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Jae-Weon Kim, Myong Cheol Lim, Jeong-Yeol Park, and Seung-Hyuk Shim serve as editors of the Journal of Gynecologic Oncology (JGO), but have no role in the decision to publish this article. No other conflict of interest relevant to this article was reported.

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INTRODUCTION

In 2012, cervical cancer was ranked the fourth in incidence and mortality among female cancers worldwide. Globally, cervical cancer had an estimated 528,000 new cases and was responsible for 266,000 deaths in 2012 [1]. Recently, the decreased incidence and mortality rates in developed countries have been attributed to the effectiveness of the screening test for cervical cancer. However, the incidence rate remains high in developing countries, where it accounts for 85% of all cervical cancer cases [2].

According to the Korea Central Cancer Registry data, there were 224,177 new cases of cancer in Korea in the year 2012. After excluding carcinoma in situ cases, cervical cancer was diagnosed in 3,584 cases, which comprised 1.7% of total cancer incidence, and ranking cervical cancer as the seventh most common cancer among females [3].

Although the incidence rate of cervical cancer shows a gradually decreasing trend, the incidence increased from 1993 through 2002 in women in their 20s and in those who were 70 years or older. As the incidence of cervical cancer decreased, an increase in the incidence of cervical cancer with carcinoma in situ was observed in all ages (20–80 years) [4]. This is due to early diagnosis and treatment at a precancerous stage rather than a decrease in de facto incidence of cervical cancer [2,5].

The most important risk factor for cervical cancer is the persistent high-risk human papillomavirus (HPV) infection. The rate of chronic HPV infection is approximately 10%–20% in countries with a high occurrence of cervical cancer and approximately 5%–10% [6] in countries with the low occurrence of cervical cancer. In Korea, the infection rate is reported to be approximately 10%–15%, although different results have been reported [7-10].

The test for HPV, which is a recognized cause of cervical cancer, has been recently included in the screening for cervical cancer. Additionally, the bivalent and quadrivalent HPV vaccines are being administered clinically. With effective treatments like surgery or concurrent chemoradiation therapy (CCRT), the cure rate of cervical cancer is up to 80%–90% in the early stages (stages I–II), and 60% in stage III. However, the prognosis is still poor with cancer progression to an advanced stage or recurrence.

The present guidelines are based on "The Practice Guidelines for Gynecological Cancers V2" (2010) and recent changes have been added. Key questions from clinical situation were put to thorough discussion with experts in such diverse fields as oncology, pathology, radiation oncology, radiology, and nuclear medicine. We also added an appendix with the evidence tables and the levels of evidence/recommendation.

The present practice guidelines for cervical cancer used the pathological classification (**Table 1**, modified World Health Organization [WHO] classification) recommended by the Gynecological Pathology Study Group of the Korean Society of Pathologist (GPSGKSP). There are 2 classification systems available for cervical cancer staging, the tumor, node, and metastasis (TNM) and International Federation of Gynecology and Obstetrics (FIGO) classification systems. The guidelines that used the FIGO staging were revised in early 2009 (**Table 2**).

The objective of these practice guidelines is to establish standard policies on issues in clinical practice related to the management in cervical cancer based on the results in published

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for hospitalized patients with T2D with mild to moderate glycaemic control treated without injectable therapies at home. Mounting evidence from randomized controlled trials and this real-world study indicate the efficacy and safety of different DPP4i in the management of hospitalized patients with T2D.

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multivariable analysis of the factors involved in test failure is consistent with the literature and so is a strong indicator of the validity of our results. While we demonstrated that heparin could not be held solely responsible for non-reportable results in those patients, we were not able to assess the impact of other treatments on cfDNA testing. It is theoretically possible that other treatment commonly used in patients with auto-immune disorders (such as steroids for example) negatively impacted cfDNA testing as well. Hui et al. reported increased fetal fraction in a patient with a history of severe autoimmune thrombocytopenia following the introduction of an immunosuppressive treatment by steroids [31]. Such reports raise the question of the impact of treatment on cfDNA testing and further studies should focus on understanding this complex relationship.

Conclusion

Our study ruled out the hypothesis that heparin treatment has an impact on cfDNA screening and found that autoimmune diseases are associated with test failure. A limitation of our work lies within its retrospective nature and further studies with larger samples and prospective design should help improve our knowledge of the factors involved in non-reportable test result.

Authors' contributions

Conceptualization: YD, AB. Validation: JMC, AL. Formal analysis: JJ, AL. Investigation: SG, AD, PK, LL. Data curation: PK, LL, AD. Original draft: YD, SG, AB. Review: all authors. Visualization: JMC. Supervision: AB, JMC. All authors revised the manuscript for important intellectual content. All authors reviewed and agree to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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Competing interests

JMC, PK and LL are employees of Laboratoire CERBA, in which they are also shareholders. The remaining authors have no competing interests to disclose.

