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Hospital volume-outcome relationship in vulvar cancer treatment: a Japanese Gynecologic Oncology Group study

Dear Editor,

The concept of volume-outcome relationship was originally introduced by Luft et al. [1] more than four decades ago in 1979. In their initial report, the study team intended to introduce the idea of regionalizing surgical service to improve the surgical outcome, and the fundamental knowledge of volume-outcome relationship is nested in that the more experience is associated with the better performance [1,2]. Since then, a number of studies have examined the volume-outcome relationship in gynecologic malignancies including ovarian, cervical, and endometrial cancers in in the past decades [3-13].

Yet, little has been examined about the volume-outcome relationship in vulvar cancer. In Japan, vulvar cancer is considered a rare tumor with the population incidence being around 0.2–0.4 per 100,000 [14]. This incidence rate is far lower compared to Western countries (approximately one-tenth to one-sixth) [14]. Due to the rarity, vulvar cancer has been understudied in Japan in the past. Therefore, information on volume-outcome relationship will be valuable to outline and reform the management strategy for women with vulvar cancer. The objective of the study was to examine the volume-outcome relationship for vulvar cancer treatment among the Japanese Gynecologic Oncology Group (JGOG)-affiliated centers.

This is a secondary exploratory analysis of a previously organized nationwide retrospective observational study by querying the JGOG-1075S database [15]. The study protocol was approved by the ethics committee of each participating institution (hosting institution, Kurume University; Institutional Review Board registration No. 14034), and was registered at the University Hospital Medical Information Network (registration No. UMIN000017080). Details of study outlines and contents were described previously [15]. Briefly, this nationwide study examined the consecutive 1,061 women with stage I-IV invasive vulvar cancer who received primary treatment care at 109 JGOG-affiliated centers from 2001–2010. The participating centers represented nearly two thirds of 181 JGOG-affiliated centers at that time.

The primary objective of analysis was to examine the association between hospital treatment volume of vulvar cancer and survival outcome. For the exposure allocation, hospital treatment volume over the 10-year study period was collected that included any treatment modality for primary therapy after the vulvar cancer diagnosis (surgery, chemotherapy, and radiotherapy). For the outcome measures of survival endpoint, progression-free survival (PFS) and overall survival (OS) were assessed. PFS was defined as the time interval from

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vulvar cancer diagnosis and the first recurrence/progression or death from disease, and OS was defined as the time interval from vulvar cancer diagnosis to death from any cause. Cases without survival event at the last follow-up were censored.

Cox proportional hazard regression models with restricted cubic spline transformation were fitted for analysis. Due to relatively limited sample size, a parsimonious adjustment was used to assess the survival effects of hospital treatment volume. A priori prognostic factors were entered in the final model (age, histology, and stage). This analytic approach was preplanned prior to the analysis. In a sensitivity analysis, the study cohort was restricted to histology cases without invasive Paget's disease. In addition, the study cohort was limited to surgical cases that had radical vulvectomy with inguino-femoral lymphadenectomy. The cohort was also restricted to stage IB or higher diseases. All the analysis was based on the 2-tailed hypothesis, a $p < 0.05$ was considered statistically significant. IBM SPSS Statistics (version 25; IBM Corp., Armonk, NY, USA) and R statistics (version 3.5.3; R foundation for Statistical Computing, Vienna, Austria) were used for the statistical analysis.

For the patient demographics in the study cohort, the median age of the study cohort was 72 years (interquartile range [IQR], 62–79), and the majority of vulvar cancer were squamous tumors (72.4%). Stage I disease were most frequently diagnosed in this cohort (37.4%), and the majority of patients received surgical treatment (75.4%). The median follow-up was 58.2 months (IQR, 23.6–86.2) among the censored cases, and disease recurrence/progression and deaths from any causes were recorded in 423 and 349 cases, respectively.

Survival effects of hospital treatment volume was examined in the whole cohort with all histology cases ($n=1,061$). The median hospital treatment volume was 9.5 (IQR, 5–14) cases per the 10-year study period. Hospital treatment volume of 23 cases or more over the 10-year study period represented the top-decile volume center. After adjusting for age, histology types, and cancer stage, there was no association between hospital treatment volume and PFS ($p=0.820$; **Fig. 1A**) or OS ($p=0.511$, **Fig. 1B**).

