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Conization and lymph node evaluation in low-risk cervical cancer. Is it time to avoid radical surgery? Retrospective series and literature review

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ABSTRACT

Objectives: To evaluate the oncologic and obstetric outcomes of patients with low-risk cervical cancer who underwent conization and lymphatic evaluation to preserve fertility.
Methods: Data were collected retrospectively from September 2013 to February 2021. Eligibility criteria included Women with cervical cancer (aged <45 years) who underwent fertility preservation treatment, [stage IA1 with positive lymphovascular space invasion (LVSI), stage IA2, or stage IB1 (≤2 cm) with less <10 mm cervical stromal invasion, according to the International Federaltion of Gynecology and Obstetrics (FIGO) 2018 staging system] aged ≤45 years who wished to preserve their fertility were included in this study. All patients were treated with cervical conization(s) and laparoscopic lymph node evaluation [pelvic lymphadenectomy and/or sentinel lymph node (SLN) mapping]. Oncologic and obstetric outcomes were evaluated.
Results: Overall, 31 patients met the inclusion criteria; 15 (48.3%) women were nulliparous. There were 8 IA1LVSI+ (25.8%), 11 IA2 (35.4%) and 12 IB1 (31.7%) tumours, according to 2018 FIGO stage classification. Most patients had squamous cell carcinoma (77.4%). Lymphovascular space involvement was found in thirteen patients (41.9%). Reconization was performed in 17 (54.8%) patients, of which 6(35.2%) were done due to compromised margins, 4(23.5%) for margins under than 3 mm, 3(17.6%) for unreported or coagulated margins and 4(23.5%) because previous conization was done in another institution and we could not obtain the paraffin blocks for pathology review. Twenty patients had MRI and eleven CT scan. Nine (30%) patients had a complete bilateral pelvic lymph node dissection, 9 (26.6%) had SLN mapping with pelvic lymphadenectomy, and 13 (43.3%) had SLN mapping alone after bilateral SLN identification at surgery. After a median follow-up of 41.4 months (range 2–90 months), no recurrences have been detected. In terms of obstetrial outcome, 11 patients attempted pregnancy and 9 became pregnant. First-trimester miscarriage occurred in one patient. Five patients delivered at term by caesarean section, one of them requiring hysterectomy at the time of delivery. Pathology did not show residual disease. Two patients had a vaginal delivery at 38 weeks. One pregnancy is still ongoing.
Conclusion: Cervical conization with lymph node assessment by SLN mapping/lymphadenectomy is an oncologic safe procedure in patients with low-risk cervical cancer.

Introduction

Cervical cancer is currently the fourth most common cancer in women worldwide and in 2018, approximately 570,000 women developed cervical cancer and 311000 women died from it [1]. Almost 40% of women with cervical cancer are diagnosed at child-bearing age, this is between the ages of 20 and 44 years. Furthermore, 46% of cases are diagnosed with disease confined to the cervix, which allows the possibility of fertility-sparing treatment [2].

Radical trachelectomy procedure is recognized as the standard treatment for women with lesions <2 cm who wish to preserve fertility as per National Comprehensive Cancer Network (NCCN) guidelines [3]. However, overall complication rate of radical trachelectomy is considerable (55.1% of patients), although intra-

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operative and severe postoperative complications are rare (2% and 4.1%, respectively) [4]. Long-term complications of such procedure encompass high risk for further pregnancies [5]. Common complications include cervical stenosis and cervical insufficiency, which can lead to difficulty in conceiving, preterm delivery, first or second-trimester miscarriage, and preterm premature rupture of membranes [5–10]. In addition, approximately half of patients have no residual disease in trachelectomy specimens after a diagnostic conization [11–13].

Several studies have reported a low rate of parametrial spread in selected groups of patients with early-stage disease and favorable prognostic features, defined as tumours <2 cm with <10 mm of cervical stromal invasion and negative pelvic nodes. In these patients, rates of parametrial spread have been found to be less than 1% [14]. With all of the above data in mind, numerous studies of patients treated with non-radical surgery (cone biopsy or simple trachelectomy) report recurrence rates between 0% - 13% [15–18].

