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Review

The current evidence for the use of minimally-invasive surgery in endometrial cancer

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The aim of the present study is to review the current available data regarding the use of minimally-invasive surgery in endometrial cancer patients and investigate the feasibility and safety of it for cancer control. We also reviewed the current understanding of sentinel lymph node mapping and the use of robotic surgery in endometrial cancer. Studies have consistently demonstrated better short-term outcomes of minimally-invasive surgery in endometrial cancer compared to laparotomy such as less blood loss, shorter hospital stay, and fewer wound complications. Large randomized clinical trials and meta-analyses also suggest the feasibility and safety of minimally-invasive surgery in terms of oncologic outcomes especially in patients with early stage disease. Although evidence for advanced stage disease and patients with high risk for recurrence are still lacking, the current available data seem to support the use of minimally-invasive surgery for those patient groups as well. A large body of literature supports the role of sentinel lymph node mapping in endometrial cancer with a high sensitivity and a low false negative rate, as well as a favorable negative predictive value. Studies also show that robotic surgery is a safe and effective alternative to conventional laparoscopic surgery for endometrial cancer staging but further long-term data are required. Further prospective studies with long-term follow-up are warranted to evaluate the feasibility and safety of minimally-invasive surgery especially in patients with advanced stage disease and high risk for recurrence. However, the current available data support the use of minimally-invasive surgery in all patient groups of endometrial cancer.

Keywords

Endometrial cancer; Minimally-invasive surgery; Laparoscopy; Laparotomy; Gynecology

1. Introduction

Endometrial cancer is the most common gynecological cancer in developed countries with new 380,000 patients diagnosed worldwide in 2018 [1]. The incidence of endometrial cancer is increasing due to increasing rates of obesity and life expectancy. The disease is detected in early stages in almost 80% of women, which results in cure rates greater than 90% [2].

The standard surgical treatment of endometrial cancer includes total hysterectomy and bilateral salpingo-oophorectomy. The staging procedure includes lymph node dissection including both pelvic and para-aortic lymph nodes depending on histopathology and extent of disease spread. It also encompasses sentinel lymph node mapping and selective sampling. However, the current clinical guidelines do not suggest laparoscopy or laparotomy as a preferred surgical approach. Traditionally, laparotomy was used for surgical treatment, but since the 2000s, the frequency of performing laparoscopic approach has increased. Many studies have demonstrated the safety and feasibility of laparoscopic approach especially in early stages of endometrial cancer [3, 4]. For example, studies reported that laparoscopic hysterectomy was associated with lower rates of wound infection, less blood loss, shorter hospital stay compared to laparotomy and demonstrated no significant difference in overall survival (OS) or disease-free survival (DFS) [5]. Most studies, however, were limited to subjects with clinically or pathologically early stages. This raises concerns regarding the feasibility of minimally-invasive surgery (MIS) in patients with advanced disease status or risk factors for disease recurrence.

The purpose of this review is to compare the efficacy and safety of laparoscopy versus laparotomy in the surgical treatment of endometrial cancer. We reviewed the literature on early stage disease and advanced stage disease separately. We also examined the use of sentinel lymph node mapping and robotic surgery in endometrial cancer surgery.

2. Early stages of endometrial cancer

Evidence for the use of MIS in early stage endometrial cancer and patients with low risk for recurrence is relatively well established compared to advanced disease and high risk patients. Studies have demonstrated that laparoscopic approach is associated with better perioperative outcomes such as less blood loss, shorter hospital stay and lower rates of surgical site infection [6–8]. Randomized clinical trials with large numbers of patients have also illustrated that the patients who received laparoscopic surgery had oncologic survival outcomes similar to those who received laparotomy for early stage endometrial cancers [9, 10].

