10.6% increase in the 5-year overall survival compared with pelvic lymphadenectomy alone. Considering previous results of retrospective and prospective studies, standard primary surgery for low-risk endometrial cancer would include hysterectomy and bilateral salpingo-oophorectomy, but would not include lymphadenectomy. On the other hand, the therapeutic role of lymphadenectomy should be continuously assessed in intermediate- and high-risk endometrial cancer because combined pelvic and para-aortic lymphadenectomy might have a survival benefit. The 5-year survival rates were reportedly 79–85% for patients with stage III endometrial cancer who had been treated at tertiary hospitals in which para-aortic lymphadenectomy was routinely performed,[13,19] but it was 65% for patients with stage III endometrial cancer and no gross swelling of para-aortic nodes who had been treated at tertiary hospitals in which para-aortic lymphadenectomy was not performed.[20]

Many physicians regard breast cancer as a systemic disease and lymph node metastasis as an indicator that distant metastasis has already occurred.[21] With this theory, removal of lymph nodes is not important to survival. In fact, lymphadenectomy for patients with breast cancer and lymph node metastasis is currently performed less commonly than in the past. However, it is not that simple in endometrial cancer.

The FIGO staging system was recently changed.[22] In endometrial cancer, FIGO stage IIIC is now divided into two categories: IIIC1 and IIIC2. Para-aortic lymph node involvement is categorized as a single substage: IIIC2. The reason for this change is that previous data suggested a worse prognosis if para-aortic nodes are involved. However, the prognosis seems to depend on treatment as well as the extent of disease. In 2000, Mariani *et al.* showed that the 5-year overall survival for patients who had undergone para-aortic lymphadenectomy was 85% compared with 71% for patients who had not undergone para-aortic lymphadenectomy ($P = 0.06$) according to the data of 51 patients with lymph node metastasis.[13] In 2007, Fujimoto *et al.* reported that the 5-year disease-related survival for patients who had undergone para-aortic lymphadenectomy was 69% compared with 54% for patients who had not undergone para-aortic lymphadenectomy ($P = 0.19$) according to the data of 63 patients with lymph node metastasis.[23] In 2011, the author and colleagues also reported that the 5-year overall survival for 28 patients who underwent combined pelvic and para-aortic lymphadenectomy and were positive for pelvic node metastasis and negative for para-aortic node metastasis was 89% compared with 47% for 37 patients who underwent pelvic lymphadenectomy alone and were positive for lymph node metastasis, and 60% for 28 patients who underwent combined pelvic and para-aortic lymphadenectomy and were positive for para-aortic node metastasis.[24] All of these studies suggest that lymph node metastasis is associated with a wide spectrum of prognoses for endometrial cancer and that endometrial cancer can be cured by appropriate removal of regional lymph nodes even if some lymph nodes are already affected. Although the systemic theory has a larger number of supporters in the field of breast cancer, gynecologists should not apply the systemic theory to endometrial cancer.

Differences in failure patterns between surgical procedures with and without para-aortic node dissection may support the therapeutic efficacy of para-aortic lymphadenectomy.[25] In terms of failure sites in the SEPAL study, there was a higher rate of para-aortic node failure in the pelvic lymphadenectomy alone group than in the pelvic and para-aortic lymphadenectomy group (5.1% vs 0.6%, $P = 0.0004$). Para-aortic node recurrence was a failure pattern peculiar to the pelvic lymphadenectomy alone group. In addition, when only those patients who had received adjuvant chemotherapy were considered, there was still a higher rate of para-aortic node failure in the pelvic lymphadenectomy alone group than in the pelvic and para-aortic lymphadenectomy group (9.5% vs 1.3%, $P = 0.0036$). Adjuvant chemotherapy (cisplatin + adriamycin + cyclophosphamide/paclitaxel + carboplatin/docetaxel + carboplatin) might not be able to replace surgical removal as a treatment for metastatic lymph nodes.

Pitfalls of Randomized Surgical Trials

Although the SEPAL study supported the therapeutic efficacy of para-aortic lymphadenectomy in endometrial cancer, it was a retrospective cohort study. Thus, another prospective study is needed to validate the therapeutic effect of para-aortic lymphadenectomy. However, should such a study be a randomized controlled study? Some physicians would not participate in a randomized controlled trial in which pelvic lymphadenectomy versus combined pelvic and para-aortic lymphadenectomy is compared for patients with high-risk endometrial cancer because they think highly of the effectiveness of para-aortic lymphadenectomy and would feel uneasy about performing pelvic lymphadenectomy alone. Experienced gynecologic

oncologists tend to be familiar with para-aortic lymphadenectomy and its benefits and may decline participation in such a randomized controlled trial. Conversely, doctors with limited experience may be assigned the task of performing para-aortic lymphadenectomy, and the desired outcome may not be achieved because of the doctors' inadequate experience. Both scenarios give rise to a situation in which quality control of treatment might be reduced in the para-aortic lymphadenectomy group. Nonparticipation of such physicians would result in a selection bias in randomized studies, and conclusions based on the results of such studies would not be reliable. A randomized controlled study is, therefore, not the best format with which to demonstrate the full benefits of lymphadenectomy. A prospective cohort study may be a reasonable option for the trial and may even be the most appropriate method with which to assess the therapeutic significance of lymphadenectomy for high-risk patients.

Extent of Para-aortic Lymphadenectomy

Although the addition of para-aortic lymphadenectomy to pelvic lymphadenectomy might have a survival benefit in intermediate- and high-risk endometrial cancer, it is not actually quite that simple. Para-aortic lymph nodes are usually categorized into the areas above and below the inferior mesenteric artery (Fig. 1). Some sentinel node mapping studies in endometrial cancer showed that more than half of para-aortic nodes identified as sentinel were located above the inferior mesenteric artery.[26,27] In 2008, Mariani *et al.* showed that 77% of patients with para-aortic lymph node metastasis harbor disease above the inferior mesenteric artery.[28] In 2010, Fotopoulou *et al.* showed that 54% of patients with stage IIIC and 70% of patients with para-aortic node metastasis harbor disease above the inferior mesenteric artery.[29] They indicated the need for systematic lymphadenectomy including the pelvic and para-aortic area up to the renal vessels. In the SEPAL study, almost all patients in the pelvic and para-aortic lymphadenectomy group underwent removal of the section above the inferior mesenteric artery. Combined pelvic and para-aortic lymphadenectomy without removal of the area between the inferior mesenteric artery and renal veins might be insufficient to improve survival for patients with high-risk endometrial cancer. In a future study, to assess the therapeutic role of lymphadenectomy, information on the surgical field should be obtained and reported. Like Piver's classification of hysterectomy in cervical cancer, it is desirable that worldwide classification is defined.

Complications with or without Para-aortic Lymphadenectomy

Although selective lymphadenectomy does not increase morbidity,[30,31] systematic lymphadenectomy requires a longer operation time and increases postoperative complications. In Benedetti-Panici's trial, both early and late postoperative complications occurred significantly more frequently in patients who had undergone pelvic lymphadenectomy (31% in the lymphadenectomy arm and 14% in the no-lymphadenectomy arm, $P = 0.0001$).[4] Similarly, in the ASTEC trial, more patients in the lymphadenectomy arm developed postoperative complications than in the no-lymphadenectomy arm.[5] Kodama *et al.* reported that the most frequent complication was lymphedema and that the second most frequent complication was ileus.[32] Considering these facts, systematic lymphadenectomy should not be performed for patients who have little possibility of receiving benefits from lymph node dissection. We then need to consider what kind of surgery should be performed for patients other than those at low risk. The SEPAL study suggested that combined pelvic and para-aortic lymphadenectomy has a survival benefit for intermediate- and high-risk patients. This leads to the question of whether para-aortic lymphadenectomy itself increases perioperative complications, which has not been well discussed. The author and colleagues conducted a retrospective analysis to compare morbidity rates with and without para-aortic lymphadenectomy.[33] The incidence rate of leg edema that originates in systematic lymphadenectomy is reportedly about 25%.[34,35] Our study also showed that the most frequent complication was leg edema and that its incidence rate was 26%. In addition, that study showed that para-aortic lymphadenectomy did not increase leg edema.[33] The incidence rate of ileus that originates in systematic pelvic and para-aortic lymphadenectomy is reportedly 8–50% in patients with a malignant gynecologic tumor.[36–38] Fujita *et al.* reported that postoperative ileus occurred in 13% of patients who underwent para-aortic lymphadenectomy, but severe ileus occurred in only 1.4% of patients who underwent para-aortic lymphadenectomy.[37] They concluded that para-aortic lymphadenectomy is a feasible and safe operative procedure. Fagotti