The study cohort was then restricted to cases without invasive Paget's disease ($n=909$). The median hospital treatment volume of this subcohort was 9 (IQR, 5–12) cases per the 10-year study period. After controlling for age, histology types, and cancer stage, there was no association between hospital treatment volume and PFS ($p=0.591$; **Fig. 1C**) or OS ($p=0.626$, **Fig. 1D**). Similarly, when the study cohort was restricted to women who underwent radical vulvectomy and inguino-femoral lymphadenectomy or restricted to cases with stage IB or higher diseases, there was no association between hospital surgical volume and survival outcome (data not shown).

To outline the overview of volume-outcome relationship in vulvar cancer survival, a systematic literature review was performed (**Supplementary Method 1**). Briefly, three public search engines (PubMed, Scopus, and Cochrane Central Register of Controlled Trials) were utilized, and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were consulted. Inclusion criteria were studies examined the survival outcome of women with vulvar cancer per treatment volume. A literature search was performed on September 20, 2020, and there was only one study that examined the survival effects of volume-outcome relationship in squamous type vulvar cancer [16]. Annual hospital surgical volume of 9 or more cases was statistically not associated with all-cause mortality compared to less than 9 cases (hazard ratio=0.9; 95% confidence interval=0.9–1.0; $p=0.05$).