The aim of our study was to describe our experience in patients with low-risk cervical cancer treated with conization and lymph node assessment and to report disease free survival, overall survival, fertility preservation rate and obstetric outcomes. We conducted a literature review to evaluate which patients are the best candidates for this surgery and which are the benefits over radical trachelectomy.

Methods

This two-institution, binational, retrospective cohort study of prospectively collected data in patients with early-stage low-risk cervical cancer who wishing to preserve their fertility from September 2013 to February 2021 at the Gynecologic Oncology Department of Sanatorio Allende Cordoba, Argentina and Clínica Andes Salud Concepción, Chile. The inclusion criteria included patients who: (1) desired to preserve fertility; (2) were ≤45 years old; (3) had histological confirmation of squamous, adenocarcinoma or adenosquamous cervical carcinoma; (4) had stage IA1 with LVSI to IB1 disease, according to the International Federation of Gynecology and Obstetrics (FIGO) 2018 staging system; (5) tumour size ≤2 cm on final pathology; (6) depth of invasion ≤10 mm; (7) cone margins negative for malignancy; and (8) had a radiographically confirmed tumour limited to the cervix without evidence of lymph node or other metastasis.

All patients had a gadolinium-contrasted abdominopelvic magnetic resonance imaging study (MRI) or contrasted abdominopelvic computed tomography (CT) before the surgery for lymph node evaluation before surgery. Patients were informed that this procedure was an experimental option, and the standard treatments were radical hysterectomy, radical trachelectomy or chemoradiation. Each patient signed an informed consent to agree with the performance of this surgery.

Diagnostic cone specimens were studied by a pathologist with expertise in gynaecologic oncology, with particular attention given to tumoral size, depth of invasion and presence of LVSI and margin status. We considered 3 mm as safe margin. Surgery included cone biopsy/loop electrosurgical excision (LEEP) and lymph node assessment by laparoscopic sentinel lymph node (SLN) biopsy with ultrastaging or complete pelvic lymphadenectomy. Systematic pelvic lymphadenectomy was omitted when bilateral SLNs were identified. Uterine manipulators were not used during the procedure. Cervical cerclage was not placed in any patient.

Follow-up consisted of a schedule of clinical, cytologic and colposcopy assessment every 3–4 months for the first 2 years, every 6 months for the next 3 years, and then yearly. In our institutions, colposcopy is routinely used in the follow-up of patients with cervical cancer. Descriptive statistics were performed. Data are presented as median and range. Categorical variables are reported as absolute value and percentage. The primary endpoint was progression-free survival calculated from the date of surgery to the date of recurrence or last available follow-up visit. Kaplan–Meier survival estimate was calculated using STATA Version 13.1 (Stata Corp., College Station, TX, USA).

Literature review

A literature search of PubMed, MEDLINE and Embase was performed using the following keywords: 'cervix neoplasm', 'cervical cancer', 'large loop excision of the transformation zone (LLETZ)', 'conization', 'cone', 'simple trachelectomy', 'non-radical' and 'less radical'. Reference lists of all articles identified were reviewed. The inclusion criteria were as follows: (1) original articles and case series published in English; and (2) articles including information about conization or simple trachelectomy with pelvic lymphadenectomy. For repeated publications by the same team on a similar topic, the series comprising the largest number of patients (or the most complete data) was retrieved. We excluded Case reports, review articles, and reports on the management of tumours in children and surgical treatment of cervical cancer during pregnancy.

Results

Thirty-two women accepted the conservative approach. One patient was excluded because of grossly positive lymph nodes during lymphadenectomy; therefore, 31 patients were studied. Table 1 summarizes the patients and tumor characteristics. Fifteen patients (48.3%) were nulliparous. The median age was 31.5 years (range 23–41), and the median tumour size was 14.7 mm (range 2–20). Eight patients had stage 1A1 with LVSI (25.8%), 11 had stage 1A2 (35.4%) and 12 had stage 1B1 (38.7%). Twenty-four patients had squamous carcinoma (77.4%). Lymphovascular space involvement was detected in thirteen patients (41.9%).

In terms of diagnostic procedure, 13 had punch biopsies and 18 LEEP. Reconization was performed in 17 (54.8%) patients, of which 6(35.2%) were done due to compromised margins, 4 (23.5%) for margins under 3 mm (as per recommended by institutional tumor board), 3(17.6%) for unreported or coagulated margins and

Table 1
Patient and tumour characteristics (n = 31).