et al. conducted a prospective study to elucidate the incidence of ileus in patients who had undergone para-aortic lymphadenectomy. They reported that postoperative ileus occurred in 50% of patients who had undergone para-aortic lymphadenectomy and that severe ileus occurred in 11% of patients who had undergone para-aortic lymphadenectomy. However, all patients with severe ileus recovered with only conservative management.[38] The author and colleagues showed that the incidence rate of ileus after combined pelvic and para-aortic lymphadenectomy was 12%, but severe ileus occurred in only 1.4% of patients.[33] That study showed a significant increase in postoperative ileus secondary to the addition of para-aortic lymphadenectomy, but no significant difference in severe ileus with or without para-aortic lymphadenectomy (1.4% vs 0.7%, $P = 0.58$). Based on the results of these studies, the author emphasizes that postoperative ileus after para-aortic lymphadenectomy occurs with a relatively high incidence rate, but is manageable.

In addition, the author and colleagues showed that para-aortic lymphadenectomy did not increase postoperative thrombosis, lymphocyst development, or intraoperative organ injury and concluded that para-aortic lymphadenectomy is a safe operative procedure when performed by experienced surgeons in tertiary centers.[33]

New Strategy for Preventing Leg Edema

As described in the previous chapter, leg edema is the most frequent complication after lymphadenectomy.[32,33] Postoperative leg edema is a serious complication and a chronic disease that lasts a lifetime in most cases.[39] Sentinel lymph node navigation surgery is a promising treatment for lowering the frequency of postoperative leg edema in patients with cervical carcinoma of the uterus. However, it is unknown whether sentinel lymph node navigation surgery can be applied in endometrial cancer.[40] According to the results of previous studies, adjuvant radiation therapy and number of resected lymph nodes are risk factors for leg edema.[34,35,41] A new strategy for decreasing the incidence of postoperative leg edema has been proposed. Abu-Rustum suggested that removal of circumflex iliac nodes distal to the external iliac nodes (CINDEIN) is likely to be a factor contributing to the risk of postoperative leg edema.[42] CINDEIN, which are the most distal external iliac lymph nodes (Fig. 1), have been called circumflex iliac nodes,[42] distal external iliac lymph nodes,[43] and suprainguinal nodes[27,44] in the literature, and they commonly comprise an enlarged lobular conglomerate of lymphatic channel-rich nodal and adipose tissue. There are three routes of lymphatic spread in endometrial cancer. The first route is from the fundus toward the adnexa and infundibulopelvic ligaments to the para-aortic nodes. The second route is from the lower and middle thirds of the uterus in the base of the broad ligaments toward the lateral pelvic wall. The third route is along the round ligaments to the CINDEIN. However, this third route might be a minor site in terms of metastasis. Matsumoto *et al.* reported that CINDEIN metastasis occurred the least often among all metastatic sites in endometrial cancer.[44] Niikura *et al.* reported that CINDEIN can be detected as sentinel lymph nodes in endometrial cancer, but the rate of detection was only 3.6%.[27]

In 2010, the author and colleagues showed that removal of CINDEIN was an independent risk factor for leg edema after lymphadenectomy as well as adjuvant radiation therapy and resection of more than 31 lymph nodes based on data of patients with endometrial cancer.[45] In 2011, we also showed that removal of CINDEIN was associated with an increased incidence of leg edema based on data of patients with cervical cancer.[46] Hareyama *et al.* showed an efficacy of CINDEIN-sparing lymphadenectomy for reducing postoperative leg edema based on data of more than 300 patients.[47] Although elimination of CINDEIN dissection may be helpful in reducing the incidence of leg edema, CINDEIN are regional lymph nodes of endometrial cancer. The author and colleagues investigated the metastatic incidence of CINDEIN in endometrial cancer. The incidence rate of CINDEIN metastasis was 10% in stage IIIC (node-positive) cases.[48] However, the incidence rate was only 1.7% among all cases of endometrial cancer. Matsumoto *et al.* reported that these incidences were 14.8% in node-positive cases and 3.8% in all cases.[44] Although the incidence in all cases in their study was slightly higher than that in our study, low-risk cases might not have been included in their study. From the viewpoint of CINDEIN metastasis in endometrial cancer, we do not believe that elimination of CINDEIN dissection can be performed in all patients with endometrial cancer. The author also showed that high-risk histology results (grade 3 endometrioid cancer or non-endometrioid cancer) and pelvic node metastasis were independent risk factors for CINDEIN metastasis.[48] Removal of CINDEIN can be eliminated in patients with G1/G2 endometrial cancer. If possible, CINDEIN should be preserved in patients with endometrial cancer because preservation of CINDEIN

might result in a reduction in the incidence of postoperative lower-extremity lymphedema.

Disclosure

The author declares no conflicts of interest.

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REVIEW ARTICLE

Randomized controlled trial versus comparative cohort study in verifying the therapeutic role of lymphadenectomy in endometrial cancer

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Abstract A consensus regarding the therapeutic role of lymphadenectomy in endometrial cancer has not been reached because of conflicting negative results of randomized controlled trials and positive results of a cohort study. Since the effects of new treatments tend to be overestimated in observational studies, positive results of an observational study should be validated by a future trial. However, special difficulties are presented in randomized controlled trials in surgery. External validity is important for guaranteeing the reliability of a result of the trial. Physicians' recruitment of eligible patients into a trial depends on the confidence of those physicians for a surgical procedure, workplace environment and feelings of personal responsibility relevant to patients' risk of recurrence. When two surgical procedures are compared in a randomized controlled trial, technical quality control may be reduced in the complicated surgery group due to experienced surgeons' non-participation. It is highly possible that the recruitment issue is a threat to external validity. Therefore, a randomized controlled trial may not be the best format for demonstrating the full benefits of complicated surgery. Multiple studies have demonstrated that the results of well-designed observational studies can be reliable and are comparable with those of randomized controlled trials. Journal editors and funding sources are requested to become more generous with observational studies, especially prospective cohort studies.

Keywords Endometrial cancer · Randomized surgical trial · Recruitment · Selection bias · Observational study

Introduction

Evidence-based medicine categorizes different levels of clinical evidence according to the strength of freedom from various biases. A randomized controlled trial (RCT) is the preferred design for a clinical trial. Prospective cohort studies are ranked below RCTs, and retrospective cohort studies are ranked still lower because of the biases inherent in the observations. In terms of providing 'proof,' case reports are considered to be of little value, and expert opinion has the very lowest ranking. RCTs definitely rank at the top of all types of clinical studies. Therefore, the results of RCTs tend to be taken on blind faith. In fact, such a situation was observed in the gynecologic oncology field during the period from 2008 to 2009. Negative results of two randomized controlled trials on the therapeutic effect of lymphadenectomy in endometrial cancer became accepted worldwide [1, 2]. Many physicians in Japan also started expressing a negative opinion about the therapeutic role of lymphadenectomy in endometrial cancer despite the fact that there were limitations in the designs of both trials. RCTs must be internally valid, but the results are relevant only to a definable group of patients in a particular clinical setting. Namely, RCTs inevitably have limitations of external validity [3, 4]. On the other hand, the results of two studies published in the *New England Journal of Medicine* in 2000 showed that well-designed observational studies and RCTs overall can produce similar results [5, 6].

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In this article, we discuss the issue of external validity and future possibilities for observational studies.

