Title: New recommendations for cancer screening and surveillance in patients with Werner syndrome

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Werner syndrome (WS) is an autosomal recessive premature aging disorder caused by mutations in the *WRN* gene. It is characterized by the development of age-related diseases, such as juvenile bilateral cataracts, gray hair, hair loss, insulin-resistant diabetes mellitus, atherosclerosis, and cancer after adolescence. The leading causes of death in patients with WS are coronary heart disease and cancer. Due to improvements in the management of diabetes and dyslipidemia, deaths from atherosclerotic disease have decreased dramatically, and life expectancy has increased to 59 years.[1]

The average age of cancer onset has increased in patients with WS, from 36.9 years in 1966 to 49.7 years in 2023.[2,3] However, since the average age at the onset of cancer is younger in patients with WS than in healthy individuals, early detection and treatment are critical.[3]

In patients with WS, the morbidity of non-epithelial tumors, such as malignant melanoma, meningioma, soft tissue sarcomas, osteosarcomas, and hematologic tumors (myelodysplastic syndrome and multiple myeloma), is higher than that in the general population, and the frequency of multiple primary cancers is higher.[2,4,5] The ratio of epithelial to non-epithelial tumors is 1:1.5 in patients with WS, compared with 10:1 in the general population.[3] However, recent reports indicate that the incidence of epithelial tumors, such as thyroid, lung, and breast cancers, is increasing, and the ratio of epithelial to non-epithelial tumors is 1.6:1. This change may reflect the increased life expectancy of patients with WS. [2]

Guidelines of cancer screening in patients with WS are insufficient. Ultrasound screening for thyroid cancer and annual full-body skin examinations are recommended for malignant melanomas.[6] The most common types of malignant melanoma in patients with WS are acral lentiginous melanoma and mucosal melanoma, particularly in nasal mucosa, palms, and soles.[4] Neurological evaluations of signs and symptoms are also important to screen for intracranial tumors.[7]

Recently, we have received many inquiries regarding cancer screening and treatment in patients with WS. Based on the types of cancers commonly observed in patients with WS and the specific problems with screening tests, we proposed a strategy for cancer screening and surveillance in patients with WS, as shown in Table 1.

In general, recommendations for cancer screening in Japan include radiography or endoscopy for gastric cancer, fecal occult blood tests for colorectal cancer, radiography or sputum cytology for lung cancer, mammography and palpation for breast cancer, and cytology or human papillomavirus (HPV) tests for cervical cancer. World Health Organization also strongly recommends HPV tests for cervical cancer.[8] However, because WS is caused by a defect in the WRN protein, which is involved in DNA metabolism, radiation that can cause DNA damage may be carcinogenic. WS cells are susceptible to X-ray-induced chromosomal aberrations; therefore, excessive irradiation should be avoided.[9] Interview and physical examination should

also be performed assuming non-epithelial tumors, which are more common in WS.

For cancer screening in young-onset progeria syndromes, such as Bloom syndrome, characterized by abnormal DNA repair mechanisms arise from mutations in the *BLM* gene, ultrasound and MRI are preferred over X-rays and CT scans.[10] Blood cell counts to screen for hematologic tumors and routine skin examinations with minimal UV exposure to screen for skin cancers are also recommended. The benefits of routine screening for osteosarcoma have yet to be established, and imaging should be considered as necessary, with attention to signs and symptoms. Therefore, the proposed cancer screening for WS includes the use of ultrasound and MRI, rather than X-rays.

Patients with WS can receive chemotherapy and surgery, similar to other patients with cancer. Treatments for cancer are advancing, and early detection may prolong survival. Although we have recommendations for cancer screening in WS for the first time, there is a lack of information on the effectiveness of the screening program, including the age of initiation, the appropriateness of the intervals, and the cost-effectiveness. Therefore, further studies are warranted.

We expect that the newly proposed malignancy screening strategy will improve the quality of life and prognosis of patients with WS.

Authors' contributions

Y.M., H. Kato, and K.Y. managed the project. Y.M. and K.A. drafted and revised the manuscript. K.A., Y.M., H.Kato., H.Kaneko., Y.K., T.T., T.O., S.M., H.N., A.T., K.W., M.T., M.K., K.Y. critically reviewed the manuscript. All the authors contributed to reviewed and approved the final manuscript.

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Conflict of Interest disclosure

The authors declare no conflict of interest.

Ethics approval statement

The study adhered to the tenets of the Declaration of Helsinki. The study received approval from the Ethics Board of Chiba University on 27th July 2016 (approval number: 278) and from the Ethics Board of Kyoto University on 29th January 2020 (approval number: R2370). Written informed consent was obtained from patients before enrollment.

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Table 1. Recommendations for Cancer Screening and Surveillance in Patients with Werner Syndrome (2024)

Cancer type	Frequency	Screening type	Interval/timing	Notes
Thyroid cancer	High	Palpation, ultrasound	Annual	
Lung cancer	Less	Chest X-ray	Annual	Avoid smoking
Breast cancer	Less	Breast ultrasound	Every 2 years	Avoid excessive alcohol intake
Meningioma	High	Interviews for headache, dizziness, and neurological symptoms Brain MRI	Every 6 months MRI, if necessary	
Soft tissue sarcoma,	High	Soft tissue visual inspection and	Annual	

osteosarcoma		palpation Interviews for Bone pain		
Malignant melanoma	High	Skin visual inspection	Annual	Avoid excessive exposure to ultraviolet light. Use of sunscreen is recommended
Leukemia, myelodysplastic syndromes	High	Blood cell counts	every 3 months	
Pancreatic cancer	Less	Abdominal ultrasound	If diabetes develops or there's sudden glycemic control deterioration	

Gastric and colorectal cancer	Less	Fecal occult blood tests.	Annual	Upper gastrointestinal endoscopy is preferred over gastric fluoroscopy