INTERNATIONAL JOURNAL OF GYNECOLOGICAL CANCER

Impact of 'low-volume' metastasis in sentinel lymph nodes: reconsidering options for no further treatment

Rene Pareja

Astorga Oncology Clinic & National Cancer Institute, Medellin & Bogotá, Colombia

Correspondence to
Dr Rene Pareja, Gynecologic Oncology, Clinica ASTORGA, Medellin calle 8 # 43C 101, Colombia; ajerapener@gmail.com

Received 30 January 2019
Accepted 30 January 2019

Detection of sentinel lymph nodes in cervical cancer has become a standard procedure in most cancer centers in the USA; in fact, the National Comprehensive Cancer Network guidelines suggest this technique as an alternative to complete pelvic lymphadenectomy (category IIB).[1] However, the European Society of Gynaecological Oncology guidelines[2] still consider sentinel lymph node mapping an experimental procedure and recommend pelvic lymphadenectomy in patients undergoing radical hysterectomy for early-stage cervical cancer. Thus far, the evidence in the literature shows favorable bilateral identification rates and low false negative rates when sentinel lymph nodes are detected bilaterally, as confirmed by the SENTICOL-1 trial.[3] One of the unresolved questions on the subject of sentinel lymph node mapping focuses on the management of patients when 'low-volume disease' is detected. In other words, what should we do when we find micrometastasis (>0.2 to ≤2.0 mm) or isolated tumor cells (<0.2 mm)?

In this issue, the study's authors present a subanalysis of the data gathered in the SENTICOL-1 trial and evaluate the impact of 'low-volume' disease on oncologic outcomes, reporting on the 3-year survival of patients included in that study.[4] Briefly, from a population of 136 patients in whom sentinel nodes were detected, with a bilateral detection of 76.5% (104/136), there were 21 patients with 26 positive sentinel lymph nodes (eight macrometastasis, eight micrometastasis (alone or in combination), and eight isolated tumor cells), of which 11 patients received adjuvant pelvic radiotherapy (eight with macrometastasis, two with micrometastasis, and two with isolated tumor cells). After a median follow-up of 36 months (range 1–69), 13 patients relapsed, 11 with negative lymph nodes and two with positive sentinel lymph nodes (one with macrometastasis and one with micrometastasis). The authors concluded that evidence of micrometastasis or isolated tumor cells in early cervical cancer did not impact progression-free survival.

Thus far in the literature, there are two major studies evaluating the impact of micrometastasis and isolated tumor cells on oncologic outcomes. The first study was published by Cibula and colleagues,[5] and it included 645 patients that werecollected retrospectively from eight institutions. Macrometastasis and micrometastasis were identified in 47 and 46 patients, respectively. After a median follow-up of 40 months, the presence of macrometastasis and micrometastasis was associated with significantly decreased overall survival (hazard ratio (HR) 6.85, 95% confidence interval (CI) 2.59 to 18.05, and HR 6.86, 95% CI 2.09 to 22.61, respectively). The authors concluded that micrometastasis in the sentinel node is associated with poor prognosis. In another retrospective study from Brazil published in 2016, the authors included 83 patients who underwent radical hysterectomy and pelvic lymphadenectomy with negative nodes on routine pathological processing, and then performed ultrastaging on all lymph nodes (1138). The authors reported a rate of micrometastasis of 7% and an odds ratio of 11.7 (p=0.017) for recurrence among patients with micrometastatic disease.[6]

These studies, along with the one by Mathevet and colleagues published in this month's journal, are retrospective or post-hoc in nature, which raises the concern that the level of evidence is not optimal to appropriately answer the question of whether low-volume metastasis impacts overall outcomes. According to a recent publication from Cibula and colleagues,[7] in order to adequately answer this question in a prospective manner, it would require a sample size of 100 cases with micrometastasis and 600 cases of negative lymph nodes to identify a 10% increase in recurrence rate between groups with negative lymph nodes and micrometastasis—certainly a task that would be challenging, even if multiple international centers were included.

The authors are to be commended for adding yet another contribution to the literature from the SENTICOL trial. However, this article raises some important questions and one must recognize several important limitations, which include: biases inherent to the retrospective analysis; lack of homogeneity in the indications of adjuvant treatment; heterogeneous treatment regimens; and lack of stratification due to the presence of other risk factors such as tumor

Linked

► http://dx.doi.org/10.1136/ijgc-2018-000089

Check for updates

To cite: Pareja R. *Int J Gynecol Cancer* 2019;**29**:445–446.

size, lymph-vascular invasion, stromal infiltration, or pre-operative brachytherapy. However, perhaps the most important concern with this study is that there was a very low number of recurrent events, thus raising the possibility of under-reporting the true incidence of recurrence in the setting of 'low-volume' disease.

Two very important trials are currently ongoing that will hopefully shed additional light on this very important question in our field, the SENTICOL-3 (NCT03386734) and the SENTIX (NCT02494063) trials. For now, it might be prudent to err on the side of caution and consider additional treatment fo patients with at least micrometastasis, particularly given the very aggressive nature of recurrent cervical cancer.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

REFERENCES

1. National Comprehensive Cancer Network. *NCCN clinical practice guidelines in oncology. Cervical cancer (version I.2018)*, 2018.
2. Cibula D, Pötter R, Planchamp F, *et al*. The European Society of gynaecological Oncology/European Society for radiotherapy and Oncology/European Society of pathology guidelines for the management of patients with cervical cancer. *Radiother Oncol* 2018;127:404–16.
3. Lécuru F, Mathevet P, Querleu D, *et al*. Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J Clin Oncol* 2011;29:1686–91.
4. Guani B, Dorez M, Magaud L, *et al*. Recurrence risk after sentinel lymph node biopsy in patients with early cervical cancer: follow-up results after 3 years of a prospective study (SENTICOL). *Int J Gynecol Cancer* 2019;30. doi:10.1136/ijgc-2018-000089. [Epub ahead of print: 4 Jan 2019].
5. Cibula D, Abu-Rustum NR, Dusek L, *et al*. Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. *Gynecol Oncol* 2012;124:496–501.
6. Colturato LF, Signorini Filho RC, Fernandes RC, *et al*. Lymph node micrometastases in initial stage cervical cancer and tumoral recurrence. *Int J Gynaecol Obstet* 2016;133:69–75.
7. Cibula D, McCluggage WG. Sentinel lymph node (SLN) concept in cervical cancer: current limitations and unanswered questions. *Gynecol Oncol* 2019;152:202–7.