The largest clinical trial investigating the feasibility and safety of laparoscopic approach in endometrial cancer conducted so far is the LAP2 trial. In 2009, the Gynecologic Oncology Group (GOG) performed a prospective randomized clinical trial comparing laparoscopic surgery against laparotomy in 2,616 patients. The results revealed that laparoscopic approach was associated with shorter length of hospital stay and lower rates of postoperative complications. The authors thereby suggested laparoscopy as the new standard of care for patients with endometrial cancer [6]. The same group of patients were investigated for a follow-up study after a median of 59 months since their operations. OS was found to be similar between the patients who were treated with laparoscopy and those who were treated with laparotomy while DFS showed a small, statistically non-significant increase for the patients who underwent laparoscopic surgery [11]. The estimated hazard ratio for DFS for laparoscopy relative to laparotomy was 1.14 (90% CI 0.92-1.46), falling short of the protocol-specified definition of non-inferiority. It should be noted, however, that the LAP2 trial mostly involved patients with early stage disease, raising questions about the generalizability of the results to those with advanced stage disease. Due to the fact that the majority of the patients were with early stage disease, the actual overall recurrence rates were substantially lower than anticipated. The patients who received laparoscopic surgery demonstrated 11.4% of 3-year recurrence while those who received laparotomy showed 10.2%. The estimated 5-year OS was almost identical in both arms at 89.8%.

Another evidence that is frequently cited is from the Laparoscopic Approach to Cancer of the Endometrium (LACE) trial. It is a multinational, randomized equivalence trial which randomized patients into either laparoscopy or laparotomy for the treatment of endometrioid endometrial cancer stage I [10]. The authors investigated 407 women who underwent laparoscopy and 353 women who underwent laparotomy and found equivalent DFS at 4.5 years and no difference in OS between the two groups. The DFS at 4.5 years was 81.6% with laparoscopy vs. 81.3% with laparotomy (between-group difference 0.3%, 95% CI-5.5%-6.1%), meeting the criteria for equivalence. Like the LAP2 trial, the majority of the patients enrolled in this study were with early stage disease without evidence of lymph node metastasis. Hence, it is possible that the good overall prognosis of early stage endometrial cancer patients may have diluted drawbacks of laparoscopy if there were any.

Malzoni *et al.* also performed a prospective randomized trial to look at 159 patients with clinical stage I endometrial cancer. The para-aortic lymphadenectomy was performed in all cases. The authors found a reduction in blood loss, shorter operative time, and shorter length of hospital stay in the laparoscopy group in accordance with previous findings by others [12].

Other studies with smaller numbers of patients consistently reported that intraoperative surgical complications were comparable between the patients who underwent laparoscopic surgery and laparotomy [4, 6, 13]. Substantial data regarding short-term outcomes such as blood loss, length of hospital stay, and surgical complications seem to favor laparoscopic approach. Accumulating data also support the comparable results in DFS and OS between the two surgical methods [14]. With these relatively strong evidence, in recent years, the laparoscopic approach has largely replaced laparotomy as the choice of surgical treatment for early stage endometrial cancer [15, 16].

3. Advanced stages of endometrial cancer

Most studies comparing the performance of laparoscopy against laparotomy in endometrial cancer evaluated small numbers of patients. Furthermore, most of those patients were at early stages of the disease and the median duration of follow-up of them was relatively short. Therefore, the generalization of the obtained results from these patients to those with advanced stages of the disease is limited. Endometrial cancer is a disease with different histopathology which subsequently has different clinical outcomes due to various tumor biology. In comparison to early stage diseases, there are limited data assessing the feasibility and safety of laparoscopic management of endometrial cancer with high risk factors such as advanced stage and type II histology. Type II endometrial cancer tends to be detected in an advanced stage compared to type I endometrial cancer. The patients with type II endometrial cancer are older, and more likely to have systemic disease, thereby requiring post-operative adjuvant treatment [17–19]. Therefore, these patients should be evaluated separately from those with early stages of endometrial cancer.

To the best of our knowledge, there is no study that investigated those with intermediate risk factors alone in the literature. In the LAP2 trial, stage 1B accounted for only 12% of the patients reviewed. Although further data are required to support the feasibility and safety of laparoscopic surgery in patients with advanced stages, the current available data seem to suggest that laparoscopic approach is also feasible in this group of patients. The *post hoc* analysis of the LAP2 trial including early stage patients with grade 3 endometrioid adenocarcinoma and type II histopathologies (n = 507) demonstrated that the patients with high grade uterine cancers who underwent laparoscopic surgery had similar rates of recurrence and survival as those who underwent laparotomy [20]. In 2012, a multi-center retrospective study was conducted on 191 patients with high-grade and type II endometrial cancer. It was the first study performed in this high risk patient group. The authors concluded that high risk histopathology was not a contraindication for laparoscopic approach [21]. A multi-center retrospective study in which the authors reviewed 283 patients with type II endometrial cancer who underwent hysterectomy either by MIS or laparotomy also drew similar conclusions [22]. In that study, Monterossi *et al.* compared 142 patients who received laparotomy against 141 pa-