Age	
Median (range)	31.5% (23–41)
Gravida (%)	
G0	14 (45.1%)
G1	14 (45.1%)
G2	3 (9.6%)
Stage (%)	
IA1	8 (25.8%)
IA2	11 (35.4%)
IB1	12 (38.7%)
Histology (%)	
Adenocarcinoma	7 (22.5%)
Squamous	24 (77.4%)
LVSI *(%)*	
No	18 (58%)
Yes	13 (41.9%)
Diagnotic procedure (%)	
Cervical biopsy	13 (41.9%)
LEEP	18 (58%)

LEEP, loop electrocautery excision; LVSI, lymphovascular space invasion.

4(23.5%) because previous conization was done in another institution and we could not obtain the paraffin blocks for pathology review (Table 2). Twenty patients underwent contrasted abdominopelvic MRI and 11 patients had contrasted abdominopelvic CT scan.

Lymph node assessment was performed laparoscopically in all patients. Nine (30%) patients had a complete bilateral pelvic lymph node dissection, nine (26.6%) had SLN mapping and systematic pelvic lymphadenectomy, and 13 (43.3%) patients had SLN mapping alone after bilateral SLN were identified at surgery. SLN technique was performed using patent blue dye or Indocyanine green (ICG), injected directly to the cervix at hours 3 and 9 (1 cc submucosal and 1 cc 1 cm deep in each point) of the cervix, right before the second LEEP procedure. Sentinel nodes were retrieved or bilateral lymhadenectomy was always the first surgical step in all cases. The avarange number harvested SLN was 2.3 (range 1–3), and for complete lymphadenectomy was 12.2 (range 6–22). There were no intra-operative complications. One patient (in the complete lymphadenectomy group) had an asymptomatic lymphocyst which resolved spontaneously. The median hospital stay was 1.36 days (range 1–3 days) (Table 3).

After a median follow-up of 41.4 months (range 2–90 months), no recurrence has been detected. The disease-free survival and overall survival at 5 years were 100%. A total 67.7% of patients had ≥2 years of follow-up and 32.5% of patients had ≥5 years of follow-up.

In terms of obstetric outcome, 11 patients attempted pregnancy and 9 became pregnant (Table 4). First-trimester miscarriage occurred in one patient. Five patients delivered at term via caesarean section. One of them required hysterectomy for obstetric complications and pathology did not show residual disease. Two patients had a vaginal delivery at 38 weeks. One pregnancy is still ongoing.

Table 2
Pathological results.

Reconization (%)	
No	14 (45.1%)
Yes	17 (54.8%)
Causes	
Residual disease	6 (32.5%)
Margin ≤3 mm	4 (23.5%)
Coagulated margin	3 (17.6%)
No pathology	4 (23.5%)
Tumoral size	
Median (range)	14.7 (2–20)
Stromal invasion	
Median (range)	4 (1–10)

Table 3
Surgical approach and complications.

Conization + SLN	13 (41.9%)
Conization + lymphadenectomy	18 (58%)
Lymph nodes	
Median (range)	8.5 (2–22)
SLN	
Median (range)	2 (0–3)
Blood loss	
Median (range)	50 (50–500)
Surgical time	
Median (range)	120 (45–180)
Transfusion (%)	
Yes	0 (0)
Intra-operative complications (%)	
Yes	0 (0)
Postoperative complications (%)	
Yes	1 (3.2%)

SLN, sentinel lymph node.

Table 4
Oncologic and obstetric outcomes.

Oncologic outcomes	
Median (range)	41.4 (2–90)
Recurrence (%)	
Yes	0 (0)
Obstetric outcomes (n = 9)	
First-trimester loss	1
Term delivery	7
Ongoing pregnancy	1

Discussion

Our study showed that disease-free survival and overall survival at 5 years were 100%. The fertility preservation rate was 96.8%, with a 29% pregnancy rate, 11.1% first-trimester miscarriage and 89.9% full-term pregnancy. To our knowledge, this is the largest series on conization and lymph node assessment in early-stage cervical cancer in South America.

