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Poor Prognosis in Esophageal Cancer Patients with Postoperative Complications

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Abstract: We investigated the relationship between postoperative complications and prognosis in esophageal cancer patients. Two hundred five patients with esophageal cancer were divided into three case groups. Group A (n = 100) consisted of cases without postoperative complications. Groups B (n = 58) and C (n = 47) consisted of cases with minor and major postoperative complications. The 5-year survival rates were 41.8%, 21.3%, and 20.2% in groups A, B, and C, respectively. There was a significant difference in the prognosis between groups A and B, and also between groups A and C. Any patients who died within 5 years without a relapse their cases were excluded from the study; the 5-year survival rates were 46.7%, 32.3%, and 22.5% in groups A, B, and C, respectively, with a significant difference between groups A and B. There were no significant differences between the three groups regarding the patient characteristics. These results therefore indicate that postoperative complications might contribute to a poor prognosis in cancer patients.

Key Words: postoperative complication, prognosis, esophageal cancer

Introduction

Postoperative complications, especially febrile complications, are considered to possibly positively affect the prognosis of cancer patients by stimulating immunoreactivity, thus resulting in an improved prognosis.[1,2] However, many authors have also reported that contrary findings, such as febrile complications, may contribute to a high rate of recurrence.[3,4] Immunologically, the systemic inflammatory response syndrome (SIRS) causes immunosuppression through hypercytokinemia.[5] We previously reported that excessive surgical stress during a thoracolaparotomy was found to enhance tumor metastasis and thus resulted in a poor prognosis in rats.[6] One mechanism of this phenomenon might be due to active oxygen production. In rats, we proved that excessive surgical stress during a thoracolaparotomy generated more lipid peroxide in the liver than a laparotomy as well as enhanced liver metastatic nodules.[7] Our results thus seem to indicate that postoperative complications result in a poor prognosis for surgically treated patients. We therefore investigated the relationship between the postoperative complications and prognosis in esophageal cancer patients.

Materials and Methods

In this study, 205 patients with esophageal cancer who underwent an esophagectomy between April 1979 and December 1994 were analyzed. These cases were divided into three groups, A, B, and C. Group A consisted of cases without postoperative complications. Group B included cases with minor postoperative complications such as minor anastomotic leakage, atelectasis, lung fibrosis, subcutaneous emphysema, chylothorax, pericardial effusion, liver dysfunction including hyperbilirubinemia, pancreatitis, pancreatic, fistula, small subphrenic abscess, an erosion or ulcer of the esophageal substitute, and transient ischemic attack. Group C comprised cases with major complications such as major anastomotic leakage, pneumonia, pyothorax, lung edema, adult respiratory distress syndrome, cardiac infarction, necrosis of the esophageal substitute, postoperative massive bleeding, mediastinitis, lung infarction, and reoperation due to ileus. Groups, A, B, and C consisted of 100, 58, and 47 cases, respectively. Any patients who died within 5 years without relapse were excluded from the study, thus resulting in a total of 91, 52, and 31 cases in Groups A, B, and C, respectively. Patients who received more

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than 30 Gy of radiotherapy and intensive chemotherapy using cisplatin were designated as the radiotherapy group and chemotherapy group, respectively.

Statistical Analysis

The survival rate was calculated using Kaplan-Meier's method. Any significant difference in the survival rate between the groups was determined based upon Log-rank and generalized Wilcoxon tests. Fisher's probability test was used to compare the patient characteristics among the groups. A *P*-value of less than 0.05 was considered significant.

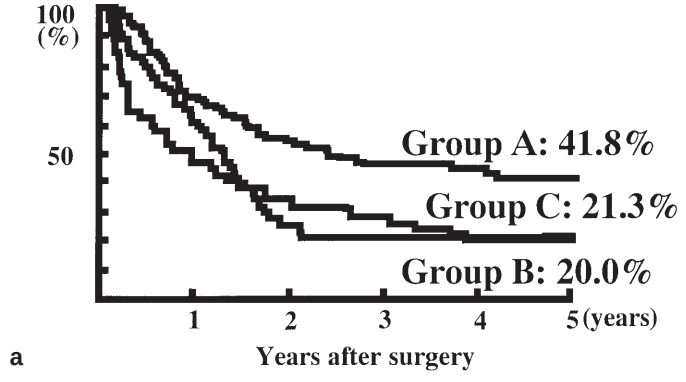
Results

Table 1 shows the patient characteristics in Groups A, B, and C. There were no significant differences in the patient characteristics between the three groups. How-

