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일차성 상피성 난소암/난관암/복막암에서 종양감축술 후 발생한 수술부위 감염의 임상적 결과

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Clinical Outcomes Associated with Surgical Site Infection in Epithelial Ovarian, Fallopian, and Peritoneal Cancer Patients Undergoing Cytoreductive Surgery

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The most common cause of postoperative morbidity is surgical site infection (SSI). Because certain SSIs can be avoided, risk factors should be assessed prior to surgery, and modifiable ones should be addressed. SSI occurs in approximately 6%-20% of women undergoing surgical cytoreduction for epithelial ovarian/fallopian/peritoneal cancer (EOFPC). This high rate is due to the highly complex nature of cytoreductive surgery and the risk of contamination with ascending microorganisms in vaginal, cervical and gastrointestinal operative sites. Accumulated evidence showed that SSI worsens survival by delaying the initiation of adjuvant chemotherapy. As a result, SSI should be avoided as much as possible, and gynecologic surgical teams should be aware of how to prevent it. This review examines the prevalence, risk factors, clinical significance, and likelihood of SSI following cytoreductive surgery for EOFPC.

Key Words: Surgical wound infection, Ovarian cancer, Prevalence, Risk factor, Prevention

Introduction

One of the most common causes of healthcare-associated morbidity is surgical site infection (SSI). It extends hospital stays and enhances readmission and reoperation rates, as well as medical costs.[1] Potential pathogenic bacteria can arise from the vagina, endocervix, and skin during gynecologic procedure, which is a unique element. These microorganisms have the ability to ascend from the vagina to the pelvic cavity, causing morbidity.[2] As a result, SSIs are one of the leading causes of readmission after hysterectomies.[3]

Ovarian cancer is the most lethal gynecologic neoplasm, and its prevalence is steadily rising in Korea.[4] Because ovarian cancer has no distinctive symptoms and no reliable screening method, over 70% of patients are found to have advanced disease at the time of diagnosis.[5] Cytoreductive surgery, which removes all primary and metastatic diseases directly, or with multi-organ resection, which debulks down to a minimal residual disease, is the basis

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of treatment for patients with advanced disease.[6] Because patients with minor residual tumors have a better survival rate, intensive surgical procedures with larger incisions and high complexity are unavoidable; thus, the risk of SSI is substantial.[7-11]

Although the incidence of SSI in ovarian cancer in Korea is unknown, SSI rates for women undergoing cytoreductive surgery have been previously reported to vary from 6% to 20%.[7-11] SSI is linked to higher postoperative mortality and chemotherapy delays. Furthermore, SSIs cause patients to have a lessened chemotherapy response and a higher likelihood of developing platinum-resistant malignancies, making SSI an independent risk factor for overall survival. Therefore, its occurrence and treatment measures have the potential to improve perioperative quality.

In this review, we evaluated the occurrence and outcomes of SSI in patients with epithelial ovarian/fallopian/peritoneal cancer (EOFPC) and identified risks to help reducing SSIs after cytoreductive surgery.

Definition of SSI

SSIs are infections that occur within 30 days of a surgical operation or within 90 days if an implant is left in place after the procedure, and affect either the incision or tissues deep into the operation site, according to the Centers for Disease Control and Prevention (CDC). A wound is considered infected if it meets any of the CDC definitions, which include the pathogen isolation from an aseptically obtained fluid or tissue culture from the wound; purulent drainage from the incision, with or without laboratory confirmation of infection; local signs and symptoms of infection, such as erythema and warmth; and a surgeon's diagnosis of wound infection.[1]

Classification of SSI after a Gynecologic Surgery

SSIs are divided into three categories: superficial, deep, and organ/space incisional. After a gynecologic procedure, this rule is applied to SSI. Vaginal cuff cellulitis is a superficial SSI that affects the superficial tissues at the vaginal surgical margin after a vaginal hysterectomy. Pelvic cellulitis is a deep incisional SSI that contains an infected fluid collection or hematoma that surrounds the retroperitoneal area at the vaginal apex without abscess formation. Organ/space SSIs include adnexal infection and pelvic abscess.[1,2]