tients who received MIS. The authors found no between-group differences in survival outcomes. When performing subgroup analysis, OS and DFS were comparable between the two groups in the patients with stage I and II endometrial cancer. However, the authors found a trend toward improved OS in patients with stage III endometrial cancer in the laparotomy group, although the difference was statistically non-significant (*P*-value: 0.063). They concluded that high-risk histopathologies should not be considered a contraindication for MIS in patients with endometrial cancer. Koskas *et al.* also compared 93 laparoscopic and 21 robotic surgeries with 114 laparotomic surgery in high risk endometrial cancer patients, and found that DFS and OS were not different between the surgical groups in accordance with other studies [23]. A retrospective study assessing the long-term outcomes of laparoscopy and laparotomy according to low, intermediate, and high risk groups of endometrial cancer found similar results [24]. The authors found that the OS was comparable in all three patient groups between laparoscopy and laparotomy. In 2020, Papadia *et al.* published a study, in which the authors evaluated the surgical data and oncologic outcome of histologically proven stage IIIC endometrial cancer patients. The authors performed a systematic lymph node dissection both in pelvic and para-aortic lymph nodes in all patients. It was found that MIS had better perioperative outcomes and did not impair survival in stage IIIC endometrial cancer patients. OS after 60 months of follow-up did not differ between the patients who received laparoscopy versus those who received laparotomy. Both univariate and multivariate analyses revealed that the methods of surgical approach did not affect survival [25].

The use of laparoscopy in type II endometrial cancer should also be addressed separately. This type has a close biological kinship to ovarian and fallopian tube carcinoma, including the peritoneal pattern of cancer dissemination [26]. Chromosomal instability and p53 mutations are characteristics of serous carcinoma. Clear-cell carcinomas do not show immunoreactivity for p53 and hormone receptors including estrogen and progesterone [27]. In a retrospective study that evaluated the patients with serous or clear-cell endometrial cancer without peritoneal carcinomatosis, the authors found that laparoscopy was not inferior to laparotomy [28]. In that study, 53 women underwent laparoscopy while 36 women underwent laparotomy. The mean number of removed pelvic lymph nodes was similar between the two groups while the mean number of dissected para-aortic nodes was significantly greater in the laparoscopic group (11 ± 9 for laparoscopic group vs. 6 ± 9 for laparotomy, *P*-value = 0.006). The median duration of follow-up was 38 months for the laparoscopy and 47 months for the open surgery. The OS at 5 years were similar in both groups, 86% for laparoscopy and 78% for laparotomy. The DFS was also similar at 58% versus 51%, respectively (*P*-value = 0.312). Another recently published review article analyzed nine studies on the management of high-risk endometrial cancer patients in regards to different types of surgical approach [29]. The authors concluded that MIS appears to be safe in all retrospective studies reported in the literature. They all demonstrated better perioperative outcomes and similar survival outcomes. Although the pathologic characteristics and clinical behaviors of type II endometrial cancers are similar to ovarian and fallopian tube cancers in many ways, the usual pattern of spread differs between the two malignancies. While ovarian cancer mainly spreads by direct dissemination often causing peritoneal carcinomatosis, endometrial cancer spreads by lymphatic or hematogenous metastasis. This difference may have played a role in allowing MIS in endometrial cancer even in those patients with advanced stages.

Although it is undeniable that long-term survival analysis should be further supported by randomized controlled trials in these groups of patients, the current data suggest the feasibility of MIS for endometrial cancer in advanced stages of the disease. The latest guidelines by the European Society of Medical Oncology (ESMO)-European Society of Gynaecological Oncology (ESGO)-European Society for Radiotherapy & Oncology (ESTRO) also recommend the use of laparoscopic approach in the low and intermediate risk endometrial cancer (level of evidence 1, the strength of recommendation A) [30]. In consideration of the fact that the patients with type II endometrial cancer are older and more likely to have advanced stages of the disease compared to those with type I endometrial cancer, it may even be advantageous to perform laparoscopic surgery in type II endometrial cancer patients because it reduces surgical morbidity and allows faster recovery after surgery, which in turn allows shorter interval between surgery and adjuvant treatment.

