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Letter to the Editor

## Wait-time for adjuvant radiotherapy and oncologic outcome in early-stage cervical cancer: A treatment implication during the coronavirus pandemic



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Dear Editor,

In 2021, the global pandemic caused by a novel coronavirus disease 2019 (COVID-19) continues to be a major health threat. Per the World Health Organisation statistics, there have been more than 100,000,000 confirmed cases of COVID-19 globally, including nearly 2,210,000 deaths as of 31st January 2021 [1].

The COVID-19 pandemic has not only directly claimed lives, but also has indirectly caused a serious health crisis in delaying care to cancer patients across

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multiple continents [2,3]. In oncologic care, the wait-time for treatment initiation is a critical component for patient prognosis [4]. In cervical cancer, prior studies examined survival effects of wait-time for surgical treatment or definitive radiotherapy [5,6], whereas the prognostic impact of adjuvant radiotherapy wait-time has not been studied. In addition, although the current National Comprehensive Cancer Network guidelines recommend the duration of definitive radiotherapy for locally advanced cervical cancer (within 8 weeks), they do not specify the optimal adjuvant radiotherapy wait-time after radical hysterectomy in early cervical cancer [7]. The objective of this study was to examine the association between post-hysterectomy radiotherapy wait-time and oncologic outcomes in women with early-stage cervical cancer.

This study used the nationwide retrospective surgical database in the Japanese Gynecologic Oncology Group mechanism (JGOG-1072S) [8]. The institutional review board's approval was obtained from participating centres. Women with clinical stage IB–IIB cervical cancer who underwent primary radical hysterectomy and pelvic lymphadenectomy followed by pelvic irradiation from 2004 to 2008 were assessed. Exposure allocation was adjuvant radiotherapy wait-time, defined as an interval from radical hysterectomy to the initiation of post-operative whole pelvic radiotherapy. Outcome measures included all-cause mortality and disease-free survival. As covariates, information pertinent for radiotherapy was collected: (i) duration of pelvic irradiation, defined by an interval from the initiation to the completion of whole pelvic radiotherapy, (ii) total radiation dose, (iii) use of concurrent chemotherapy during the radiotherapy (radiosensitisation), and (iv) radiotherapy discontinuation/delay.

A Cox proportional hazards regression model with restricted cubic spline transformation was fitted to assess the non-linear association between adjuvant radiotherapy wait-time and oncologic outcome (all-cause mortality and disease recurrence). The exposure–outcome association was adjusted for age, histology type, pathological parametrial involvement, pelvic lymph node metastasis, tumour size, lymphovascular space invasion, deep stromal invasion and radiotherapy information as above. The effect size was expressed with adjusted–hazard ratio (HR) with a corresponding 95% confidence interval (CI). Week 4 was set as the referent because of the median value of the adjuvant therapy wait-time in this study cohort.

In a sensitivity analysis, the study cohort was restricted to those who had high-risk surgical–pathological factors (lymph node metastasis and/or pathological parametrial tumour involvement) or those who received concurrent chemotherapy as radiosensitisation during the whole pelvic radiotherapy. All the analyses were based on a two-

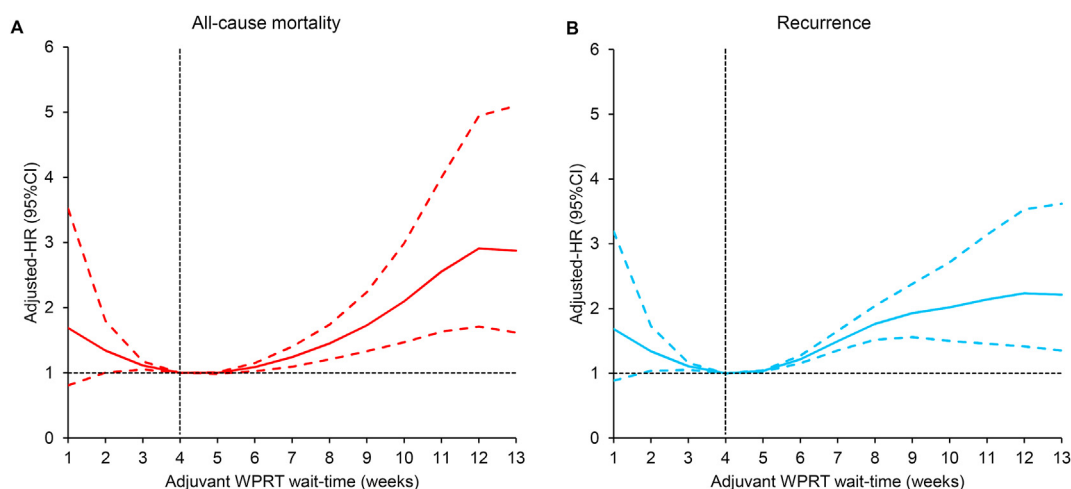
tailed hypothesis, and a  $P$ -value of  $<0.05$  was considered to be statistically significant.

A total of 1541 women were examined. The median age was 50 years (interquartile range [IQR] 40–59 years). Squamous histology ( $n = 1,169$ , 77.2%) and stage IB1 ( $\leq 4$  cm) disease ( $n = 755$ , 49.9%) were the most frequent tumour characteristics. The median adjuvant radiotherapy wait-time was 4.1 weeks (IQR 3.1–5.9 weeks). The median duration of pelvic irradiation was 5.6 weeks (IQR 5.0–6.3 weeks). The vast majority received at least 45 Gy for radiation dose ( $n = 1,412$ , 93.3%), and nearly 60% had concurrent chemoradiotherapy ( $n = 859$ , 56.7%). Radiotherapy postponement and discontinuation were reported in 67 and 41 women, respectively.