Therapeutic role of lymphadenectomy in endometrial cancer: previous discussion

The therapeutic effect of lymphadenectomy in endometrial cancer has been the subject of great debate in recent years. The results of two randomized trials published in 2008–2009 led the authors to conclude that pelvic lymphadenectomy does not have a therapeutic effect for clinical stage I patients [1, 2]. Clinical stage I cases include mainly low-risk cases and some intermediate- and high-risk cases. The conclusion drawn by the authors would be correct for low-risk cases. However, some physicians have overgeneralized the results of these RCTs and started applying this conclusion to high-risk patients as well. In addition, some physicians have started expressing a negative opinion about the efficacy of lymphadenectomy without considering the variety of procedures. This is an unreasonable and dangerous assumption because it may result in high-risk patients not receiving optimal treatment. The point attracting the most criticism in these two RCTs is the very low rate of implementation of para-aortic lymphadenectomy. The para-aortic area is the most frequent site in which sentinel nodes are most frequently identified [7] and the second most frequent site in which metastasis is pathologically diagnosed [8]. Para-aortic node metastasis has been detected in more than half of patients with pelvic lymph node metastasis [9, 10]. Furthermore, the significance of the para-aortic area between the inferior mesenteric artery and the renal vein has been recognized [9], and removal of the area may be integral to demonstrate the full benefit of lymphadenectomy. Within this framework, the surgery performed in the two RCTs, i.e., pelvic lymphadenectomy, cannot show the full benefit of lymphadenectomy.

Results of the SEPAL (Survival Effect of Para-aortic Lymphadenectomy in Endometrial Cancer) study suggest that combined pelvic and para-aortic lymphadenectomy has a therapeutic effect in intermediate-/high-risk endometrial cancer [11]. The lymphadenectomy in the SEPAL study included routine removal of the para-aortic area between the inferior mesenteric artery and the renal vein. Since that study was a retrospective cohort study, another study is needed to validate the therapeutic effect of para-aortic lymphadenectomy. In fact, it appears that some randomized studies are being planned to validate this issue and will be implemented in the near future. However, should such a study be a RCT?

Pitfalls of randomized trials

The results of randomized trials on the same topic often disagree. Horwitz clarified several methodologic sources for the contradiction on the basis of data for over 200 RCTs in cardiology and gastroenterology, dividing the sources for the contradiction into two categories: those related to the design of the trials and those related to interpretation [12]. The design issues include eligibility criteria, baseline differences in the available population and variability in the treatment protocol for the principal or concomitant therapies and management of intermediate outcomes. The interpretation issues include variability in regulatory treatment compliance, frailty of double-blinding and the use of different outcomes. Despite these causes of contradictory results of RCTs, each study must be internally valid. However, the results of each study are relevant to only a definable group of patients in a particular clinical setting—i.e. RCTs must be less valid externally [3, 4]. This is an important issue and one on which we focus in this article. Meta-analyses are standardly conducted when several trials on similar topics produce contradictory results. However, such trials probably demonstrate heterogeneity in terms of treatment protocol and management of intermediate outcomes, and meta-analyses require considerable homogeneity among trials. Therefore, the results of meta-analyses may be misleading by obscuring important distinctions among trials. It may therefore be desirable for each trial to be individually assessed [12].

Special problems of randomized surgical trials

Special difficulties are encountered in RCTs for surgical procedures. First, blinding is not available. The effect of not using concealed random allocation can be as large or larger than the effects of worthwhile interventions [13, 14]. Second, the timing of conducting a randomized trial to assess a promising but immature surgical procedure may influence study results. A surgical procedure generally becomes refined with time, and complications decrease with use of the procedure. Consequently, changes in the superiority of treatments are very likely to occur with advances in skills [15]. Third, variations in any one surgical procedure are common and may influence clinical outcome. Treatment with protocols that have the same name but which are performed using different procedures may lead to different outcomes. Standardization of a surgical procedure is therefore an important issue [16]. According to the European Society for Medical Oncology (ESMO) guideline, use of lymphadenectomy for patients with clinical stage I endometrial cancer is at the discretion

of the surgeon. For patients with clinical stage II endometrial cancer, pelvic lymphadenectomy is recommended, but para-aortic lymphadenectomy is at the discretion of the surgeon [17]. In Europe, lymphadenectomy in many cases of endometrial cancer does not seem to include para-aortic node dissection, while lymphadenectomy in one of the two institutions participating in the SEPAL study routinely included para-aortic node dissection. Fourth, external validity tends to be more greatly hampered in a randomized surgical trial. The effectiveness of surgery depends on the skill of the surgeon, whereas the effectiveness of drugs is unrelated to the physician's skill. In the Emory Angioplasty versus Surgery Trial (EAST), the clinical benefit of percutaneous transluminal coronary angioplasty (PTCA) compared with that of coronary-artery bypass grafting (CABG) for patients with multivessel coronary artery disease was assessed by performing a prospective, randomized comparison [18]. Of the 842 eligible patients, 392 (46.6 %) agreed to participate. The CABG group ($n = 194$) and the PTCA group ($n = 198$) did not differ significantly in any-cause rate of death and Q-wave myocardial infarction. The remaining patients eligible for entry into the trial (450, 53.4 %) were not approached for several reasons, of which the attending or referring physician's refusal to participate was a major factor ($n = 353$) and refusal by the patient was a minor factor ($n = 97$). Of these 450 patients, 270 underwent CABG, 168 underwent PTCA and 12 underwent other therapies. The 3-year survival for the non-randomized group ($n = 450$) was 96.4 %, which was significantly better than that for the randomized group ($n = 392$; 93.4 %) ($p = 0.044$) [19]. Two plausible explanations can be provided for the survival difference between the non-randomized group and randomized group. One is that prognosis of patients in the non-randomized group may have been better than that of patients in the randomized group. Another is that physicians' judgment based on experience may be more important for treatment decision-making than a random choice. In a nutshell, valuing the care of individual patients may be more important than the uncritical adopting of results of RCTs. Physicians generally tend to use CABG for patients who have three-vessel disease or proximal left anterior descending artery stenosis [20]. Therefore, the physicians may have subconsciously used the right treatment in the right disease status. PTCA and CABG are appropriate treatments for distinct conditions. This problem results in a selection bias that threatens external validity. In particular, life-threatening situations cause difficulties in the recruitment of eligible patients into a randomized surgical trial. Namely, the recruitment issue cannot be separated from ethical issues. Fifth, funding of surgical trials is often a difficult issue [16]. In general, industry funding is less accessible for surgical trials, and pharmaceutical companies are a major source of funding for medical trials.

Because of these obstacles, it would seem to be difficult to conduct a randomized surgical trial. Between 1980 and 1996 most studies on surgical procedures were retrospective observational studies and only 7 % of all studies were based on RCTs [21–22]. In addition, there have been few RCTs comparing surgical procedures. In 1994, 76 % of randomized surgical trials were on medical treatment versus medical treatment, 18 % were on surgical treatment versus surgical treatment and 6 % were on medical treatment versus surgical treatment [24].

Selection bias: threat to external validity

The recruitment issue is closely related to the success or failure of a randomized surgical trial. It is a threat to external validity, which is almost a synonym of generalizability. Many studies have been conducted by dividing the issues into patients' reasons and physicians' reasons [23, 25–37]. Typical patients' reasons for declining to participate in RCTs are preference for one form of treatment [25, 26], disagreement with the idea of randomization [26–28], desire to be involved in the decision-making process [28, 29] and insurance coverage [23]. On the other hand, typical physicians' reasons for nonentry of eligible patients into RCTs are preference for one form of treatment [26], negative impact on the doctor–patient relationship [25, 30, 31], time constraints [25, 26], lack of staff and training [25], difficulty with informed consent [31], feelings of personal responsibility [31], risk of recurrence [32], priorities of individual care [33] and incentives [34]. Some factors are related to each other and therefore not independent. Time constraints and lack of staff may be synonyms for additional work load [35]. Feelings of personal responsibility, risk of recurrence and priorities of individual care may be batched together as an ethical issue [36]. Before 2006, the most common reason for nonentry of eligible patients by physicians was reported to be concern about the doctor–patient relationship. However, in a colon cancer study, Abraham et al. demonstrated that a preference for one form of surgery by the patient or the surgeon was the most common reason for nonentry of eligible patients and that concern about the doctor–patient relationship was not important [26]. In general, technically simple surgery is widely performed while complicated surgery is performed for patients judged by experts to be at high risk for poor prognosis. Experts can conduct both simple and complicated surgery, but non-experts may be able to perform only simple surgery. This systematic bias should be given attention in the planning of an RCT. If there is an RCT in which lymphadenectomy versus no