4. Robotic surgery in endometrial cancer

The U.S. Food and Drug Administration (FDA) approved the use of robot-assisted laparoscopic surgery for gynecologic patients. Since then, this surgical approach has been widely implemented both for benign and malignant gynecologic diseases [31]. A recent Safety Communications from the U.S. FDA, however, has raised concerns about the safety and effectiveness of robotic surgery in cancer treatment [32]. There are not many studies that directly compared oncologic outcomes of robot surgery against laparotomy to date [33]. Furthermore, the majority of patients enrolled in the past large clinical trials that evaluated the feasibility of robot surgery including the GOG LAP2 and LACE trials, were at early stage disease or had low risk for recurrence. This raises questions about the validity of the results regarding the performance of robot surgery because of the very low recurrence rates of the low risk group of enrolled patients [6, 10]. While the majority of clinical trials comparing robotic surgery, conventional laparoscopic surgery and laparotomy reveal comparable outcomes among the three different approaches, those trials were mostly based on the patients with low risk, early stage disease [34–36]. The safety of robotic surgery in advanced stages still remain unknown.

The data from previous studies on robotic surgery show large variations, with recurrence rates ranging from 1.2% in one study to as high as 14.8% in another [14, 37]. It is relatively well-established that robotic surgery is a suitable alternative to conventional laparoscopic surgery in early stages of endometrial cancer. A meta-analysis evaluating the safety and effectiveness of robot surgery versus conventional laparoscopy and laparotomy reviewed 24 published studies [35]. In that study, Park *et al.* found that the patients who received robotic surgery had favorable perioperative outcomes compared to laparotomy. Even when compared to conventional laparoscopic surgery, robotic surgery was associated with less blood loss, shorter duration of hospital stay, lower rates of conversion to laparotomy and intraoperative complications. The authors also analyzed patient-reported outcomes (PRO), which revealed that robotic surgery was associated with a significantly lower pain score and less use of fentanyl for postoperative pain control. However, the majority of the patients included in this meta-analysis had stage 1 and grade 1 endometrial cancer, which could not exclude potential selection bias.

Conversely, further clinical data are needed to verify the feasibility of robotic surgery in patients with intermediate and high risk factors. A recent single-center retrospective study conducted on patients with intermediate risk endometrial cancer questions the feasibility of robotic surgery [33]. The authors compared the oncologic outcomes of 77 patients who received robot surgery and 58 patients who received laparotomy for stage I endometrioid endometrial cancer. The patients had intermediate risk features, specifically less than 50% myometrial invasion and grade 2 or 3 cellular differentiation or greater than 50% myometrial invasion with grade 1 or 2 cellular differentiation. Among the patients, 79.3% of them received vaginal brachytherapy and 20.7% received external beam radiotherapy postoperatively. The authors observed eight patients with recurrence and all these patients had received surgical treatment via robot-assisted laparoscopy. In that study, the authors partially attributed the reason for observing high recurrence rates in robotic surgery to the fact that the patients in the robotic surgery had longer interval to start adjuvant radiotherapy following hysterectomy compared to the laparotomy group. The surgeons purposely waited longer periods between surgery and adjuvant treatment in the robotic group in order to prevent vaginal cuff dehiscence (12 weeks for robotic surgery whereas 6-8 weeks for laparotomy). This reflects that the results of this study may only capture an early portrait of the implementation period of robotic surgery into practice, which warrants further clinical trials to clarify this.

With the advancement of robotic surgery, other remarkable achievements have also been observed. The reduction in the size of the instrument (such as 3-mm trocar instruments) which is termed ultra-MIS, and the use of single-port are among them [38]. Single-port access laparoscopic surgery is a well-known procedure that has earned great interest from surgeons due to its improvement in cosmetic outcomes. However, its long learning curve and difficult maneuvers still remain concerns. The implementation of single-port surgery in robotic platform may allow surgeon to overcome these barriers [39].