According to the American College of Surgeons' National Surgical Quality Improvement Program (ACS NSQIP), a bowel leak itself is not considered an organ/space SSIs unless it is accompanied by an abscess or purulence. However, because bowel contents pushed into the peritoneal cavity necessitate further operation and act as a nidus for possible infection, bacteremia, and sepsis, some studies included these patients in organ/space SSIs.[7] Because bowel surgery has become more common in cytoreductive surgery for EOFPC, and bowel leakage could potentially lead to infections, a broader definition may be required to prevent SSIs.

Incidence of SSI in Cytoreductive Surgery

Following cytoreductive surgery for epithelial ovarian cancer, the rate of SSI was reported to be 6%-20% (Table 1).[7-12] In comparison to the general incidence of SSIs, which was according to CDC is expected to be 2.8%,[13] the incidence of SSIs after cytoreductive surgery is substantially greater. As previously stated, the substantial surgical aspect of cytoreductive surgery for EOFPC could be the reason.

Table 1. SSI incidence following a cytoreductive surgery

Study	SSI (%)	Sample size (n)	Group	Study design
Tran et al.[7]	10.8	888	USA	Retrospective review
Matsuo et al.[8]	15.9	276	USA	Retrospective review
Lippitt et al.[9]	20.0	219	USA	Prospective quality improvement study
Mahdi et al.[10]	6.5	2,231	USA	Retrospective review
Johnson et al.[11]	6.0	635	USA	Prospective quality improvement study
O'Donnell et al.[12]	15.9	339	UK	Prospective quality improvement study

SSI, surgical site infection.

Table 2. Risk factors of SSI following a cytoreductive surgery, which was proven with multivariate analysis

Risk factors		OR or HR (95% CI)	Reference
Non-modifiable factor	Older age	1.23 (1.13-1.34)	7
		1.03 (1.002-1.06)	8
	ECOG performance status (1)	1.32 (1.05-1.66)	7
	ECOG performance status (2+)	2.53 (1.86-3.43)	7
	Body mass index (kg/m^2)	1.41 (1.12-1.76)	7
		1.09 (1.04-1.13)	12
	ASA level >2	1.68 (1.07-2.64)	7
	Diabetic requiring insulin	4.16 (1.37-12.6)	8
		5.00 (1.61-15.5)	12
	Hypertension	3.49 (1.77-6.9)	8
	Dyslipidemia	2.21 (1.08-4.53)	8
	Peripheral vascular disease	3.82 (1.09-13.37)	7
	Gastroesophageal reflux disease	2.13 (1.23-3.71)	7
	Advanced stage disease	4.49 (1.05-19.3)	8
	Nodal metastasis	2.36 (1.23-4.54)	8
	Operating time (per hour)	1.18 (1.03-1.36)	7
	High surgical complexity (vs. low)	4.19 (1.61-10.88)	7
	Bowel resection	2.31 (1.01-5.3)	8
	Suboptimal surgery	1.85 (1.40-2.45)	7
Modifiable factor	Wound drain (vs. none)	3.23 (1.68-6.19)	12
	Staples (vs. subcuticular suture)	3.58 (1.84-6.97)	12
	Decreased bicarbonate at postoperative day 3	0.86 (0.75-0.99)	8

SSI, surgical site infection; OR, odds ratio; HR, hazard ratio; CI, confidence interval; ECOG, European Cooperation Oncology Group; ASA, American Society of Anesthesiology.