lymphadenectomy is compared for patients with low-risk endometrial cancer, most institutions would participate in this trial because the prognosis for both groups would be good. However, let us consider the situation of an RCT in which lymphadenectomy versus no lymphadenectomy is compared for patients with high-risk endometrial cancer. Many physicians would not participate in this trial because they would feel uneasy about a strategy of no lymphadenectomy for high-risk patients. A similar situation may arise in the case of an RCT in which pelvic lymphadenectomy versus combined pelvic and para-aortic lymphadenectomy is compared for patients with high-risk endometrial cancer. It is very likely that some experts would not participate in this trial because they would think highly of the effectiveness of para-aortic lymphadenectomy and they would be reluctant to perform lymphadenectomy without para-aortic node dissection. An experienced surgeon might be familiar with complicated surgery and its benefits and would then decline participation in an RCT. Conversely, a surgeon with limited experience may be assigned the task of performing such complicated surgery, and the desired outcome may not be achieved due to inadequate experience of the surgeon. Both scenarios give rise to a situation in which quality control might be reduced in the complicated surgery group. Nonparticipation of such institutions or physicians would result in a selection bias in the RCT, and conclusions based on the results of such an RCT would not be reliable. In a nutshell, a high-risk group may not be suitable for a randomized surgical trial. Although patients' preference is of course an important part of selection bias, the solution to the problem of physicians' preference seems to be a priority. Benson et al. reported that one-third of the physicians never pursued a clinical trial because of conflict with the priorities of individual care and excessive follow-up time [33].

Possible solutions for randomized surgical trials

Some possible solutions for the barriers to randomized surgical trials have been proposed. McCulloch et al. emphasized the need for prospective audit data collection and a system for continuous performance evaluation [38]. These are essential prerequisites for determining the need for randomized surgical trials. They also insisted on the importance of a non-randomized phase II trial conducted prior to randomized surgical trials because variations in surgical technique are determined, suitable end points are defined and required sample sizes are estimated in such studies. They reported the following important points that should be considered when conducting a randomized surgical trial. First, blinding is always difficult, but blinded observers should be used routinely for evaluating outcomes. Second, prospective audit data collection, quality control studies and phase II surgical studies could reduce the problems of timing randomized surgical trials (the learning curve). Third, a surgical procedure should be clearly defined and observed in a randomized surgical trial. Photographic or video evidence are recommended for maintaining surgical quality control [39]. Pathological specimens could help document the quality of the treatment. Fourth, variation in each surgeon's skill must be controlled on an integral premise. The premise includes minimization of nonentry of eligible patients into RCTs. As for surgeons' equipoise, van der Linden proposed a non-randomized surgeons design in an RCT [40]. In such a trial, patients are randomly allocated to two groups of surgeons who perform their operation of choice. Since both groups of surgeons are thoroughly familiar with their method of choice, this design might minimize unfairness based on technical factors. Chang et al. proposed a pre-randomization design in which the patient is randomized to a treatment group before being asked to consent to the assigned treatment [30]. However, neither of these designs has become the final solution. Klabunde et al. showed that patients with fee-for-service coverage were more than twice as likely to be enrolled than were patients with other types of coverage [23]. Albrecht et al. showed that physicians' appropriate manners and strategic methods at the time of informed consent were associated with improved accrual [37]. Insurance coverage or strategic physician communication may play a role in improvement of patients' participation. Abraham et al. showed that recruitment was significantly and negatively associated with an increased caseload [26]. Taylor et al. showed that more than two-thirds of physicians participating in a study on rare malignant tumors reported benefit to the institution as a primary incentive [34]. The distribution of supportive staff, such as data managers, or incentives, such as benefit to the institution, should be taken into consideration to reduce additional work load.

Despite the above-described possible solutions for randomized surgical trials, McCulloch et al. signaled the need for study types other than randomized trials [38]. They reported that prospective non-randomized designs that minimize known biases should be considered sympathetically by journals and funding bodies. Although van der Linden [40] was well aware of the pitfalls of randomized surgical trials, he seemed not to be able to outgrow attachment to RCTs. Nonentry of eligible patients, particularly that caused by physicians' non-participation due to lack of confidence by the physician for a surgical procedure, an inadequate workplace environment and the physician's feeling of responsibility for risk of recurrence is a problem that occurs in randomized surgical trials.

Randomized controlled trial versus cohort study

It seems that the hierarchy of clinical studies is immovable and that the RCT will maintain its established first-rank position in the hierarchy. In general, it has been reported that observational studies tend to conclude that any new treatment is better than that used on the standard arm, while RCTs seem likely to conclude that the new treatment is not better; putting it differently, the effects of new treatments tend to be overestimated in observational studies [13, 41–43].

Two interesting reports in which the results of RCTs and observational studies on the same topic were compared were published in 2000. Benson and Hartz demonstrated that estimates of treatment effects from observational studies and RCTs were similar in 17 areas of 19 diverse treatments. They concluded that estimates of treatment effects in observational studies are either consistently larger than or qualitatively different from those obtained in RCTs [5]. Concato et al. [6] conducted a study on the basis of the results of a meta-analysis of reports published in five major journals, namely, *Annals of Internal Medicine*, *British Medical Journal*, *Journal of American Medical Association*, *Lancet*, and *New England Journal of Medicine*. When the same topic is dealt with, the results of RCTs are inconsistent in some series. On the other hand, the results of observational studies on the same topic are mostly consistent. As a result, observational studies have narrow confidence intervals and RCTs have broad confidence intervals. Concato et al. concluded that the results of well-designed observational studies do not overestimate the magnitude of the effects of treatment compared with those in RCTs [6]. Considering the results of the two reports, it does not seem that well-designed observational studies are always inferior to RCTs.

Why did RCTs have broader confidence intervals in the study conducted by Concato et al. [6]? RCTs have been conducted using very limited groups. First, the population is scaled down by ineligibility criteria. The population is further scaled down due to patients' preference, doctor's prejudice and intentions of the host organization. The number of subjects finally entered in the study is much smaller than the original population (Fig. 1). Inability to recruit an adequate number of participants is the greatest threat to the success of RCTs.

In addition, subjects excluded from an RCT tend to have a poorer prognosis than that of subjects included in the trial, and this limits generalizability [5, 44]. In 1983, Chalmers et al. pointed out this recruitment issue. Case-fatality rates between treatment groups were found in 9 % of the blinded-randomization studies, in 24 % of the unblended-randomization studies, and in 58 % of the nonrandomized studies [13]. Putting it differently, subjects included in an RCT are not only a small fraction of the original population but are also a biased group with regard to prognostic risk, thereby explaining why the results of RCTs cannot be widely applied. On the other hand, subjects enrolled in an observational study account for a large fraction of the original population, and the results can therefore be widely applied.

RCTs definitely rank at the top of all types of clinical studies. However, if the exclusion criteria are the same and potential prognostic factors are controlled in observational studies, the results of well-designed observational studies can be reliable and bear comparison with those of RCTs. In 2010, Abraham et al. also compared the results of meta-analysis of nonrandomized studies on laparoscopic resection for colorectal cancer with those of meta-analysis of RCTs and concluded that meta-analysis of observational studies is as accurate as that of RCTs [45].