In addition to the lack of solid data on long-term oncologic outcomes of robot surgery in endometrial cancer, there is another limitation in the current data. In many of the published studies to date, the robotic surgery consists of an early experience for the surgeons. Outcomes with robotic surgery improve with numbers performed [40]. This may have biased the results in favor of conventional laparoscopic surgery, in which surgeons have more experience compared to robotic surgery. The data available to date should be considered an early portrait in the implementation of robotic surgery as the data represent the initial work in the field. It should also be noted that most studies were retrospective cohort reviews, and some matched retrospective reviews. Therefore, the quality of evidence is still low despite the fact that some studies included large numbers of patients.

It should also be noted that the choice of surgical approach in endometrial cancer still remains the result of surgeon preference after discussion with the patient. One of the factors that are often considered when making such choices is its cost. Although variations exist by regions, robotic surgery may cost expensive enough to have the patient hesitate to receive it even though she is considered a good candidate for robotic surgery. It should also be taken into account that nearly 80% of women with endometrial cancer are obese and possess concurrent comorbidities [41]. They have a greater likelihood to have surgical complications post-operatively. When recognizing potential complications and the costs associated with necessary treatment, it may be argued that robotic surgery has comparable or even lower costs [42–48]. However, the evidence is inconsistent presumably due to the heterogeneity of clinical settings by region, with some publications indicating still higher costs for robotic surgery hence not justifying its use [49–51]. This issue requires further research that incorporates patient demographics, likelihood of complication occurrence, and regional healthcare policies into considerations.

Despite the fact that further data are required especially in regards to long-term oncologic outcomes of robotic surgeries, the literature published to date demonstrates that patients who receive robot surgery experience less blood loss, reduced length of hospital stay, and less postoperative pain compared to those who receive laparotomy. Similar results were obtained in morbidly obese women with endometrial cancer as well [49, 52–55].

5. Sentinel lymph nodes

The diagnosis of nodal metastases can change the management of patients. It often requires them to undergo adjuvant treatment after surgery. Recently, the sentinel lymph node mapping and selective removal of them is rapidly gain-

ing acceptance in endometrial cancer. It is becoming an ideal compromise to evaluate nodal involvement because evidence shows that it reduces perioperative morbidity that may occur due to a systematic and complete lymph node dissection. It has also been shown to improve the detection of lymph node metastasis with the ultra-staging analysis [56]. Systematic literature reviews and meta-analyses of nearly 5,000 cases support the role of sentinel lymph node sampling in endometrial cancer by showing a high sensitivity and a low false negative rate, as well as a favorable negative predictive value [57–59]. Minimizing complications due to complete lymph node dissection such as lymphedema and pain may reduce hospital stay and healthcare cost. This may be achieved by sentinel lymph node dissection while still maintaining high diagnostic accuracy [60]. The FIRES trial, the largest prospective study investigating the use of sentinel lymph node mapping was published in 2017 [57]. In that trial, the authors performed a robotic indocyanine green (ICG) sentinel lymph node mapping in 340 patients. Then they performed a systematic pelvic lymph node dissection in all patients and a systematic paraaortic lymph node dissection in 58% of the patients. The results showed a sensitivity to detect node-positive disease of 97.2% (95% CI 85.0%-100%), and a negative predictive value of 99.6% (95% CI 97.9%-100%). The authors concluded that sentinel lymph node sampling can safely be performed and may replace a systematic lymph node dissection during staging procedures of endometrial cancer.

In a recently published article, Chaowawanit *et al.* compared the outcomes of sentinel lymph node mapping between conventional laparoscopic surgery versus robotic surgery in endometrial cancer patients [61]. It was found that sentinel lymph node mapping using ICG in laparoscopic surgery had better overall detection rate than robotic surgery (97% vs. 88%, *P*-value = 0.046). However, there was no significant difference in the identification time of sentinel lymph nodes and dissection time between the two groups. Another study compared sentinel lymph node mapping between single-port access robotic surgery and multiport robotic surgery [62]. Moukarzel *et al.* found a bilateral sentinel lymph node detection rate among the single-port access robotic surgery group of 85.7%, slightly higher than that in the multiport robotic surgery group (76.9%, *P*-value = 0.64), suggesting the feasibility of sentinel lymph node mapping even in the single-port access robotic platform.

