J Gynecol Oncol. 2024 Jul;35(4):e107
https://doi.org/10.3802/jgo.2024.35.e107
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Expert Opinion

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The SHAPE trial: is good is good enough?

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OPEN ACCESS

Received: Apr 6, 2024
Revised: Apr 9, 2024
Accepted: Apr 9, 2024
Published online: May 13, 2024

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

The radical hysterectomy was first described by John Clark as a way of removing large tumors at a time when surgery offered the only hope for cure in patients with cervical cancer [1]. Since that time, radiation treatment planning and delivery has become increasingly sophisticated with excellent outcomes and decreased morbidity in patients with locally advanced cervical cancer. As a result, the radical hysterectomy is now reserved for early-stage good prognosis tumors. Even when this surgery is limited to early cancers, some patients with high risk factors will need adjuvant radiation to prevent local failure [2]. While radical hysterectomy is an effective modality for patients with early cervical cancer, the morbidity of the surgery is greater than that of a simple hysterectomy with respect to blood loss, urinary injury, and bladder atony. Several investigators have reported very low rates of parametrial involvement in patients with early cervical cancer calling into question the need for a radical procedure in women with small good-prognosis tumors [3]. The SHAPE trial has now demonstrated non-inferiority between radical hysterectomy and simple hysterectomy with respect to local recurrence in patients with 2009 International Federation of Gynecology and Obstetrics stage IA2 and IB1 cancers less than 2 cm in size and with less than 10 mm of stromal invasion on excisional biopsy or less than 50% of the stromal depth on magnetic resonance imaging [4].

The fact that the SHAPE trial demonstrated the non-inferiority of simple hysterectomy to radical hysterectomy is a major achievement given that non-inferiority trials of this nature are difficult to design and conduct [5]. Most trials in medicine are designed as superiority trials. These are conceptually easy to understand. A trial is considered positive if the experimental treatment outcome is statistically better than the control with respect to the primary outcome. However, most surgical trials require a non-inferiority design. This occurs when a new procedure is tested that might offer advantages over the standard treatment and we want to make sure our primary outcomes, such as the risk of cancer recurrence, are not different from the standard treatment. In this trial design, one must pick a non-inferiority margin in the primary outcome that one would be willing to accept to gain the benefit of the new procedure. These benefits could include lower cost, shorter surgical times, less complex procedures, or a lower morbidity of the new procedure. The smaller the difference in the primary outcome we willing to accept for these benefits, the larger the trial needs to be to declare the new procedure non-inferior with respect to the non-inferiority boundary. In most surgical trials the events of interest such are relatively uncommon. Therefore, these types of trials require a large number of subjects. For this reason, most surgical procedures are not tested in a randomized fashion [6]. In addition, many non-inferiority trials are not designed around a clinically

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meaningful endpoint, but rather on the number of patients that can recruited into the trial, yielding a non-inferiority boundary that may not be clinically acceptable [7]. In addition, the results of many non-inferiority trials cannot exclude the non-inferiority boundary and are considered inconclusive with respect to the non-inferiority boundary [5].

The SHAPE trial was a non-inferiority trial comparing simple hysterectomy to radical hysterectomy with a primary endpoint of non-inferior pelvic failure rate between the procedures [4]. In the original statistical analysis plan the primary endpoint was the pelvic recurrence-free survival. This was an event-based analysis with the estimated rate of pelvic failure in the control arm of 7%. However, the observed event rate was significantly less than anticipated. This necessitated a change in the primary endpoint to a landmark analysis of pelvic recurrence at 3 years. Power calculation around this new endpoint showed an 85% power to detect a 4% difference in the pelvic recurrence rate. At the conclusion of the trial, the pelvic recurrence at 3 years was 2.52% for simple hysterectomy and 2.17% in the radical hysterectomy groups. This difference of 0.35% (90% confidence interval=1.62–2.32) was within the declared non-inferiority limit of 4% and thus the trial met the primary end-point of non-inferiority. Overall, the groups were well balanced with respect to the use of sentinel lymph node biopsies and the rate of adjuvant therapy. Adjuvant radiation was given to 9.2% of the patients after simple hysterectomy as compared to 8.4% after radical hysterectomy. Paradoxically, adjuvant therapy was given more often for positive margins in the patients with radical hysterectomies than simple hysterectomies (1.74% vs. 1.18%). The results of the SHAPE trial show that negative margins and similar rates of local control can be achieved with less radical surgery.