Therapeutic role of lymphadenectomy in endometrial cancer: a future plan

Chalmers et al. [13] pointed out the following with regard to observational studies and RCTs: a therapy that does not

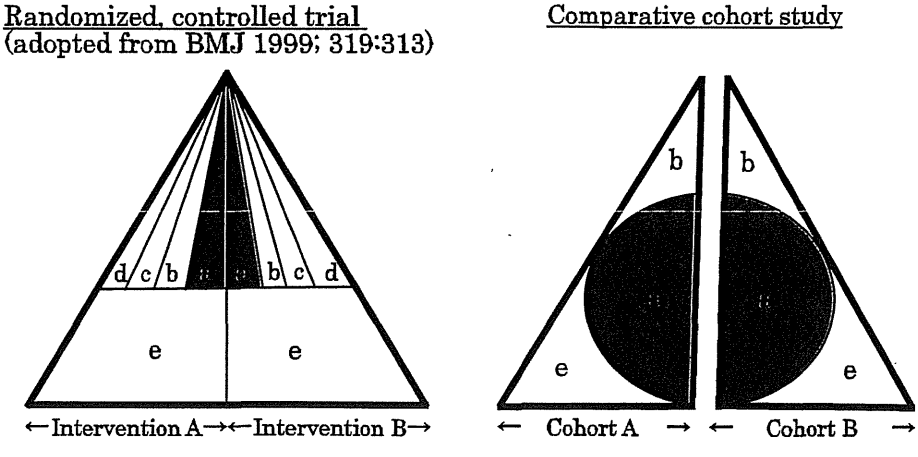

Fig. 1 Differences in inclusion and participation according to research design. *a* Subjects, *b* patient non-participation (patient preference), *c* not invited to participate (administrative oversight or practitioner preference), *d* center non-participation (not invited or center preference), *e* ineligible (eligibility criteria are generally stricter in a randomized controlled trial than in a comparative cohort study)

appear better based on the results of cohort studies can probably be discarded. However, in evaluating a positive result of a cohort study, investigators and readers should keep in mind the high false-positive rate of observational studies and, therefore, the need for further study, preferably an RCT. If a new therapy is found to be effective by a well-designed RCT, there is much less need for confirmation. If a new therapy is not found to be effective by an RCT, the reader should recall the high false-negative rate of RCTs.

Given previous results reported in high-level journals [1, 2, 11], the therapeutic role of lymphadenectomy should be continuously assessed in endometrial cancer because combined pelvic and para-aortic lymphadenectomy showed survival benefit for patients with intermediate-/high-risk prognosis in a well-designed observational study. Is a prospective randomized trial to validate the therapeutic effect of lymphadenectomy for intermediate- and high-risk endometrial cancer possible to conduct? It is difficult for high-risk patients to be treated in a randomized surgical trial because of selection bias that mainly includes physicians' non-participation. If such a trial is conducted, quality control might be reduced in the technically complicated surgery group. An RCT is, therefore, not the best format for demonstrating the full benefits of complicated surgery. A prospective cohort study may be the most appropriate method for assessing the therapeutic significance of technically complicated surgery for high-risk patients.

Conflict of interest We declare that we have no conflict of interest.

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Ultrastaging of para-aortic lymph nodes in stage IIIC1 endometrial cancer: A preliminary report

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HIGHLIGHTS

- Occult para-aortic node metastasis is frequently found in stage 3C1 uterine cancer.
- Local treatment of para-aortic area should be considered in stage 3C1 uterine cancer.

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ABSTRACT

Objective. The aim of this study was to determine the rate of occult metastasis, including isolated tumor cells, in para-aortic lymph nodes of patients with stage IIIC1 endometrial cancer who underwent pelvic and para-aortic lymphadenectomy.

Methods. A series of 15 patients who had undergone combined pelvic and para-aortic lymphadenectomy during the period from 2004 to 2010 and who were diagnosed as being positive for pelvic node metastasis but negative for para-aortic node metastasis were included in this study. Ultra-staging by multiple slicing, staining with hematoxylin/eosin and cytokeratin, and microscopic inspection was performed on a total of 242 para-aortic lymph nodes.

Results. Eleven (73.3%) of the 15 patients had occult para-aortic lymph node metastasis. Two patients (13.3%) had macrometastasis and nine patients (60.0%) had isolated tumor cells. Type 2 endometrial cancer tended to have a higher rate of occult metastasis than that of type 1 cancer (90% vs. 40%, $P=0.07$). The rate of occult para-aortic node metastasis was not related to the number of metastatic pelvic nodes. Five patients suffered recurrence in the lung or in the intraabdomen, but lymph node recurrence was not found in any case.

Conclusion. Patients with stage IIIC1 endometrial cancer have a potentially high rate of occult para-aortic node metastasis. Local treatment of the para-aortic region should be considered in patients with stage IIIC1 endometrial cancer until effective adjuvant therapy is established.

Introduction

In the field of breast cancer, many groups support the systemic theory; which regards lymph node metastasis as an indicator of poor prognosis, and surgical removal of lymph nodes as unimportant for survival [1]. Lymphadenectomy is therefore currently performed less commonly in breast cancer patients than it has been in the past. However, some groups support the spectrum theory, which does not always regard lymph node metastasis as an indicator of poor prognosis, and regards locoregional treatment as important for survival [2]. It is unclear which of these theories applies to the biological behavior of endometrial cancer.

The International Federation of Gynecology and Obstetrics (FIGO) staging system for endometrial cancer has recently been changed [3]. As the data suggest that the prognosis of endometrial cancer is worse if the para-aortic nodes (PANs) are involved, stage IIIC has now been divided into stage IIIC1 (positive pelvic nodes without positive PANs) and stage IIIC2 (positive PANs with or without positive pelvic nodes).

Although two randomized clinical trials failed to show a therapeutic benefit for pelvic lymphadenectomy in endometrial cancer [4,5], we recently reported that systematic lymphadenectomy including

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para-aortic lymphadenectomy has a therapeutic benefit in patients with intermediate- or high-risk endometrial cancer [6]. We also demonstrated that combined pelvic and para-aortic lymphadenectomy has a therapeutic benefit in patients with lymph node metastasis [7]. The para-aortic region has been shown to be a critical site for sentinel nodes in endometrial cancer [8,9]. Therefore, treatment of PANs might be a key factor for successful treatment of endometrial cancer.

Although it is possible that patients with stage IIIC1 endometrial cancer have occult PAN metastasis, a consensus regarding treatment of PANs in such cases has not been reached. The rate of occult disease in PANs for patients with stage IIIC1 endometrial cancer has remained unclear. Ultra-staging including serial sectioning and immunohistochemistry enables detection of occult lymph node metastasis including micrometastasis. In this study, the rate of occult PAN metastasis was assessed in patients with pelvic lymph node metastasis who were previously diagnosed as being negative for PAN metastasis. The importance of locoregional treatment of PANs in patients with stage IIIC1 endometrial cancer should be reconsidered.

Materials and methods

Study population

This study was carried out using data for 280 patients with endometrial carcinoma for whom extensive surgical staging including lymphadenectomy was performed in the Department of Obstetrics and Gynecology, Hokkaido University Hospital and Hokkaido Cancer Center from 2004 to 2010. All patients underwent a work-up with computed tomography and magnetic resonance imaging to detect distant metastases in the preoperative setting and underwent lymphadenectomy in addition to hysterectomy and bilateral salpingo-oophorectomy.

Of those patients, 155 patients (55.4%) were in stage IA (FIGO 2009), 47 (16.8%) were in stage IB, 12 (4.3%) were in stage II, 10 (3.6%) were in stage IIIA, 15 (5.4%) were in stage IIIC1, 30 (10.7%) were in stage IIIC2, and 10 (3.6%) were in stage IV (Table 1). One hundred thirty patients (46.4%) had grade 1 endometrioid adenocarcinoma, 78 patients (27.9%) had grade 2 endometrioid adenocarcinoma, 31 patients (11.1%) had grade 3 endometrioid adenocarcinoma, 24 patients had serous adenocarcinoma, 10 patients had clear cell carcinoma, 5 patients had mixed type adenocarcinoma, and 2 patients had other types of carcinoma. Fifty-three patients (18.9%) had lymph node metastasis. Two hundred sixty-one patients (93.2%) underwent pelvic lymphadenectomy plus para-aortic lymphadenectomy and 19 patients (6.8%) underwent pelvic lymphadenectomy alone. In terms of adjuvant treatment, chemotherapy consisting of a platinum-based regimen has been used for cases with intermediate-/high-risk factors in both institutions.

Fifteen patients who had undergone combined pelvic and para-aortic lymphadenectomy, who were diagnosed as positive for pelvic node metastasis but negative for para-aortic node metastasis (equivalent to the new FIGO stage IIIC1), were included in this study. Seven of these patients were treated at Hokkaido University Hospital and eight were treated at Hokkaido Cancer Center.

Ultrastaging of para-aortic lymph node metastasis

Ultra-staging was performed for a total of 242 PANs diagnosed as negative for metastasis, to assess them for microscopic tumor cells including isolated tumor cells. Ultra-staging was performed by multiple slicing, staining, and inspection of specimens.

