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Safety of minimally invasive radical hysterectomy in cervical tumors <2 cm

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'A single death is a tragedy, a million deaths are a statistic'

Joseph Stalin

The simultaneous publications of the Laparoscopic Approach to Cervical Cancer (LACC) trial by Ramirez et al[1] and the study of the National Cancer Database by Melamed et al[2] showed that minimally invasive radical hysterectomy was associated with worse disease-free survival compared with the open approach. One of the most strongly criticized points in both studies has been the lack of information about oncologic safety of minimally invasive radical hysterectomy in cervical tumors <2 cm. In the LACC trial the methodological design did not allow the detection of differences in cancer outcome in tumors <2 cm, given the small number of outcomes of interest; however, when looking at absolute numbers, there were five recurrences in the minimally invasive surgery group compared with one in the laparotomy group. In the study by Melamed et al the authors state that they were "unable to estimate precisely the associations between minimally invasive surgery and all-cause mortality among subgroups in which few deaths occurred, such as the sub-group of women who had tumors smaller than 2 cm in the greatest dimension".

Despite this lack of evidence regarding the safety of radical hysterectomy in this sub-group of patients, some gynecologic oncologists continue to offer minimally invasive surgery to patients with cervical tumors <2 cm.

In this issue of *International Journal of Gynecological Cancer*, Xu Chen et al[3] publish a retrospective comparative study evaluating the oncologic outcome in patients with early stage cervical cancer with tumor size <2 cm (determined by physical examination, magnetic resonance imaging (MRI) or ultrasound) who underwent laparoscopic versus abdominal radical hysterectomy in three hospitals in China. The study included 325 patients (129 patients who underwent laparoscopic radical hysterectomy and 196 patients who underwent laparotomy). After a median follow-up of 51.8 months in the laparoscopy group and 49.5 months in the laparotomy group, the authors found a worse 5-year disease-free survival in the laparoscopy group compared with the open surgery group (97.7% vs 90.4%; p=0.016). There was no statistically significant difference in overall survival.

Unfortunately, we do not have a standard methodology when assessing pre-operative tumor size, and worse, the accuracy of pre-operative tumor size (estimated by physical examination, ultrasound, computed tomography or MRI) does not always match the final pathology results. Recently, Uppal et al[4] published a multicenter retrospective study including 815 patients with early stage cervical cancer, with two main objectives: (1) to compare the oncologic outcomes between open and minimally invasive radical hysterectomies performed in academic institutions in the USA and Canada; and (2) to compare the pre-operative tumor size to the post-operative (pathology-determined) tumor size and determine the difference in outcomes on the basis of the use of pre-operative versus post-operative tumor size, especially in the sub-group of patients with tumor size <2 cm. Regarding this last objective, the authors evaluated the ability to determine pre-operative tumor size in 744 patients with early stage cervical cancer (after excluding 71 patients from one site that did not collect data regarding the pre-operative tumor size) who had undergone tumor size measurements both pre-operatively and post-operatively. From those, 184 patients had visible tumors >2 cm whereas 291 patients had no visible disease on pre-operative assessment, but 58 (19.9%) patients had tumors >2 cm on final pathology. Conversely, of 257 patients with pre-operative visible tumor size <2 cm, 89 (34.6%) patients had tumors >2 cm on final pathology. Therefore, one could interpret the results of this study as showing that each time there is no visible tumor, one in five patients will have a tumor >2 cm on final pathology. Similarly, if one determines that a visible cervical tumor is <2 cm, there is a one in three chance of underestimating its true size. This is a very concerning finding! In that same study the authors reported that, among 264 patients with tumors <2 cm on final pathology, there were two (2.4%) patients of 82 who had a recurrence in the open group and 16 (8.8%) patients of 182 who had a recurrence in the minimally invasive group (p=0.06). Although the difference is not statistically significant, this is a four-fold increase in recurrences. Additionally, in the risk-adjusted analysis of patients with tumor size <2 cm (excluding those with no residual tumor on final pathology), the minimally invasive approach was independently associated with a higher likelihood of recurrence (adjusted HR 6.31, 95% CI 1.24 to 31.9).

