumor metastasis remarkably in an experimental model. We would like to propose that this phenomenon be termed “surgical oncotaxis”. This effect has previously been attributed to some mechanisms of immunosuppression, excessive secretion of corticoids, and active oxygen production of granulocytes. An increase in lipid peroxide (LPO) in the liver was observed after a thoracotomy, but a strong radical scavenger of a DL-alpha-tocopherol-L-ascorbic acid 2-0-phosphate diester (EPC-K1) restrained LPO levels in the liver and the effect of tumor metastasis in parallel.

As clinical strategies for restraining the surgical oncotaxis, the control of any cytokine storm after surgery and/or the scavenging of active oxygen appears to be possible and hopeful, since it might be intermediated by cytokine. When pre-administration findings for EPC-K1 and methylpredonisolone were compared, EPC-K1 was found to be more suitable for restraining surgical oncotaxis, because serum LPO was only controlled with EPC-K1. The cytokine storm which occurs after surgery is augmented by a second stimulation, such as the administration of lipopolysaccharide, and no drug could control this well experimentally.

Postoperative complications are a clinical model of a second stimulation (a so-called second attack). Our data showed the prognosis of a group with complications to be worse than that of a group without them even though no difference existed in the background of the esophageal cancer patients studied. Based on these results, safe surgery and the choice of minimally invasive surgery are the best ways to control surgical oncotaxis. Following a major surgical procedure, such as a thoracotomy, the use of corticoids and/or radical scavengers can contribute to restraining surgical oncotaxis. (*Ann Thorac Cardiovasc Surg* 2005; 11: 4–6)

Key words: surgical stress, cytokine, active oxygen, thoracotomy, tumor metastasis

Introduction

For many years, we have investigated the relationship between surgical stress and tumor metastasis, because we postulated that excessive surgical stress might have a negative effect on the prognosis of cancer patients.¹⁾ Recently,

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minimally invasive surgery using a laparoscopic technique has come into use and has been employed for cancer surgery. Although minimally invasive surgery is now being focused on to improve the quality of life of patients, it could also lead to a better prognosis for postoperative cancer patients.

We used a thoracotomy and/or laparotomy model in rats for excessive surgical stress. In the experimental model, a thoracotomy actually remarkably enhanced tumor metastasis.¹⁾ We propose that this phenomenon be termed “surgical oncotaxis”.

This effect has been attributed to a number of mecha-

nisms, including immunosuppression after excessive surgical stress and delay of recovery,²⁾ excessive secretion of corticoids under excessive surgical stress,³⁾ and, as we have previously postulated, the participation of active oxygen, in consideration of the following facts. It is well known that many forms of stress may produce active oxygen from leukocytes through the action of cytokines,⁴⁻⁶⁾ which can damage endothelial cells^{7,8)} and cause circulatory disturbance in organs by counteraction of nitric oxide.⁹⁾ If cancer cells are in the blood flow under these circumstances, they could easily be implanted and invade an organ's tissue.

If the participation of active oxygen from leukocytes could be proven, radical scavengers would be indicated clinically to lessen excessive surgical stress to minimally invasive stress, resulting in a better prognosis. Moreover, control of active oxygen might also be achieved by the control of a cytokine storm after excessive surgical stress. As a result, the control of cytokine storms could contribute to a better prognosis for cancer patients.

In this paper, we summarized our experimental and clinical research on surgical stress and its enhancing effect on tumor metastasis (surgical oncotaxis), and how to control it.

Enhancing Effect on Tumor Metastasis of Excessive Surgical Stress^{1,10)}

As operative interventions, thoracotomy (T) and/or laparotomy (L) were performed 48 hours after intravenous inoculation of Sato lung cancer (SLC) in Donryu rats. The results clearly demonstrated that a thoracotomy or a thoracotomy (TL) significantly enhanced the number of metastatic lung nodules and reduced survival time in these rats. The enhancing effects on tumor metastasis were related to the degree of operative stress induced by performance or non-performance of a thoracotomy and to operation time.