The slicing process consisted of cutting five pairs of 4-μm-thick serial sections (10 sections in total) from archival, formalin-fixed, paraffin-embedded blocks containing all para-aortic nodes examined. Pairs of serial sections were cut at 120-μm intervals (Fig. 1). Sixty-eight paraffin-embedded blocks were examined, each containing several para-aortic nodes. A total of 680 sections were prepared.

Table 1
Clinical background of patients with endometrial cancer who underwent extensive surgical staging including lymphadenectomy during the study period.

	Total patients (N=280)
Age (years)	
Median (range)	59 (14–78)
FIGO surgical stage	
1A	155
1B	47
2	12
3A	10
3B	1
3C1	15
3C2	30
4	10
Tumor grade/histology	
Endometrioid	
G1	130
G2	78
G3	31
Non-endometrioid	
Serous	24
Clear	10
Mixed	5
Others	2
Myometrial invasion	
<1/2	177
≥1/2	103
Adnexal involvement	
Negative	257
Positive	23
Lymph node metastasis	
Negative	227
Positive	53
Lymphadenectomy	
PLX+PALX	261
PLX alone	19

PLX: pelvic lymphadenectomy, PALX: para-aortic lymphadenectomy.

The staining process consisted of hematoxylin and eosin staining of one section from each pair, and AE1/AE3 monoclonal antibody staining (Nichirei, Tokyo, Japan) of the other section from the pair (340 sections were stained with hematoxylin and eosin, and 340 were stained with cytokeratin). Staining was performed using an automated immunostainer (NexES, Ventana, Tucson, AZ).

During the inspection process, microscopic tumors were classified as isolated tumor cells (smaller than 0.2 mm in diameter), micrometastasis (0.2 mm to 2 mm in diameter), or macrometastasis (larger than 2 mm in diameter).

Statistical analysis

Correlations between variables were evaluated using the chi-square test or Fisher's exact test. The statistical significance level was set at 0.05. Statistical analyses were performed with StatView J-5.0 (SAS Institute, Cary, NC).

Results

Table 2 shows the clinicopathological characteristics of the 15 patients included in this study. The median age of those patients was 59 years (range: 42–76 years). Seven patients had endometrioid adenocarcinoma and eight had non-endometrioid carcinoma. Six patients had metastasis in a solitary pelvic lymph node and nine patients had metastasis in two or more pelvic lymph nodes. The median number of pelvic lymph nodes harvested was 55 (range: 25–76), and the median number of PANs harvested was 14 (range: 6–32). All patients had PANs removed, but four patients, including one obese patient and two patients with a preoperative diagnosis of cervical cancer, did not have nodes located

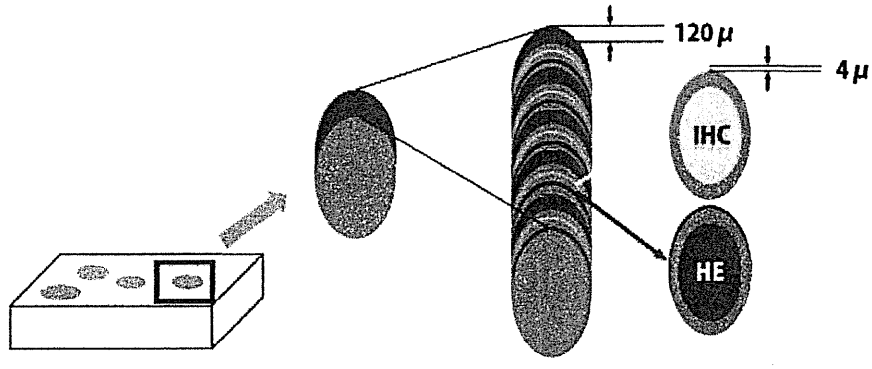

Fig. 1. Slicing for ultra-staging. Five pairs of 4-μm-thick serial sections were cut from archival, formalin-fixed, paraffin-embedded blocks. Pairs of serial sections were cut at 120-μm intervals.

above the inferior mesenteric artery removed. Two patients underwent hysterectomy and salpingo-oophorectomy followed by adjuvant chemotherapy prior to undergoing lymphadenectomy including PAN dissection because of severe genital bleeding. All patients received adjuvant chemotherapy consisting of a platinum-based regimen. None of the patients underwent radiation therapy or concurrent chemo-radiation therapy after lymphadenectomy.

Eleven (73.3%) of the 15 patients had occult PAN metastasis, comprising two patients (13.3%) with macrometastasis (Fig. 2) and nine patients (60.0%) with isolated tumor cells (Fig. 3). Five patients suffered recurrence in the lung or in the intraabdomen, but lymph node recurrence was not found in any case. The median time to recurrence from lymphadenectomy was 12 months (range: 8–19 months). Three (33.3%) of the nine patients with isolated tumor cells in PANs suffered non-lymphogenous recurrence, and 2 (50.0%) of the four patients without tumor cells in PANs suffered non-lymphogenous recurrence.

Table 3 shows the relationships between pathological characteristics and occult PAN metastasis. Occult PAN metastasis was identified in 40% of patients with type 1 endometrial cancer and 90% of patients with type 2 endometrial cancer ($P=0.07$). The rate of occult PAN metastasis identified by ultra-staging tended to be associated with tumor histology. When patients who had received chemotherapy before lymphadenectomy were excluded, the rate of occult PAN metastasis still tended to be associated with tumor histology. The rate of occult PAN metastasis was not related to the number of PANs removed, the number of nodes above the inferior mesenteric artery removed, or the number of metastatic pelvic nodes.

Discussion

In the field of breast cancer, there have been two competing theories regarding treatment of regional lymph nodes. Many groups support the systemic theory, which regards the cancer as a systemic disease, and lymph node metastasis as an indicator that distant metastasis has already occurred [1]. According to this theory, lymph node metastasis is an indicator of poor prognosis. Surgical removal of lymph nodes is not considered important for survival, and as a result, lymphadenectomy is currently performed less commonly in breast cancer patients than it has been in the past. However, some groups support the spectrum theory, which regards lymph node involvement to be important, but not necessarily an indicator that distant metastasis has already occurred. According to this theory, lymph node metastasis is not always an indicator of poor prognosis, and locoregional treatment is therefore important for survival [2].

Although the systemic theory has a larger number of supporters in the field of breast cancer, the systemic theory does not necessarily seem to apply to the biological behavior of endometrial cancer. The characteristics of patients with endometrial cancer and lymph node metastasis seem to be varied. Data from patients with endometrial

Table 2
Results of ultrastaging of 15 cases with stage IIIC1 endometrial cancer.

	Histology	LVSI	OVM	PC	PLN metastasized n	PLN removed n	PAN removed (326b1 removed) n (n)	CBL	Ultrastaging PAN	Positive site	Recurrence
1	G1	+	−	+	1	64	14 (0)	+	Negative		−
2	G2	+	−	+	3	25	6 (0)	−	Negative		Lung
3	Clear	+	−	−	3	33	8 (1)	+	Negative		Abdomen
4	G1	−	−	−	2	61	17 (6)	−	Negative		−
5	Serous	−	−	−	1	34	10 (0)	−	ITCs	326b2	−
6	Serous	+	−	+	1	62	14 (6)	−	ITCs	326b2	−
7	Serous	+	−	−	1	26	16 (8)	−	ITCs	326b2, 326b1	−
8	Serous	+	+	+	3	53	25 (17)	−	ITCs	326b2, 326b1	Lung
9	G3	+	−	+	2	48	12 (0)	−	ITCs	326b2	Lung
10	Serous	+	+	+	12	66	32 (20)	−	ITCs	326b2, 326b1	Abdomen
11	G2	−	−	−	2	76	19 (9)	−	ITCs	326b2	−
12	Serous/clear	+	+	+	4	75	25 (11)	−	ITCs	326b2	−
13	G2	+	+	−	2	41	11 (4)	−	ITCs	326b2	−
14	G3	−	−	−	1	55	10 (5)	−	Macro	326b2, 326b1	−
15	Clear	−	−	−	1	56	23 (10)	−	Macro	326b2	−

LVSI: lymphovascular space invasion, OVM: ovarian metastasis, PC: peritoneal cytology, PLN: pelvic lymph node, PAN: para-aortic lymph node, 326b1: PAN above an inferior mesenteric artery, 326b2: PAN below an inferior mesenteric artery, CBL: chemotherapy before lymphadenectomy, G1: endometrioid adenocarcinoma grade 1, G2: endometrioid adenocarcinoma grade 2, G3: endometrioid adenocarcinoma grade 3, Serous: serous adenocarcinoma, Clear: clear cell adenocarcinoma, ITCs: isolated tumor cells, Macro: macrometastasis.