Table 1. Characteristics of the groups

	Group A	Group B	Group C	Significance
Age (mean)	61.2	61.1	60.6	NS
Sex (F/M)	19/72	7/45	2/29	NS
Location				NS
Cervical	7 (8)	2 (4)	1 (3)	
Upper third	12 (13)	9 (17)	4 (13)	
Middle third	39 (43)	22 (42)	19 (61)	
Lower third	27 (30)	14 (27)	4 (13)	
Abdominal	6 (7)	5 (10)	3 (10)	
Histology				NS
Well defined	26 (29)	14 (27)	13 (42)	
Moderately defined	41 (45)	23 (44)	10 (32)	
Poorly defined	16 (18)	6 (12)	7 (23)	
Others	8 (9)	9 (17)	1 (3)	
Stage				NS
0	21 (23)	7 (13)	4 (13)	
1	6 (6)	4 (8)	1 (3)	
2	5 (5)	7 (13)	0	
3	28 (31)	12 (23)	12 (39)	
4	31 (34)	22 (42)	14 (45)	
Radiation therapy	42 (46)	24 (46)	12 (39)	NS
Chemotherapy	17 (19)	9 (17)	5 (16)	NS
Operative approach				NS
Thoracolaparotomy	49 (54)	31 (60)	23 (74)	
Transhiatal	42 (46)	21 (40)	8 (26)	

Percentages shown in parentheses
NS, not significant



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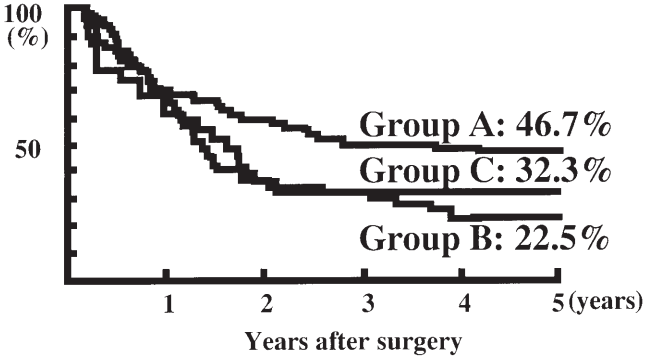

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Fig. 1. a Survival curves of all cases of resected esophageal cancer patients. A *vs* B: Log-rank, $P = 0.0094$; generalized Wilcoxon, $P = 0.0157$. A *vs* C: Log-rank, $P = 0.0004$; generalized Wilcoxon, $P = 0.0001$. **b** Survival curves of resected esophageal cancer patients who died due to recurrence of the primary cancer during the 5-year study period. A *vs* B: Log-rank, $P = 0.0162$; generalized Wilcoxon, $P = 0.0418$. A *vs* C: Log-rank, $P = 0.0775$; generalized Wilcoxon, $P = 0.0786$

ever, regarding the histological stages, group A included a higher percentage of stage 0 cases, while group C had a higher percentage of stages 3 and 4 cases. Women comprised 20.9%, 13.5%, and 6.4% in groups A, B, and C, respectively. The group C cases contained a higher percentage of well- and poorly differentiated squamous cell carcinomas than groups A and B. In addition, a higher percentage of group C patients underwent a thoracolaparotomy than did the patients in groups A and B.

Figure 1a shows the survival curves of all resected esophageal cancer patients. The 5-year survival rates were 41.8%, 21.3%, and 20.2% in groups A, B, and C, respectively. A significant difference was observed between groups A and B, and between groups A and C. After excluding the patients who died within 5 years without relapse, the 5-year survival rates were 46.7%, 32.3%, and 22.5% in groups A, B, and C, respectively. A significant difference was thus seen between groups A and B (Fig. 1b). Table 2 shows the first recurrent sites in the cases of primary cancer death. Group C had the highest percentage of lymph node recurrence cases (62%), while groups A and B both had a 37% recurrence. Table 3 shows the average days postoperatively when adjuvant therapies were started in the patients undergoing radiation and/or chemotherapy: 24.5, 31.1, and 57.5 days in groups A, B, and C, respectively. A significant difference was thus observed between groups A and B, and between groups A and C.