Risk Factors of SSIs in Cytoreductive Surgery

Three earlier studies looked back at the risk variables for SSI after cytoreductive surgery for EOFPC and discovered a slew of them.[7,8,12] Table 2 summarizes the risk factors identified by multivariate analysis. Although identifying modifiable risk factors is crucial, the majority are difficult to change.[13]

Notably, the majority of SSIs are caused by the patients'

own risk factors. Infections are more prevalent in patients with a high body mass index,[7,10] which is a well-recognized etiological risk for SSI.[13,14] Obesity is also linked to a higher 30-day morbidity and 90-day mortality rate after cytoreductive surgery in women with epithelial ovarian cancer.[15] SSIs in the organ and spaces are independently associated with a history of gastroesophageal reflux disease history.[7] Despite the ambiguous link between surgical complexity and postoperative complications,[10] it was shown that surgical complexity is an independent predictor of SSI.[7] Additionally, bowl resection, which is essential for complete cytoreduction in up to 40% of cytoreductive surgery, has a 10% SSI rate.[8,16-18] A longer surgery time is linked to a higher rate of SSI.[7,10] Postoperative drainage, on the other hand, is still a point of contention.[7,10,12] Despite the diverging results of this practice, drainage has been assumed to reduce SSI by assisting in the early diagnosis of anastomotic leak following a bowel resection; hence, surgeons find it difficult to operate without it. The use of staples to close wound is also linked to an increased risk of SSI.[12] Most risk factors for SSI are not controllable, and there is not enough time to address these issues just before surgery. Therefore, a deliberate strategic alternative approach beyond recognizing of risk factors is required to reduce SSIs.

SSI after a Cytoreductive Surgery is Associated with Postoperative Mortality and Readmission

SSI induces sepsis, which is the second most prevalent cause of mortality within 30 days after a primary cytoreductive surgery, according to a meta-analysis of 23 studies involving 2,352 patients. Sepsis is directly responsible for 15% of deaths in patients with advanced-stage EOFPC.[19] Additionally, SSI is linked to an increased risk of readmission and a10-day increase in hospital stay.[8,19-21] Therefore, lowering the SSI could contribute to decrease the mortality and morbidity rates.

SSI after a Cytoreductive Surgery is Significantly Associated with Poor Prognosis of Patients with EOFPC

Patients with EOFPC, who have SSI, have poor survival outcomes. Two retrospective studies revealed that superficial and organ/space SSIs are independently linked to lower overall survival rate (Table 3).[7,8]

There are three explanations for this. First, SSI frequently leads to rehospitalization and extended hospital stays, delaying adjuvant treatment and potentially lowering cancer-specific survival rates.[7,12,22] Second, the existence of SSI could indicate a weakened cancer immune system. Because the innate immune system is fight against tumors is co crucial in disease progression,[23] a weakened immunity has a negative impact on survival. Third, SSI stimulates the proliferation of cancer cells. SSI causes tumor growth by producing proinflammatory cytokines, such as interleukin 1 and tumor necrotic factor alpha.[24] Moreover, bacterial endotoxins, such lipopolysaccharides induce tumor growth directly via Toll-like receptor 4 and nuclear factor kappa β.[25]

To enhance the overall survival of patients who had cytoreductive surgery for EOFPC, SSI must be controlled. More studies on consequences of SSI on patients with

Table 3. Effect of SSI on the survival of patients with epithelial ovarian/fallopian/peritoneal carcinoma

Study	Sample size (n)	SSI, number (%)	Statistical analysis	HR (95% CI)	Survival
Tran et al.[7]	888	96 (10.8)	Multivariate	Superficial SSI: 1.69 (1.12-2.57)	OS
				Organ/space SSI: 1.46 (1.07-2.00)	OS
Matsuo et al.[8]	276	44 (15.9)	Univariate	2.2 (1.5-3.2)	PFS
			Univariate	1.8 (1.1-3.0)	OS

SSI, surgical site infection; HR, hazard ratio; CI, confidence interval; OS, overall survival; PFS, progression free survival.

EOFPC are urgently needed, as are evidence-based interventions to reduce it.

Interventions to Minimalize the SSI in Cytoreductive Surgery

The Surgical Care Improvement Project (SCIP) started in 2006 with the goal of lowering SSI rates. The SCIP program aimed to standardize antibiotic therapy, including the time, type, and duration of antibiotics' administration, as well as glycemic control, hair removal, and normothermia.[26] Despite high compliance, there was little evidence that it reduce SSI rates.[27] Consequently, despite rigorous adherence to the SCIP guidelines, the baseline SSI rate in the preintervention cohort was as high as 16.8%; additionally, the SSI rate following cytoreductive surgery with intestinal resection was 58.5%.[28] Therefore, the need for additional interventions is indicated.