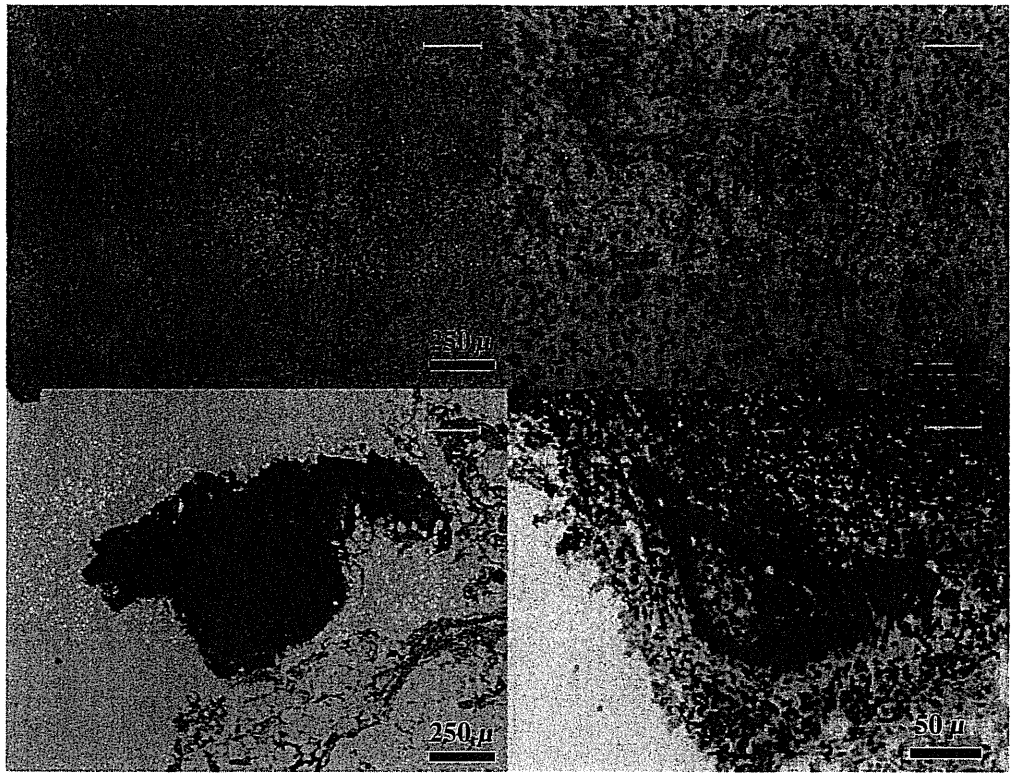

Fig. 2. Occult macrometastases show positive immunoreactivity for cytokeratin. Upper left, Case 14 (×4). Upper right, Case 14 (×20). Lower left, Case 15 (×4). Lower right, Case 15 (×20).

cancer suggest that the prognosis is worse if there is PAN metastasis. The FIGO staging system for endometrial cancer has recently been changed as a result of these data [3]. Stage IIIC has now been divided into stage IIIC1 (positive pelvic nodes without positive PANs) and stage IIIC2 (positive PANs with or without positive pelvic nodes). The para-aortic region has been shown to be a critical site

Fig. 3. Isolated tumor cells show positive immunoreactivity for cytokeratin. Upper left, Case 8 (×4). Upper right, Case 8 (×20). Lower left, Case 10 (×4). Lower right, Case 10 (×20).

Table 3
Relation between occult lesion in the para-aortic nodes and clinical factors.

	Ultrastaging		*P*-value
	Negative	Positive[a]	
Histology			
Endometrioid	3	4 (57%)	
Non-endometrioid	1	7 (88%)	0.28
G1/G2	3	2 (40%)	
G3/non-endometrioid	1	9 (90%)	0.07
Number of para-aortic nodes removed			
Less than 11	2	2 (50%)	
11 or more	2	9 (82%)	0.56
Number of the area above the IMA removed			
Less than 5	3	3 (50%)	
5 or more	1	8 (89%)	0.24
Number of metastatic pelvic node			
One	1	5 (83%)	
Two or more	3	6 (67%)	0.60

G1: endometrioid adenocarcinoma grade 1, G2: endometrioid adenocarcinoma grade 2, G3: endometrioid adenocarcinoma grade 3, Non-endometrioid: serous adenocarcinoma, clear cell adenocarcinoma, IMA: inferior mesenteric artery.
[a] Isolated tumor cells, micrometastasis, and macrometastasis.

for sentinel nodes in endometrial cancer [8,9], and PAN metastasis has been detected in 57% to 72% of patients with pelvic lymph node metastasis [10,11]. Considering these reports, treatment of PANs should be taken into consideration in the treatment of endometrial cancer. We recently demonstrated that addition of para-aortic lymphadenectomy to pelvic lymphadenectomy improved survival in patients with intermediate-/high-risk endometrial cancer [6]. We also demonstrated that prognosis of patients with stage IIIC endometrial cancer would depend much more on application of lymphadenectomy including para-aortic lymphadenectomy than nodal status [7]. In that study, the 5-year survival rate was 89.3% in patients who underwent pelvic and para-aortic lymphadenectomy and were positive for pelvic lymph node metastasis and negative for para-aortic lymph node metastasis, but it was 46.5% in patients who underwent lymphadenectomy without para-aortic lymphadenectomy alone and were positive for pelvic lymph node metastasis [7]. In addition, the prognosis of patients with stage IIIC endometrial cancer has improved as an increasing proportion of cases undergo complete surgical staging including lymphadenectomy [12]. These findings support the spectrum theory for endometrial cancer and suggest that lymph node metastasis is associated with a wide spectrum of prognoses. The authors believe that endometrial cancer can be cured by appropriate removal of regional lymph nodes even if some lymph nodes are already affected and that the spectrum theory can be applied to the biological behavior of endometrial cancer.

A systematic review of six studies which reported ultra-staging of sentinel lymph nodes in endometrial cancer, including studies of FIGO stage I–II and FIGO stage I–III patients, found that the overall rate of lymph node metastasis was 19.7%, including 5.8% with micrometastasis [13]. Khoury-Collado et al. conducted sentinel lymph node mapping by cervical injection of blue dye and Tc^{99}, and found that 12% of patients had sentinel lymph node metastasis including 3% with micrometastasis [14]. Although there has been no report regarding the results of ultra-staging of PANs in stage IIIC1 endometrial cancer, we assumed that occult PAN metastasis, including micrometastases, would be found in a larger proportion of patients with stage IIIC1 disease. Consequently, we found occult PAN metastasis in 73.3% of the patients with stage IIIC1 disease. Of course, our study has some limitations. First, the number of patients with stage IIIC was too small to draw a conclusion. Further investigation is needed to validate the results of this study. Second, there was a higher percentage of cases with non-endometrioid cancer, which might have had a great effect on the rate of occult metastasis in the PANs in the present study. However, the present study was based on a series of stage IIIC1 patients treated at the two hospitals during the study period. Interestingly, two patients who had received chemotherapy before lymphadenectomy were negative for occult PAN metastasis and two patients who did not have lymph nodes above the inferior mesenteric artery removed were negative for occult PAN metastasis. The actual rate of occult PAN metastasis, therefore, may be higher than that in the present study.

