Letter to the Editor / Editöre Mektup

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Critical review of the SHAPE trial

SHAPE çalışmasının eleştirel incelemesi

Polat Dursun[1,2], Murat Gültekin[3]

[1]*Ufuk University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Ankara, Turkey*
[2]*Turkish Gynecologic Cancer Foundation , Ankara, Turkey*
[3]*Hacettepe University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Ankara, Turkey*

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Dear Editor,

An international randomized trial comparing radical hysterectomy (RH) and *vs*. simple hysterectomy (SH) in patients with low-risk early-stage cervical cancer was recently published in NEJM by Plante et al.[1], and we read it with great interest. Although the literature excludes any relevant randomized trials, early-stage cervical cancers are traditionally treated using the RH technique pioneered by Ernst Wertheim and others >100 years ago[2]. Currently, efforts to reduce the complications and morbidity associated with RH and improve patient quality of life post-surgery are ongoing; therefore, we appreciate the SHAPE Trial researchers' efforts to improve our knowledge of this topic and improve patient outcomes. The SHAPE Trial researchers performed a non-inferiority trial that included 130 centers in 12 countries and compared SH and RH in patients with low-risk cervical cancer (lesions ≤2 cm with limited stromal invasion). They noted that, "SH was not inferior to RH with respect to the 3-year incidence of pelvic recurrence and was associated with a lower risk of urinary incontinence or retention"[1]. each year, almost 600,000 cases of cervical cancer occur worldwide, of which nearly 80% occur in undeveloped or developing countries. Although the researchers wrote that their results cannot be generalized to developing countries, as practicing gynecologic oncologists from a developing country, we also think that some patients with cervical tumors <2 cm might benefit from and urgently need less radical surgery, especially in low resource settings in which there is limited or no screening or radiotherapy facilities, operative infrastructure, or trained gynecologic oncologists. In contrast to what was written, we strongly believe that clinicians in developing and undeveloped countries can make good use of the SHAPE Trial findings; however, before we can reach a definitive conclusion, we have some criticisms and concerns about the Trial, as detailed below, that we think must be addressed.

- The study was conducted at 130 centers; however, we would like to definitively know if a central pathology and imaging review was performed.
- A contentious issue for us is that laparoscopic surgery was performed in both the SH and RH groups. debate about the use of laparoscopic/robotic surgery in patients with cervical carcinoma is ongoing[3]. Although the LACC Trial reported that the oncological outcome was the worst in patients who underwent laparoscopic/robotic surgery for cervical cancer, the SHAPE Trial routinely used laparoscopic/robotic surgery. We believe that this non-inferiority study should have compared abdominal SH and abdominal RH and excluded minimally invasive techniques to yield more definitive findings. In addition, the SHAPE Trial researchers did not provide the number of patients in the SH and RH groups who underwent laparoscopic and/or robotic surgery and did not mention if there were any differences in overall and disease-free survival between the two groups. Also missing from their report are the number of patients in each group who underwent full pelvic lymphadenectomy, sentinel lymphadenectomy, and no lymphadenectomy, as well as clearly stated outcomes. Consequently, we think that the researchers' use of both abdominal and laparoscopic/robotic SH and RH might be among the important confounding factors related to their findings; therefore, in general, we think

Address for Correspondence/Yazışma Adresi: Polat Dursun MD,
Ufuk University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology; Turkish Gynecologic Cancer Foundation, Ankara, Turkey
Phone: +90 532 384 51 58 **E-mail:** pdursun@yahoo.com **ORCID ID:** orcid.org/0000-0001-5139-364X
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that the study population was too heterogeneous to reach a definitive conclusion. For example, some patients underwent laparoscopic/robotic SH, some underwent RH, and some underwent sentinel lymphadenectomy and some did not. The study also lacks clarity regarding the use of any uterine manipulators. Finally, the 12.5% pelvic recurrence rate at 3 years in the RH group versus 0% in the SH group from Asia was an especially interesting finding, whereas the pelvic recurrence rate at 3 years in the RH group from North America was 0%. These concerns lead us to question the validity of the study's findings, which require further clarification.