Availability of data and materials

Not applicable.

Consent for publication

Not applicable.

Ethics approval and consent to participate

In line with French regulations regarding prenatal diagnosis, written informed consent was obtained from all patients as the result was used for clinical management. Laboratoire CERBA is authorized by the Regional Health Agency to perform these screening tests. Regarding patients who participated in the DEPOSA study, our local institutional review board approved this study (CPP No. 14-054) (ClinicalTrials.gov number, NCT02424474).

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Specific topics within the context of implementation include which reimbursement and incentive structures work best to facilitate implementation, what training methods are most successful in creating effective multidisciplinary teams, and how can organizational culture shift to support innovation.

Conclusion

The policies and processes for addressing polypharmacy vary widely in the EU, and many countries in the EU are not formally addressing polypharmacy management. These case studies provide examples of initiatives that can be used by countries in the process of developing new polypharmacy management activities, as well as to those looking to scale up existing programs, and highlight the importance of change management and theory based implementation strategies [30].

Supporting information

S1 File. Data collection tools.
(DOCX)

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postmitotic nuclei are located in a central position within the cell (Baluška et al., 2001). In addition, no mitotic figures have been observed along the root zone; lateral root primordia initiation was observed between 20-25 mm from RCJ (Alarcón et al., 2016). In *Arabidopsis*, the average distance to the earliest mitosis in the pericycle is 3194 µm and the first mitosis has been observed at 2205 µm from the root tip (Dubrovsky et al., 2001). In maize root, only at 20-30 mm from RCJ, some pericycle opposite xylem cells showed condensate cytoplasm, indicating they are re-entering the cell cycle (Alarcón et al., 2016). These differences might be caused by the greater elongation root rate in maize which grows 80-90 mm/day, whereas *Arabidopsis* elongates only 10 mm/day (Dubrovsky et al., 2001).

It has been shown using a tissue-specific quantitative microscopic analysis that some cells of cortex and epidermis were in the first endocycle (DNA contents between 4C and 8C) at their start of elongation. Moreover, nuclei of metaxylem elements in the transition zone accomplished one or two endocycles reaching 32C at their onset of rapid elongation (Baluška, 1987, 1990; Baluška and Kubica, 1984; Baluška et al., 1995). Recently, endoreduplication has been described to occur in plants before cells initiate differentiation (De Veylder et al., 2007). However, we did not observe a relevant number of nuclei with ploidy level higher than 4n. Moreover, if endoreduplication was a common process in maize root tip, we would expect hyperploidy to increase as we analysed zones further away from RCJ. However, hyperploidy not only did not increase in zones elongation zones, but decreased (Table 1).

It has been reported that pericycle cells remain in G1-phase until they re-enter the cell cycle (Vanneste et al., 2007). However, pericycle cells represent just a small fraction of the total amount of cells that form the root tips; epidermal and cortex cells being the most abundant types of cell in root apex. Then, if about 70% of total cells abandon meristem in G2-phase, most of the epidermal and cortex cells must be in G2 when they leave the meristem. It is assumed that epidermal and cortex cell elongation control root longitudinal growth (Alarcón et al., 2014b). Therefore, cells involved in the differentiation process that results in root elongation should be in G2 phase.

Effect of temperature on cell cycle

In our experimental conditions, optimal temperature for maize root elongation was estimated in 30°C, and root elongation decreased by 50% when roots were grown at 20°C. The difference in the several cell cycle phases between roots elongated at 30 and 20°C is presented in Table 1.

The most relevant result was that the percentage of cells in G0/G1 at 20°C diminished by 50% compared to roots grown at 30°C in EZ and DZ. The peak corresponding to G0/G1-phases practically disappeared in flow cytometry profiles at 20°C from the segment located in TZ (3 mm away from RCJ). This indicates that cells leaving meristem in G0/G1- or S-phases continue to cycle until they reach G2-phase, where they stop. In addition, we observed that these changes in transition zone are quicker at 30°C. The changes in percentage in G0/G1 reached a stable value that did not change along the TZ, but this fact occurred in EZ when roots were grown at 20°C. In the same way, the strongest changes in S- and G2/M-phases at 30°C occurred in TZ, but they took place in the zone EZ at 20°C. It is well known that cell cycle time increased at suboptimal temperatures (Giménez-Martín et al., 1977). Therefore, cells at 30°C presented a shorter cell cycle time, as they go through the cell cycle phases more rapidly.

In summary, data reported in this work indicate that cells controlling root elongation in maize abandon meristem in G2-phase. When cells leave meristem in G1- or S-phases, they continue the cycle until they reach G2-phase, and then they stop. These results reveal the role of cell cycle on the balance between the cell proliferation and differentiation processes which occur in the meristem and the elongation zone of the root.