Patients with high grade and high risk histopathology show higher incidence of nodal involvement of tumor compared to those with low risk endometrial cancer. Therefore, there may be concerns regarding the feasibility of sentinel lymph node mapping in patients with advanced stage disease or high risk for recurrence. However, the results of the studies to date seem to support the use of sentinel lymph node mapping in this patient group as well. With the exception of one retrospective multi-center study which reported a false negative rate of 20% in high risk patients, all other studies demonstrated reasonably low false negative rates. These results are comparable to what have been seen in low risk endometrial cancer patients in large clinical trials to date [56, 63–67]. In the FIRES trial, 100 patients were with high risk histopathologies. The authors obtained a false negative rate of sentinel lymph node mapping at 5% [57]. These data suggest that the completion of lymphadenectomy may be omitted even in this subset of patients without jeopardizing their oncological outcomes in high risk patients. The National Comprehensive Cancer Network (NCCN) approved the execution of sentinel lymph node mapping for staging in low- and high-risk patients in 2018. This decision was based on a number of studies showing the non-inferiority of sentinel lymph node mapping. Researchers have reported a higher detection rate of positive pelvic lymph nodes in the sentinel lymph node mapping group in comparison to the control group (odds ratio 2.04, *P*-value = 0.009), and a similar detection rate of positive paraaortic lymph nodes (odds ratio 0.94, *P*-value: 0.91) [68].

Another concern in regards to the use of sentinel lymph node sampling in endometrial cancer is possible overdiagnosis. Part of the sentinel lymph node procedure implies pathological ultra-staging of the sentinel lymph node. Due to more thorough pathological examination of dissected nodes, the incidence of diagnosis for nodal involvement by tumor has increased. This may result in an increased number of patients who are subjected to adjuvant treatment [69]. However, studies report that isolated tumor cells identified by sentinel lymph node mapping generally have an excellent outcome [70]. Therefore, the use of adjuvant treatment should be tailored to uterine factors and histology and not solely based on the presence of isolated tumor cells.

Although laparoscopic surgery is an ideal and more adapted platform to perform sentinel lymph node mapping in comparison to laparotomy, it is not impossible to obtain sentinel lymph nodes in open surgery. Studies have revealed the feasibility of hand-assisted laparoscopy during laparotomic procedures to detect sentinel lymph nodes in high risk endometrial cancer patients [71]. It was shown that real-time near-infrared technology supported by hand-assisted cameras such as VITOM^{TM} HD Exoscope and IMAGE1 S^{TM} reproduced reliable sentinel lymph node mapping and provided a promising method during laparotomic surgery for sentinel lymph node sampling [72].

Technological advancement has also been observed in the development of safe and effective tracers. In one study, the authors evaluated the detection rate and accuracy of sentinel lymph node mapping using carbon nanoparticles in laparoscopic surgery of endometrial cancer [73]. The authors demonstrated 96.5% of detection rate, which is superior to the detection rates of ICG or radiotracer dye [58, 74, 75].

6. Conclusions

The current available data seem to support the use of MIS in all patient groups of endometrial cancer. Although further studies are required, it is also suggested that robotic surgery

may be a safe alternative to conventional laparoscopic surgery especially for patients with early stages or low risk for recurrence. MIS has also been shown to have favorable perioperative outcomes compared to laparotomy. These are mainly related to shorter duration of hospital stay, less post-operative pain, less blood loss during surgery, and earlier return to routine activities while post-operative sexual activity and function seem to be less affected by the types of surgical approach [76]. The aforementioned benefits of MIS persist even beyond the short-term post-operative period up to 12 weeks after surgery [77]. Nevertheless, limitations exist in the studies reviewed in the present study, especially in regard to those patients with advanced stage disease and with high risk for recurrence. Therefore, any conclusions drawn from this review as to which surgical approach is better than the other may be immature. Further studies are required especially regarding the long-term oncologic outcomes of laparoscopic and robotic approach in advanced diseases.

Author contributions

The present study was designed, directed and coordinated by TJK as the principal investigator. TJK provided conceptual and technical guidance for all aspects of the project. JN planned and performed the analyses of the data with TJK. The manuscript was written by JN and commented on by TJK. All the authors meet the recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals provided by the International Committee of Medical Journal Editors.

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Conflict of interest

The authors of this publication disclose that there are no relevant interests to declare.

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