- Although the SHAPE Trial was originally planned as a superiority trial, due to the lack of events during follow-up, it was changed to a non-inferiority trial. It is well known that the primary weakness of non-inferiority trials, as compared with superiority trials, is that deviations from the protocol can result in false rejection of the null hypothesis that the experimental treatment is inferior[4]. The study's CONSORT flow diagram shows that 10% of the patients in the SH group violated the study protocol, versus 12.9% in the RH group. Furthermore, although 9.1% of the SH group and 8.9% of the RH group received adjuvant treatment, in our routine clinical practice, when we perform SH in patients who meet the same criteria used in the SHAPE Trial, the majority of patients do not require any adjuvant treatment, especially when the patients are carefully selected. Despite there being a similar adjuvant treatment rate in the SH and RH groups, when we look at the causes of death in Table 3, the hazard ratio (HR) for disease recurrence was 1.54 based on intention-to-treat analysis, versus 1.19 based on protocol analysis. Furthermore, the HR for extrapelvic recurrence was 3.82 based on the intention-to-treat analysis, versus 2.03 based on the protocol analysis. Interestingly, the HR for death was 0.79 although the 95% CI included 1 based on protocol analysis. How can SH be associated with fewer deaths than RH despite both groups having similar adjuvant treatment rates and higher extrapelvic recurrence rates? These findings suggest that the addition of radiotherapy to the pelvis compensates for the ineffectiveness of SH but does not prevent extrapelvic recurrence beyond the radiotherapy area. In our routine clinical practice, we generally do not administer radiotherapy or any adjuvant treatment in patients that have tumors <2 cm with no LVSI and limited depth of cervical stromal invasion. Furthermore, we generally prefer using RH to avoid unnecessary radiotherapy. The SHAPE Trial did show that adjuvant treatment had a greater sparing effect than SH, which indicates that there might have been patient selection bias.

- On the other hand, Table S2 shows that the number of patients with surgical margin positivity, tumor size >2 cm, and positive metastatic lymph nodes was higher in the RH group. Although the number of patients with poor prognostic factors was higher in the RH group, the use of adjuvant treatment was slightly more common in the SH group (9.2% *vs.* 8.4%), which might explain the similarity of the pelvic recurrence rate in both groups and the higher extrapelvic recurrence rate in the SH group, as emphasized above.

- In addition, the SUCCOR study[5] observed that preoperative LEEP or conization has a positive effect on survival following RH. Table 2 of the SHAPE Trial shows that preoperative LEEP or conization was performed in 84% of the SH group patients versus 76% of the RH group patients. All these factors (protocol violations, preoperative LEEP, and adjuvant treatment) can increase the effectiveness of SH and require additional clarification.

Another important drawback of the SHAPE Trial is the lack of adequate long-term survival data. We believe that in the absence of sufficient long-term overall and disease-free survival data, we cannot sacrifice the oncological safety associated with RH and switch to SH in cervical cancer patients to have a lower urinary incontinence rate; until many of the SHAPE Trial issues are addressed, we believe that doing so based on the SHAPE Trial findings should be carefully interpreted.

To conclude, as did the SHAPE Trial researchers, we also believe that some patients with low volume and small tumors might benefit from reducing surgical radicality; however, this should have been proven by comparing abdominal SH and abdominal RH in the absence of confounding factors such as preoperative LEEP/conization, adjuvant radiotherapy/chemotherapy, laparoscopy, and uterine manipulation.

Sincerely yours,

Ethics

Authorship Contributions

Surgical and Medical Practices: P.D., M.G., Concept: P.D., M.G., Design: P.D., M.G., Data Collection or Processing: P.D., M.G., Analysis or Interpretation: P.D., M.G., Literature Search: P.D., M.G., Writing: P.D., M.G.

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