A perioperative SSI reduction bundle of therapies beyond SCIP was designated based on gathered evidence to lower SSI rates and demonstrated their preventive effects. The SSI rate was reduced by approximately half due to a comprehensive bundle addressing the pre-, intra-, and postoperative treatment, as reported in Table 4.[9,28-31] Preoperative chlorhexidine wash, oral antibiotics with/without mechanical bowel preparation, separate fascial closure tray, gown and gloves change, and postoperative daily bathing with chlorhexidine solution were all included to cytoreductive surgery.

In gynecological cancer surgery, prophylactic use of a vacuum-assisted wound closure device could minimize SSI by 33%.[32] After a cytoreductive surgery for ovarian cancer, the use of a subcutaneous negative-pressure wound drain was found to be a useful strategy for achieving clearer wound healing and less wound complications (12.9% vs. 27.0%; p=0.032).[33] Furthermore, when compared to the controls, the SSI rate was significantly reduced from 32.0% to 8.3% in patients who underwent

Table 4. Summary of interventions recommended for SSI prevention in cytoreductive surgery

Phases	Intervention	Reference
Preoperative	Patient's education about SSI prevention	31
	4% Chlorhexidine gluconate shower night before and day of surgery	9, 28, 31
	Chlorhexidine cloths at morning admission	31
	Mechanical bowel preparation with oral antibiotics using MiraLax powder, Bisacodyl tablets, antibiotics	9
Intraoperative	Antibiotics admission	9, 31
	Complete coverage of incisional area with 2% chlorhexidine gluconate and 70% isopropyl alcohol solution or 4% chlorhexidine solution	9, 28, 31
	Redose of cefazolin within 3-4 hours after incision	9, 28, 31
	Sterile closing tray for fascia and skin closure	28, 31
	Glove change before fascia closure, gown and Instruments change if soiled	9, 28, 31
Postoperative	Good hand hygiene	28, 31
	Hand-cleansing agent readily	28, 31
	Ensure dressing removal within 24-48 hours	9, 28, 31
	Patient shower with 4% chlorhexidine gluconate after dressing removal	28, 31
	Patient education on wound care and infection symptoms	9, 28, 31
	Strict glycemic control to keep blood sugars less than 180 mg/dL	9
Post dismissal	Dismiss patient with 4-oz of 4% chlorhexidine gluconate	28, 31
	Follow-up phone call within 24-72 hours	28, 31

SSI, surgical site infection.

general surgery, colorectal or gynecologic procedure, and received negative-pressure therapy.[34] This intervention, when taken as a whole, is worth exploring for this high-risk population. Further study would be considered necessary to confirm its effectiveness.

Education for Surgeons and Perioperative Personnel

A coordinated structure to facilitate surgical strategies is one of the most significant components in limiting SSI. Evidence-based guidelines, education for healthcare personnel and patients, and monitoring are the three essential elements for SSI prevention.[35] So far, the guidelines have been formed based on accumulated research studies. A systemic examination of education found that diverse teaching methods, including through education program, were implemented in various centers. To accomplish this, entire staff, including surgeons and perioperative personnel, as well as patients, had to be involved.[36] In addition, for a suitable infrastructure, hospitals must adapt their systems and culture.[37] A committed leadership, good compliance with various elements of SSI bundle, a high degree of staff participation, and the centralization of crucial surgical activities are all important factors to successfully reduce SSIs.

Conclusion

Patients with EOFPC who undergo cytoreductive surgery are more likely to develop SSI, which is linked to increased postoperative morbidity, mortality, and worse survival rates. Therefore, controllable factors, such as wound closure material selection provide chances to prevent SSIs and limit the disrupted aspects of survival in these women.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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