This trial gives us level I evidence that a simple hysterectomy is adequate for early cervical cancer with respect to local recurrence risk. However, we must ask how good is good enough? The non-inferiority boundary for the SHAPE trial was 4%. This was justified based on the fact that the non-inferiority boundary for the LACC trial comparing minimally invasive to open radical hysterectomy was set at a 7.2% recurrence risk at 4.5 years. However, one could argue that a difference of 7.2% in recurrence is not clinically acceptable. So, is a 4% difference in local failure rate acceptable for the benefit of not doing a radical hysterectomy? First, one needs to consider the advantage of the simple hysterectomy. This will save patients from the morbidity of a radical hysterectomy including a long-term urinary incontinence rate 11.0% as compared to 4.7% with simple hysterectomy. There is also an increase in the urinary retention rate from 0.6% to 11.0% with radical hysterectomy. However, a 4% increase in local failure rate could represent a 2.5-fold increase in local recurrence. So, is the exclusion of a 4% difference in local recurrence good enough to accept a simple hysterectomy as the standard procedure in this group of patients? Probably, given the absolute risk of recurrence is low and many patients with local recurrence can be cured with additional radiation. While comparison of the rates of local recurrence between the procedures is not relevant to the primary endpoint which is the non-inferiority boundary of the trial, it is reassuring the rates of local recurrence are very similar between the two groups. The intent to treat analysis showed a relative risk (RR) of local recurrence of 1.12 for the simple hysterectomy group. However, 53 of the 700 (7.6%) patients did not receive the assigned treatment yielding a per protocol RR of local recurrence for simple hysterectomy of 1.01 [4]. Importantly, similar rates of local control were achieved without a significant increase in the use of radiation after simple hysterectomy.

The majority of patients in the SHAPE trial were treated with minimally invasive surgery. However, this should have had little impact on the outcome of the trial with respect to the

safety of simple hysterectomy. Simple hysterectomies in the SHAPE trial were more often performed using a minimally invasive technique as compared to the radical hysterectomies (83.1% vs. 71.2%), so if there were a detrimental effect of minimally invasive surgery with respect to oncologic outcome it would have increased the recurrence rate more in the simple hysterectomy arm [4]. The pelvic recurrence rates were similar between patients that had simple laparoscopic and simple open hysterectomies (3.2% vs. 3.5%). This was also true with the pelvic recurrence rates of those that underwent minimally invasive versus open radical hysterectomies (2.9% vs. 3.0%). The SHAPE trial has been criticized given that the positive vaginal margin rate was 2.7% and local recurrence rate was 3.0% in the open hysterectomy group, which was higher than that reported in the LACC trial with a positive margin status of 2.13% and a local recurrence risk of 1.28% despite the fact that the LACC trial included a higher risk population [8,9]. However, other series of open radical hysterectomies with populations similar to the LACC trial positive vaginal margin rates of 2.9% to 4.4% so there is no reason to doubt the adequacy of the surgery in the SHAPE trial [10,11]. It also should be noted that the LACC trial may not be an accurate bench-mark for events after open radical hysterectomy. While the local recurrence risk was approximately 4-times higher in the minimally invasive arm compared to the open surgery arm of the LACC trial, this high RR of local recurrence in the LACC trial was due to an abnormally low rate of local recurrence reported in the open arm of the LACC trial [8]. The open arm of the LACC trial had a recurrence rate of 2.24%. In a multicenter respective report of radical hysterectomy in a population similar to the LACC trial, the reported 3-year risk of recurrence in the open arm was 5.6% for patients with tumor less than 2 cm and 17.4% in tumors between 2 and 4 cm [11]. Another trial reported 5-year recurrence risks of 6.5% after open radical hysterectomy after surgery for tumors less than 2 cm and 13.1% for tumors between 2–4 cm [10]. This would suggest that the recurrence risk in the open arm of the LACC trial was either lower than expected by chance or recurrences in the open arm were underreported.

A major concern for any randomized trial is recruitment bias. If the investigators felt that simple hysterectomy might yield inferior results in certain higher risk cervical cancer patients, they might not recruit these patients to the trial, even if they met the entry criteria. This may cause high risk groups to be under-represented. Unfortunately, this difference is difficult to measure as it is rarely possible to determine the characteristics of the patients that were not enrolled in the trial for comparison.

It is difficult to embrace a change in a long-standing standard of care that has yielded good results. However, the SHAPE trial should make us feel confident about adopting simple hysterectomy as the treatment of choice for patients with small low-risk cervical cancers as there is no reason to think that the radical hysterectomy is necessary to achieve a negative margin or to achieve local control of the cancer. Not only are the local recurrence rates similar between simple and radical hysterectomy, there did not appear to be a significant increase the rate of adjuvant radiation therapy after surgery. However, one should always be cautious with strict adherence to the entry criteria and when in doubt and be ready to default to a more radical approach in patients that might be considered at higher risk by clinical judgement.

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