However, in a series of these experiments, our use of the lung metastatic model was criticized because localized lung surroundings might be influenced by thoracotomy. When we investigated the participation of active oxygen in surgical oncotaxis, tumor cells were found to have transformed into an AH60C carcinoma, which is a hepatocellular carcinoma of the rat that metastasizes only to the liver by inoculation from the portal vein. Three weeks after surgery, a significant difference in the number of metastatic liver nodules was noted between the TL group and the L and control (C) groups.

Lipid peroxide (LPO) levels as a marker of active oxygen production in the liver were also investigated. Liver LPO levels had increased in descending order in the TL, L, and C groups. The TL group showed the highest level of LPO in the liver on postoperative day (POD) 1, there was no significant difference from the other groups. LPO returned to its pre-surgery level on POD 3.

To lessen the effect of active oxygen, we used EPC-K1, which is a DL-alpha-tocopherol-L-ascorbic acid 2-0-phosphate diester and a strong hydroxyl radical (Senju Co., Ltd., Japan). When EPC-K1 was administered intravenously one hour before surgery, the liver LPO level in the 24 hours after thoracotomy was suppressed remarkably with a significant difference. In parallel, when EPC-K1 was administered intravenously one hour before surgery, the number of metastatic liver nodules three weeks after thoracotomy was clearly suppressed with a significant difference. These data demonstrated that active oxygen production due to excessive surgical stress is clearly related to surgical oncotaxis.

Postoperative Complications Revealed as Surgical Oncotaxis Clinically¹¹⁾

We investigated the relationship between postoperative complications and prognosis in esophageal cancer patients, because the most significant stress they experience might be caused by a postoperative complication after a thoracotomy. This would contribute to the poor prognosis of esophageal cancer patients based on our hypothesis of surgical oncotaxis.

In this study, patients with esophageal cancer who had undergone an esophagectomy between April 1979 and December 1994 in Hiroshima University Hospital were analyzed, excluding the cases of direct death. These cases were divided into three groups; group A, B and C. Groups A, B and C consisted of cases without postoperative complications, with minor postoperative complications and with major postoperative complications, respectively. Whereas there were no differences in their backgrounds of the three groups, group A revealed better prognosis than groups B and C. We confirmed that postoperative complications reflect surgical oncotaxis clinically.

Recently, Siewert JR presented clearer data on the contribution of postoperative complications to a poor prognosis in esophageal cancer patients at the 58th Annual Meeting of the Japan Esophageal Society (not published).

The Control of Surgical Oncotaxis¹²⁾

To restrain surgical oncotaxis, a clinical strategy, which involves the control of cytokine storms after surgery or the scavenging of active oxygen, appears to be hopeful, because surgical oncotaxis could be intermediated by cytokine storms. So, two types of drugs, corticoids and radical scavengers, might be used to control surgical oncotaxis. The change in serum interleukin-6 (IL-6) levels after a thoracotomy showed a remarkable increase after surgery in rats. However, administration of EPC-K1 and methylprednisolone prior to a thoracotomy restrained the increase in IL-6 afterwards. Methylprednisolone resulted in the strongest suppression of cytokine secretion.

Serum LPO levels, on the other hand, were controlled with EPC-K1 alone, which means that EPC-K1 might be an ideal drug for controlling surgical oncotaxis. However, EPC-K1 is now out of clinical use.

When lipopolysaccharide (LPS) was administered for one hour after a thoracotomy in rats (a so-called second attack), the serum IL-6 and liver LPO levels showed a remarkable increase. Neither EPC-K1 nor methylprednisolone, however, could control cytokine storms after a second attack. These findings indicate that surgical oncotaxis caused by a second attack (postoperative complications clinically) cannot be controlled enough by any drug.

Based on these results, safe surgery and the choice of minimally invasive surgery under conditions to maintain radicality are the best means to control surgical oncotaxis. In major surgical procedures, including thoracotomy, the use of corticoids and/or radical scavengers contributes not only to the prevention of multiple organ failure, but also to a better prognosis for cancer patients.

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