The median follow-up after surgery was 5.6 years (IQR 4.5–6.9 years), and 242 deaths occurred during the follow-up. When compared to the adjuvant radiotherapy wait-time of 4 weeks, longer wait-time was independently associated with increased all-cause mortality risk after controlling for patient, tumour and treatment factors ( $P = 0.020$ ; Fig. 1A): adjusted-HR was 1.45 (95% CI 1.21–1.74) for week 8 and 2.91 (95% CI 1.71–4.95) for week 12. The lower boundary of CI for all-cause mortality became  $>1.00$  after 6 weeks of wait-time. Likewise, longer adjuvant radiotherapy wait-time after radical hysterectomy was associated with increased risk of cervical cancer recurrence ( $P = 0.014$ ; Fig. 1B): adjusted-HR was 1.76 (95% CI 1.52–2.05) for week 8 and 2.24 (95% CI 1.42–3.53) for week 12. When the study cohort was restricted to women with high-risk surgical–pathological factors or to those who received concurrent chemoradiotherapy, similar associations to the whole cohort were observed in these subcohorts (data not shown).

We observed a poorer oncologic outcome with longer adjuvant radiotherapy wait-time after radical hysterectomy for early-stage cervical cancer. This was observed despite the lack of information on multiple confounders, including the underlying reason for treatment delay, perioperative surgical complication and patient comorbidities. This impact on oncologic outcome is important information to note managing the treatment of women with early-stage cervical cancer who are recommended to receive adjuvant pelvic irradiation. Although the COVID-19 pandemic has severely impacted timely care for cancer patients, our study results suggest that because of poorer oncologic outcomes, it is recommended to initiate adjuvant radiotherapy within 6 weeks after surgical treatment whenever possible.

If timely initiation of adjuvant radiotherapy is not feasible, administration of systemic chemotherapy may need to be considered as an alternative option. A recent randomised controlled trial showed a comparable survival outcome between systemic chemotherapy and



**Fig. 1. Associations between adjuvant radiotherapy wait-time and oncologic outcomes (adjusted model).** Multivariable Cox proportional hazards regression model with restricted cubic spline transformation was fitted to assess the non-linear association. The association between adjuvant radiotherapy wait-time and oncologic outcome was adjusted for patient factor (age), tumour factors (histology, lymph nodal metastasis, pathological parametrial tumour involvement, tumour size, deep stromal tumour invasion and lymph-vascular space invasion) and treatment factor (radiotherapy duration, radiotherapy dose, use of concurrent chemotherapy as radio-sensitiser). Week 4 was set as the reference due to the median value of the adjuvant therapy wait-time in this study cohort. The results are shown for (A) all-cause mortality and (B) disease recurrence. The solid colour lines represent the estimated adjusted-HR. The dashed colour lines are corresponding 95% CI. The vertical fine-dash lines indicate the median adjuvant therapy wait-time of 4 weeks. The horizontal fine-dash lines indicate the HR of 1. WPRT, whole pelvic radiotherapy; HR, hazard ratio; CI, confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

concurrent chemoradiotherapy as adjuvant therapy after radical hysterectomy for early cervical cancer (CSEM-002 trial) [9].

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### Transparency

The manuscript's corresponding authors (K.M. and M.S.) affirm that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

### Conflict of interest statement

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We have listed the

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### References

- [1] WHO coronavirus disease (COVID-19) dashboard. World Health Organization. <https://covid19.who.int/> (accessed 1/31/2021).
- [2] London JW, Fazio-Eynullayeva E, Palchuk MB, Sankey P, McNair C. Effects of the COVID-19 pandemic on cancer-related patient encounters. *JCO Clin Cancer Inform* 2020;4:657–65.
- [3] Jazieh AR, Akbulut H, Curigliano G, et al. Impact of the COVID-19 pandemic on cancer care: a global collaborative study. *JCO Glob Oncol* 2020;6:1428–38.
- [4] Hanna TP, King WD, Thibodeau S, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. *BMJ* 2020; 371:m4087.
- [5] Matsuo K, Huang Y, Matsuzaki S, Klar M, Wright JD. Effect of delay in surgical therapy for early-stage cervical cancer: an implication in the coronavirus pandemic. *Eur J Canc* 2020;139:173–6.
- [6] Ramey SJ, Asher D, Kwon D, et al. Delays in definitive cervical cancer treatment: an analysis of disparities and overall survival impact. *Gynecol Oncol* 2018;149:53–62.
- [7] Cervical Cancer. National Comprehensive Cancer Network. NCCN clinical practice guideline in oncology. Version 1. 2021.

Available online, [https://www.nccn.org/professionals/physician\\_gls/pdf/cervical.pdf](https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf). [Accessed 31 January 2021].

- [8] Matsuo K, Shimada M, Aoki Y, et al. Comparison of adjuvant therapy for node-positive high-risk stage IB-IIB cervical cancer: systemic chemotherapy versus pelvic irradiation. *Int J Canc* 2017; 141:1042–51.
- [9] Weng D, Wang H, Zhu C, et al. Randomized trial of adjuvant chemotherapy versus concurrent chemoradiotherapy in early-stage cervical cancer after radical surgery: a Chinese Gynecologic Oncology Group study (CSEM-002). *Gynecol Oncol* 2018;149:S30. <https://doi.org/10.1016/j.ygyno.2018.04.070>. . [Accessed 31 January 2021].