Odetto et al[5] published a case series from Hospital Italiano in Buenos Aires, Argentina, including 108 patients, 77% with squamous cell carcinoma, 92% stage IB1 (International Federation of Gynecology and Obstetrics, 2009), and 54% with tumors <2 cm. In that study, after a median follow-up of 39 months (range 11–83), according to tumor size, the recurrence rate was 12% in patients with tumors ≤2 cm (7/58) and 18% in patients with tumors >2 cm (9/50) (OR 0.76, 95% CI 0.26 to 2.22; p=0.62). One of the most important findings of that study is that three out of seven patients (42%) in the <2 cm group recurred with peritoneal carcinomatosis, an unusual relapse pattern in patients with early cervical cancer. Paik et al,[6] in a retrospective comparative multicentric matched-control analysis from Korea (nine institutions), including 119 patients undergoing laparoscopic radical hysterectomy and 357 patients undergoing abdominal radical hysterectomy (median follow-up 63.9 months), found a lower disease-free survival in the laparoscopy group (HR 2.74, 95% CI 1.33 to 5.65; p=0.005). In addition, they also found that with tumor size <2 cm (laparoscopy 62 vs laparotomy 186, median follow-up of 69.1 months), laparoscopy was associated with a lower rate of disease-free survival (HR 12.99, 95% CI 1.45 to 116.24; p=0.003). However, one must note that there were no statistical differences in overall survival, despite tumor size. Lastly, Pedone Anchora et al[7] published a retrospective propensity-matched control study evaluating the oncologic outcomes in 423 patients with cervical cancer undergoing radical hysterectomy (217 open and 206 laparoscopy). After a median follow-up time of 49 months (range 1–229), the authors found a higher relapse risk among patients with cervical tumors >2 cm undergoing laparoscopy (HR 2.10, p=0.03). Among 258 patients with tumors <2 cm (114 open and 144 laparoscopic procedures), the authors matched 156 patients (78 in both groups) for analysis of oncologic outcome. There was no difference in median follow-up (76 vs 47 months in the open and laparoscopy groups, respectively; p=0.068). Twenty-six patients (16.6%) were diagnosed with a relapse and seven (4.5%) died from the disease. Neither disease-free survival nor overall survival were significantly different. Although there were no statistically significant differences in oncologic outcome in patients with tumors <2 cm, the authors noted an alarming rate of carcinomatosis in 42.9% of patients in the laparoscopy group. In addition, the number of patients with tumors <2 cm lacked power to determine the safety of the laparoscopic approach.

We must recognize a number of limitations in the study by Xu Chen et al. Among these are its retrospective nature, introducing a possible source of bias, and the relatively small sample study (325 patients in the entire cohort) as well as the low number of recurrences (16 patients, 11 in the laparoscopy group and five in the open surgery group), findings that can explain the amplitude of the confidence interval (adjusted HR 4.638, 95% CI 1.261 to 17.056; p=0.021). Further limitations include the lack of uniformity in tumor dimension measurement for the entire cohort as well as no central pathology review.

There is further evidence that the minimally invasive approach when performing radical hysterectomy in patients with cervical tumors <2 cm may be associated with higher recurrence rates when compared with the open approach. This has already been demonstrated in at least five recent publications.[3–7] Joseph Stalin said "*one death is a tragedy, but a million are a statistic*". This concept resonates in the results regarding recurrence in tumors <2 cm, since these are 'diluted' in the global data of studies which leads to a tone of minimizing the true importance of the issue when counseling patients with early-stage cervical cancer regarding the surgical approach. There is an unfortunate and mistaken tone that tumors <2 cm have similar relapse rates with open and minimally invasive radical hysterectomy. However, one must highlight the fact that the literature tells us otherwise and also one must recognize that these recurrences may occur in the form of carcinomatosis, leading to a non-curable pattern of recurrence. I believe most would agree that this scenario leads to a very unfortunate and disappointing discussion with the patient regarding the potential reason for her unusual recurrence.

We as surgeons must consider the published literature and understand that, although minimally invasive surgery was for a long time believed to be the best choice for our patients undergoing radical hysterectomy, there is evidence of worse oncologic outcomes[1 2] and additional evidence that there is no difference in overall adverse events between the two approaches.[8] We await the most recent results from the LACC trial on quality of life assessment between the two groups.[9]

Given these findings, let us make sure that our patients do not become that single avoidable tragedy. I believe the time has come for everyone, as a scientific community, to follow established guidelines[10 11] and offer our patients the new standard of care of open radical hysterectomy and agree to only offer minimally invasive radical hysterectomy in the context of a clinical trial. We will soon have the results of the SHAPE trial,[12] a prospective randomized trial comparing simple hysterectomy versus radical hysterectomy in patients with low-risk cervical cancer (<2 cm), which may potentially answer the question as to whether such patients need a radical hysterectomy at all, while also recognizing that this may leave us with another unanswered question: if simple hysterectomy proves to be oncologically safe, will the minimally invasive approach still be considered viable when performing such procedure? Until then, let us all be impartial and lead our practice based on the mounting evidence in the literature for open radical hysterectomy.

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