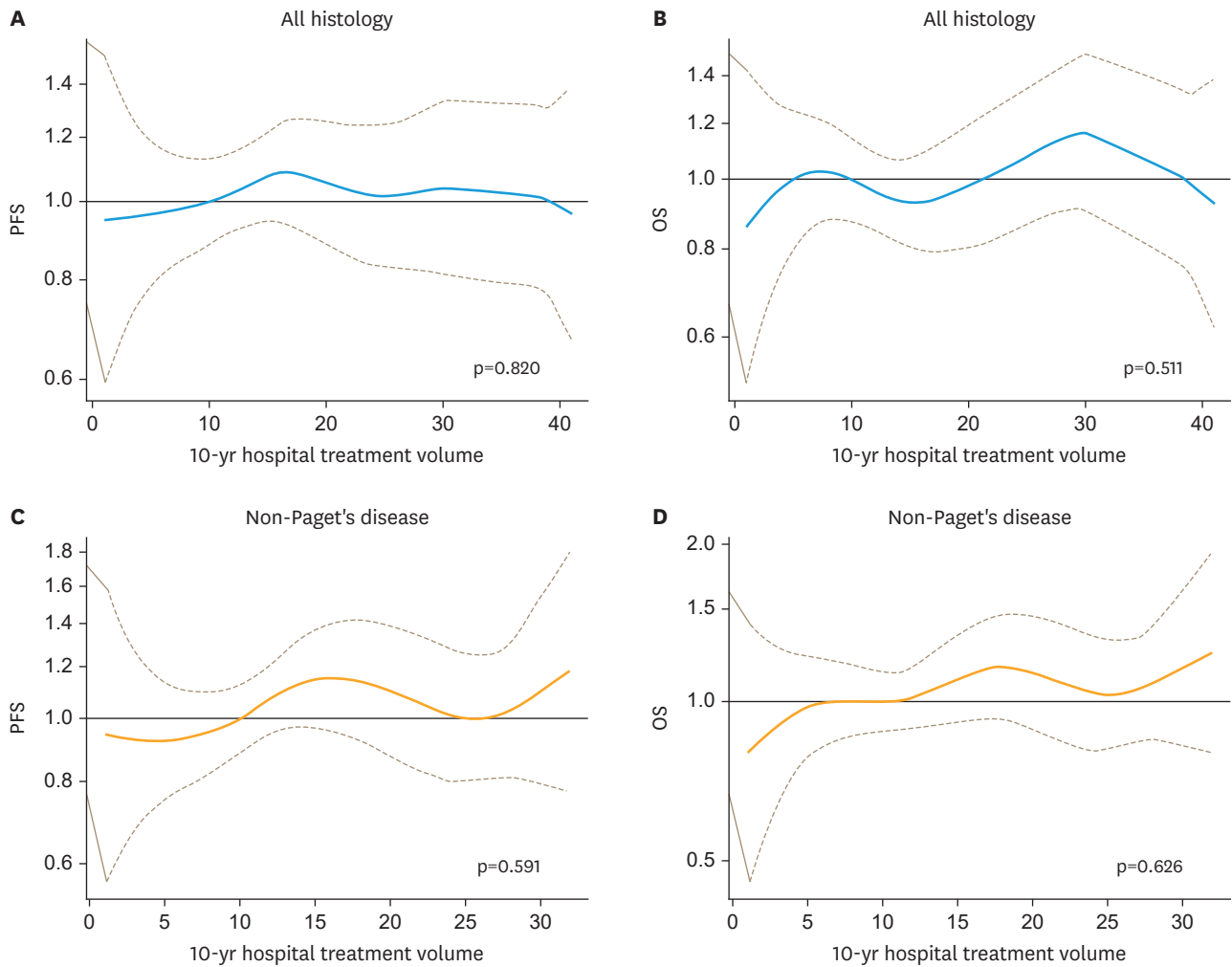


Fig. 1. Volume-outcome relationship for survival outcome. Effects of hospital treatment volume of vulvar cancer over 10-year study period on PFS (A) and OS (B) are shown in all histology types. Sensitivity analysis was performed for non-Paget disease: PFS (C) and OS (D). Cox proportional hazard regression model with restricted cubic spline transformation was used for analysis, adjusting for a priori survival factors (age, histology, and cancer stage). The p-value represents the test of non-linear association. Hospital treatment volume of 10 cases over 10-year study period was used as a referent. Bold lines represent the estimated effect size and dash lines represent 95% confidence interval. OS, overall survival; PFS, progression-free survival.

The most striking finding in our study is that in Japan hospital treatment volume of vulvar cancer is minimum to modest. On average, hospital treatment volume of vulvar cancer was only around one case a year per a center. Even top-decile volume centers, average hospital treatment volume was only few cases a year per a center. This treatment volume is far lower compared to what is reported for other disease in Japan. For instance, average number of radical hysterectomy for early cervical cancer in JGOG centers was 44 cases over the 5-year study period (approximately 8–9 cases a year) [7]. Collectively, the statistic results in the current study clearly reflects that vulvar cancer is a rare tumor in Japan, implying that most clinicians would have a limited experience in treating women with vulvar cancer.

Likely due to the extreme narrow range of hospital treatment volume, volume-outcome relationship was not observed for vulvar cancer survival in this study. In aforementioned cervical cancer study in Japan where a clear volume-outcome relationship was observed for oncologic outcome, hospital surgical volume difference for radical hysterectomy between the low- and

high-volume centers was 73 cases over the 5-year study period (approximately 14–15 cases a year) [7]. Based on this knowledge, it would be humbly advisable that designating the regional treatment center for vulvar cancer may enhance the treatment performance and outcome.

In our prior analysis of the JGOG-1075S cohort, there was an impression that treatment patterns varied across the centers [15]. In addition, more than expected number of close and positive surgical margin as well as absence of lymphadenectomy in indicated cases is certainly concerning. Together with the fact of low-case volume observed in this study, there will be an opportunity to improve treatment performance for vulvar cancer in Japan. Multi-disciplinary team approach to provide adequate surgical, chemotherapeutic, and radiotherapeutic treatments has gained importance in the treatment of vulvar cancer in recent years. For instance, vulvar reconstruction per plastic surgeons is associated with adequate surgical margin [17]. Moreover, in a recent German study where the treatment volume is considerably higher than the current study (average 5–6 cases a year per a center), positive margin rate is significantly low (9.9% vs. 22.4%) [15,18]. To this end, centralizing care of vulvar cancer to the centers with adequate treatment resource and quality would be ideal to improve outcome.

Strengths of the current study include that this study is likely one of the few studies examined the volume-outcome relationship for vulvar cancer survival. There are also several limitations in this study. First, unmeasured bias inherits this type of study. For instance, decision-making process for treatment, patient performance status and comorbidity, surgeon's experience and specialty type, and facility information were not available in this study, but all these factors impact outcomes. Surgeon's surgical volume was not assessable. Recurrence pattern was not examined in this analysis but is an important oncologic outcome [19]. Study period is somehow outdated and may not reflect the current practice. Selection bias may occur as this study does not cover entire Japanese population. Last, generalizability in different population is unknown.

In Japan, while it remains low, the incidence of vulvar cancer is gradually increasing due to the aging society [20]. Our prior analysis showed that demographics of vulvar cancer significantly changed in the past decades with increasing oldest-old and stage-shift towards more metastatic disease [15]. Nationwide, depopulation in rural areas continues to occur in recent Japan. Such national phenomenon may be another motivation to consider centralizing the care of vulvar cancer treatment. In certain disease condition, stringent criteria for surgeon and facility capability will surely improve the quality of care. This study result, together with our prior analysis, serves as a wakeup call for further attention and investigation. Society-based approach is highly warranted.

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SUPPLEMENTARY MATERIALS

Supplementary Method 1

Approach for systematic literature review.

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Supplementary Fig. 1

Systematic review selection schema.

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