MATERIAL AND METHODS

Plant material and growth conditions

Seeds of *Zea mays* L. cv DK 626 were washed three times and soaked in distilled water with aeration at 30°C. After 24 h, the seedlings, with radicles of about 1 mm length, were placed in plastic boxes on filter paper moist with distilled water. Seed were also covered with filter paper and grown in darkness. They were kept vertically for 24 h until the roots reached a length of 30±5 mm. Discs with 10 selected seedlings of uniform root length were placed in bottles containing 1.5 l of growth medium composed of a solution of 1 mM HEPES (2-hydroxyethylpiperazine-2-ethanesulfonic acid) $CaCl_2$ 1 mM and KCl 10 mM buffered growth solution, and grown at 30°C in darkness. The growth medium was aerated by an aquarium pump. After an acclimation period of 24 h, primary roots were 70-80 mm long and then roots were grown at 30°C or 20°C. Roots elongated 84.75±4.53 and 42.98± 2.40 mm/day (mean±s.d.) at 30°C and 20°C, respectively. The next day, roots of 70-80 mm reached 150-160 mm (30°C) or 115-120 mm (20°C).

Flow cytometry estimation of cell cycle progression

Primary roots grown at 30 and 20°C were dissected in several segments according to the different root zones of the root. The root cap was eliminated by removing most apical 0.5 mm and the following segments were cut: 0–1.5, 1.5–3, 3–6, 6–12 and 12–20 mm, and kept in different tubes. The segment was chopped with a razor blade for 30–60 s in a watch glass containing around 2 ml of extraction buffer [Tris-HCL 0,2 M, MgCl2-6H2O 4 mM, EDTA-Na2-2H2O 2 mM, NaCl 86 mM, Metabissulfite 10 mM, 1% PVP 10, 1% (v/v) Triton X-100 pH 7.5]. The resulting extract was passed through a 30 µm filter and centrifuged at 1500 rpm, 5 min. Then, 1 ml of staining buffer (50 µl of RNAsa 20 mg/ml, 50 µl of Propidium Iodine 0.05% and 900 µl of PBS) was added. Samples were incubated at 37°C in the dark for 30 min. Flow cytometry analysis was performed using a FC500 flow cytometer (BeckmanCoulter, Hialeah, FL, USA). At least 10,000 single nuclei (discarding doublets and aggregates) were acquired in each sample. Experiments were performed in triplicate.

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Competing interests

The authors declare no competing or financial interests.

Author contributions

Conceptualization: M.V.A., J.S.; Methodology: M.V.A., J.S.; Formal analysis: M.V.A., J.S.; Investigation: M.V.A., J.S.; Writing - original draft: J.S.; Funding acquisition: M.V.A., J.S.

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Author contributions

MRB, Conceptualization, Data curation, Software, Formal analysis, Validation, Investigation, Visualization, Methodology, Writing—original draft, Writing—review and editing; MB, Software, Formal analysis, Investigation, Methodology, Writing—review and editing; AP, LSB, Investigation, Methodology, Writing—review and editing; LK, STA, CDS, Investigation, Writing—review and editing; MM, Conceptualization, Formal analysis, Supervision, Funding acquisition, Validation, Investigation, Writing—original draft, Project administration, Writing—review and editing

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Ethics

Human subjects: Human experiments were conducted and underwent ethical review at the University of Sussex. Experiments were approved through the review process in the School of Life Sciences and were given approval identifiers ER/LK250/1, ER/CS502/1, ER/SA533/2. All participants gave informed consent. Participants were provided with an information sheet stating the possibility that the research could be published.

Animal experimentation: All procedures were carried out in accordance with institutional, national (Spain and United Kingdom) and international (European Union directive 2010/63/EU) regulations for the care and use of animals in research. All procedures received prior approval by the relevant institutional ethical committee (Instituto de Neurociencias, CSIC; University of Sussex AWERB) and were covered by the appropriate personal and project licences.

of Mff KD on mitochondrial division and mitochondrial Drp1 oligomer density. Fig. S6 shows that a second splice variant of Drp1 displays independent punctae, but that MiD51 does not. Video 1 shows two independent Drp1 punctae stably associated with ER (one goes out of the focal plane briefly). Videos 2 and 3 show Drp1 punctae translocating to mitochondria (Video 2 does not have an ER marker; Video 3 has an ER marker). Videos 4 and 5 show Drp1 punctae translocating to mitochondria, followed by mitochondrial division, after ionomycin stimulation (Video 4 does not have an ER marker; Video 5 has an ER marker). Video 6 shows an independent GFP-Mff puncta stably on ER. Video 7 shows an independent GFP-Mff puncta transferring from ER to mitochondrion (Airyscan). Video 8 shows colocalization of GFP-Drp1 and mStrawberry-Mff on ER. Videos 9 and 10 show the change in independent Drp1 punctae after ionomycin treatment. In Video 9, the punctae increase, but in Video 10 (pretreated with latrunculin A) the punctae do not increase.

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