A relationship between micrometastasis and an increased risk of recurrence has been shown in a number of malignant tumors including breast cancer [15], vulvar cancer [16], gastric cancer [17], esophageal cancer [18], and melanoma [19]. A relationship between micrometastasis in PANs and an increased risk of recurrence in endometrial cancer was not shown in the present study, probably due to the small number of patients. However, it is possible that micrometastasis in PANs is associated with an increased risk of lymphogenous recurrence because it has recently been reported that PAN recurrence was a failure pattern peculiar to lymphadenectomy without para-aortic lymph node dissection [20]. None of the patients in the present study suffered lymphogenous recurrence. On the other hand, the role of systematic lymphadenectomy in preventing non-lymphogenous recurrence may be limited. All of the patients with recurrence in the present study had non-lymphogenous metastasis. Isolated tumor cells in PANs were not associated with an increased risk of non-lymphogenous recurrence. Ultrastaging requires a great deal of labor at the scene of clinical practice, and the prognostic significance of micrometastasis or isolated tumor cells has still not been clarified in endometrial cancer. Therefore, we do not intend to recommend doing ultrastaging for all patients with stage IIIC1 endometrial cancer. However, there may be a higher rate of occult disease in PANs for patients with stage IIIC1 endometrial cancer than we expected. Locoregional treatment in the para-aortic region should be considered in patients with stage IIIC1 endometrial cancer.

Conflict of interest statement
We declare that we have no conflicts of interest.

Acknowledgment

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A Prospective Study on the Efficacy of Octreotide in the Management of Malignant Bowel Obstruction in Gynecologic Cancer

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Objective: Malignant bowel obstruction (MBO), of which symptoms lead to a poor quality of life, is a common and distressing clinical complication in advanced gynecologic cancer. The aim of this study was to prospectively assess the clinical efficacy of octreotide to control vomiting in patients with advanced gynecologic cancer with inoperable gastrointestinal obstruction.

Methods: Patients with advanced gynecologic cancer, who presented at least one episode of vomiting per day due to MBO, were enrolled in this prospective study from 2006 to 2009. Octreotide was administered when necessary at doses starting with 300 μg up to 600 μg a day by continuous infusion for 2 weeks. Primary end point was vomiting control, which was evaluated by common terminology criteria for adverse events version 3 (CTCAE v3.0). Adverse events were also evaluated by CTCAE v3.0.

Results: Twenty-two cases were enrolled in this study. Octreotide controlled vomiting in 15 cases (68.2%) to grade 0 and 3 cases (13.6%) to grade 1 on CTCAE v3.0. Overall response rate to octreotide treatment was 81.8% in our patients' cohort. Among 14 cases without nasogastric tube, the overall response rate was 93.1% (13/14). Among 8 cases with nasogastric tube, 4 cases were free of tube with decrease of drainage, and overall response rate was 62.5% (5/8). No major adverse events related to octreotide were reported.

Conclusions: We conclude that 300-μg/d dose of octreotide was effective and safe for Japanese patients with MBO by advanced gynecologic cancer. Octreotide could contribute to better quality of life by avoiding placement of nasogastric tube.

Key Words: Octreotide, Malignant bowel obstruction, Gynecologic cancer, Quality of life

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Malignant bowel obstruction (MBO) is a common and distressing clinical complication in advanced gynecologic cancer and is reported in 5.5% to 42% of terminal patients with ovarian cancer.[1–3] Vomiting secondary to MBO is a great problem in terminal patients.

Current treatments for MBO for patients with advanced cancer include the following: (1) surgery to bypass/remove the obstruction, (2) gastrointestinal drainage via a nasogastric tube, and (3) medication (antimimetics or others). Surgical treatment is often contraindicated owing to poor performance status, and many patients with gynecologic malignancies (especially ovarian cancer cases) would not be eligible for surgery because of the presence of diffuse intraperitoneal carcinomatosis, multiple partial obstruction points, ascites, and/or previous radiotherapy. Placement of nasogastric tube may be the only treatment available for inoperable cases. A nasogastric tube can achieve symptomatic relief but sometimes causes mucosal erosion, esophagitis, and aspiration pneumonia, which lead to poor quality of life. Thus, from the standpoint of the quality of life of terminal patients, the best way is to control symptoms relating to MBO without placement of nasogastric tube.

Octreotide, an analog of somatostatin, is a drug to control symptoms due to MBO. It inhibits the release and activity of gastrointestinal hormones,[4] and modulates gastrointestinal function by reducing gastric acid secretion, slowing intestinal motility, decreasing bile flow, increasing mucus production, and reducing splanchnic blood flow.[4,5]

Although several retrospective studies on the clinical efficacy of octreotide have been reported in gynecologic cancer,[6,7] there have been no prospective studies on the efficacy and safety of octreotide for MBO by patients with gynecologic malignancy in the literature. Additionally, clinical study on octreotide conducted in Japan[8] included few patients with gynecologic malignancies, which raises questions whether octreotide is effective for MBO of Japanese patients with gynecologic malignancies. Thus, the aim of this study was to prospectively evaluate the efficacy of octreotide in controlling vomiting of patients with terminal gynecologic cancer with MBO.

PATIENTS AND METHODS

From March 2006 to December 2009, 22 patients with abdominal recurrence of advanced gynecologic cancer were enrolled in this prospective study.

The patients in this study were required to be hospitalized, to be between 20 and 80 years of age, to have MBO that was refractory to conventional medical treatment, and to have a life expectancy of at least 3 weeks. Before being enrolled in this study, the patients also had at least one episode of vomiting per day on one designated day or had marked drainage of bowel contents (≥300 ml/day) from a nasogastric tube. Patients who retained normal hepatic function, as indicated by a total bilirubin of 2.0 mg/dL or less, were eligible for the study. The study excluded patients with serious complications (eg, active infection, pleural effusion, and gastrointestinal hemorrhage) and those with symptomatic brain metastasis. After enrollment, the patients received octreotide (300 μg/d) subcutaneously or intravenously as a continuous injection for 7 days. Patients who responded to this 7-day course of treatment continued to receive the drug with the same dose up to 14 days. The dose of octreotide could be increased to 600 μg/d for another 7 days if no improvement of symptoms was observed with 300 μg/d at day 7. The patients were assessed daily to determine the number of vomiting episodes, the severity of their nausea, and (if relevant) the volume of fluid draining from the nasogastric tube.

Response criteria were based on the change from baseline (24 hours before the start of treatment) to days 4, 8, and 15 in the severity of vomiting, which was graded using CTCAE v3.0. The response to treatment was graded using 3 categories (complete control [CC], partial control [PC], and no control [NC]). Patients with grade 0 vomiting on day 8 were assigned a rating of CC. The rating was PC if the grade for vomiting was decreased by one grade or more from baseline on day 8. No change or an increase of grade was regarded as NC. In patients with a nasogastric tube at baseline, extubation was allowed if drainage was reduced to less than baseline. After extubation, the response to the treatment was graded according to the following 3 categories defined by grade of nausea/vomiting: CC (grade 0), PC (only one episode of vomiting per day or nausea only), and NC (no change or increase of grade). Change of other symptoms including nausea, anorexia, abdominal distension, and fatigue were also evaluated by CTCAE v3.0. The occurrence of adverse events and abnormal laboratory findings were considered for the evaluation of safety, and the severity of adverse drug reaction was graded in accordance with CTCAE v3.0. With regard to the clinical laboratory testing, hematology, biochemistry, and urine tests were performed just before the start of the treatment with study medication and after 8 and 15 days of treatment. This study was approved by the institutional review board of Hokkaido University Hospital and was conducted in compliance with Ethical Guidelines for Clinical Studies. In accordance with the declaration of Helsinki, written informed consent was obtained from all patients before enrollment.

The results reported by Shima et al[8] were taken into consideration to calculate the sample size. Because the clinical response rate (CC/PC) for octreotide treatment was expected to be 54% based on previous Japanese study,[8] we calculated that 22 patients would be needed to detect in response to octreotide of 55%, with 80% power and a 2-sided 5% significance level.

Steel test was used to analyze the statistical difference of the number of vomiting episodes, drainage from nasogastric tube, and other symptoms including nausea, appetite loss, abdominal distension, general fatigue between baseline and each point for evaluation (days 4, 8, and 15). Significance was set at $P < 0.05$. Statistical analyses were performed with the excel 2008 (Social Survey Research Information Co, Ltd).

RESULTS

Patients' Characteristics

Demographic and baseline characteristics of 22 patients are listed in Table 1. Median age of the patients was 62 years (range, 43–79 years). Ovarian cancer was the most frequent type of malignancy (n = 12 [54.5%]), followed by cervical or endometrial cancer (n = 6 [27.3%]), primary peritoneal cancer (n = 3 [13.6%]), and double cancer of endometrium and ovary