Table 2. Initial recurrent sites in primary cancer death

	Group A (n = 41)	Group B (n = 30)	Group C (n = 13)
Lymph node	15 (37)	11 (37)	8 (62)
Organ	17 (42)	10 (33)	4 (31)
Dissemination	6 (15)	3 (10)	0
Local	3 (7)	7 (23)	1 (8)
Others	0	1 (3)	0

Percentages shown in parentheses
P = 0.2949

Table 3. Average number of days postoperatively when adjuvant therapies were started

	Average no. of days	P-value
Group A (n = 42)	24.5	A vs B 0.0199
Group B (n = 22)	31.1	A *vs* C 0.0051
Group C (n = 11)	57.5	B vs C 0.1158

Discussion

The prognostic significance of the postoperative complications has been discussed mainly with respect to colorectal, head and neck,[8,9] and lung cancer.[10,11] However, the results are still controversial. For colorectal cancer, some authors report better 5-year survival rates in patients who have recovered from sepsis or who had febrile postoperative septic complications, thus suggesting that hyperthermia may have a beneficial effect.[1,2] Other authors claim that patients with such complications have a much higher risk of recurrence and death than those with a regular postoperative course.[3,4] Grandis et al.[9] speculated that, for head and neck cancer, a postoperative wound infection resulted in immunostimulation and thus ultimately reduced local recurrence. However, contrary to their own hypothesis, they found that patients who developed postoperative wound infections were 3.2 times as likely to develop recurrent disease than patients with similarly staged tumors who did not experience an infection. Immunologically, various types of stress including operation, infection, or postoperative complications thus appeared to suppress immumoreactivity through hypercytokinemia.[5]

We previously reported that the excessive surgical stress of thoracolaparotomy enhances tumor metastasis and thus results in a poor prognosis.[6] Of course, postoperative complications of any kind are a stress to the body. One mechanism of this phenomenon might be active oxygen production. Phagocytes, like leukocytes and macrophages, are known to produce superoxide anion radicals when exposed to appropriate stimuli.[12,13] Orr et al.[14,15] reported that hydrogen peroxide released by activated polymorphonuclear leukocytes caused endothelial injury and subsequently enhanced metastasis. Weiss et al.[16] also reported that stimulated neutrophils destroyed endothelial cells in vitro by generating hydrogen peroxide.

Various types of stress, such as operative stress, are known to cause the release of cytokines. Within several hours following an increase of interleukin (IL)-6 and IL-8, IL-1 and tumor necrosis factor α increase in the blood.[17] The degree of hypercytokinemia depends upon the strength of the stresses: for example, thoracolaparotomy during esophagectomy showed the highest increase of circulating IL-6 after surgery.[18] Some cytokines stimulate polymorphonuclear leukocytes, thus increasing their ability to adhere to endothelial cells,[19] and produce active oxygen.[15] DerHagopian et al.[4] described the phenomenon that trauma and its subsequent inflammation does indeed attract neoplastic cells, and called this phenomenon "inflammatory oncotaxis." The enhancing effect for tumor metastasis caused by stresses might thus be termed "stress oncotaxis."

Ogawa et al.[20,21] proposed a second-attack theory, meaning that the first stimulation to generate hypercytokinemia does not damage the organs, but a second attack actually damages organs by generating active oxygen in leukocytes which thereafter accumulates within the organs. An esophagectomy, especially through a thoracolaparotomy, might induce severe stress, and postoperative complications could thereby increase the degree of hypercytokinemia. If cancer cells are circulating in the organs in this situation, they may likely become implanted in the organs by adhering to the endothelial cells damaged by excessive active oxygen production. Our results thus indicate that postoperative complications could be a second attacker and therefore contribute to a poor prognosis.

The characteristics of patients in each group varied, but without significance. However, the difference in the survival rates between groups A and B, and groups A and C was clear. In addition, the average postoperative day when adjuvant therapies were started was significantly different between groups A and B, and groups A and C. However, in our institution, adjuvant therapy using irradiation and/or chemotherapy did not contribute to an improvement in the prognosis (data unpublished). The differences in startup day of adjuvant therapy thus did not appear important. This fact also supports our understanding that postoperative complications contribute to a poor prognosis in cancer patients.

The survival curves of groups B and C were quite similar. This fact supports the hypothesis that even a small stimulation could produce a second attack sufficient to generate unusual cytokine production.

Based on these findings, postoperative complications might thus be a very important factor for estimating the prognosis of cancer patients after surgery. However, we must accumulate further case study results and reevaluate the data because, in this study, each group contained only a small number of patients. If our results are correct, then the use of radical scavengers might thus help to improve the prognosis of cancer patients suffering from postoperative complications.

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