To understand better the current status of non-radical surgery for fertility sparing in cervical cancer we conducted a literature review of all the case series of large cone or simple trachelectomy with lymph node assessment. (see Tables 5 and 6 for details). Eighteen studies [15–18,19–36,30,31,34] with a total of 594 patients have been published, with a 91.7% reported rate (545 patients) of fertility preservation. A 77.7% have a median follow-up time of two years or more. Among 594 patients, only 28 recurrences have been reported. This 4.7% recurrence rate is comparable to previously published data for radical trachelectomy [8,11,13,32].

There is a trend towards less radical surgery in patients with low-risk tumours who wish to preserve fertility. Recent data support conservative treatment, such as conization and simple trachelectomy with lymph node dissection, for patients with 2018 FIGO stage IA2–IB1 disease in the setting of low-risk factors. These patients have been found to have a very low risk of parametrial involvement and are therefore excellent candidates for such procedures [14,33].

Patient selection is of paramount relevance when deciding to offer preservation of fertility by means of less radical techniques. Martinelli et al. [34] reported 44 (13.7%) patients in which despite initially considered for fertility-sparing management it was, ultimately not performed. In four cases, this was due to the histological characteristics of the tumor. Another three patients declined a fertility-sparing approach after thorough oncofertility counselling, highlighting the need for a full explanation of options and risks involving such management. Furthermore, among patients who attempted the conservative approach, 10.3% were excluded as disease was more advanced than expected because lymph node involvement was encountered. In contrast, in our literature review and in our case series we found that the number of patients with positive lymph nodes was 4% and 2.7%, respectively. Of notice, we observed that some studies did not perform previous imaging studies to rule out lymph node involvement before performing so we suspect there might be some underdiagnosis.

In our series, 41.9% (13) of the patients had LVSI, similar to the percentages found in our review, which ranged from 5% [20] to 70% [27]. Park J-Y et al. [35] showed that in tumors smaller than 2 cm the percentage of invasion was 11.4% while nodal involvement in that group was 6%. Milam M.R et al. [36] also showed that when there was LVSI and depth of invasion > 4 mm there was 6.6 times

Table 5
Oncological outcomes.

Author	Year	No. intent to preserve	No. preservation	Surgery	FIGO stage	Age, median (range)	Pathology	LVSI	LN +	Follow-up, median (range)	Neoad y.	Ady.	Recurrence	Treatment after recurrence	Deaths
Rob [19]	2008	40	34	10 conization/24 simple trachelectomy	3IA1, IA2, 27 IB1	28.3	32SCC, 7AC, 1AS	17	6	47 (12–102)	–	No	2	1 CRT, 1 TAH	0
Maneo [20]	2011	37	37	Conization	36IB1	31 (24–40)	24SCC, 12AC	5	1	66 (6–168)	No	No	3	1 CRT, 1 LEEP	1
Fagotti [15]	2011	17	13	Conization	4IA2, 13IB1	33 (30–43)	12SCC, 4AC, 1 glassy	4	3	16 (8–101)	No	2	0		0
Baalbergen [21]	2011	22	22	Conization	15IA1, 7IA2	IA1 37.8 (26–66), A2 42.04 (28–66).	52AC, 6AS, 1CC	6	0	79.9 (10–131)	No	No	1	VH	0
Raju [22]	2012	15	15	Simple trachelectomy	5IA2, 10IB1	28 (20–40)	9SCC, 6AC	0	0	96 (12–120) *	No	No	0	–	0
Palaia [23]	2012	14	14	Simple trachelectomy	5IA2, 9IB1	32 (28–37)	11SCC, 3AC	0	0	38 (18–96)	No	No	0	–	1
Biliatis [24]	2012	35	34	LLETZ	NE	32 (26–43)	NS	NS	0	56 (13–132)	No	No	0	–	0
Bouchard-Fortier [25]	2014	29	27	Conization	28 IA1, 10IA2, 13IB1	34 (19–77)	26SCC, 22AC, 3AS	18	1	21 (1–112)	No	2 CRT	0	–	0
Lindsay [26]	2014	43	40	LLETZ	2IA1, 4IA2, 37IB1	29 (22–38)	28SCC, 11AC, 4AS	16	2	42 (0–91)	No	No	2	1 CRT, 1 TAH with CRT	1
Andikyan [27]	2014	10	10	Conization	7IA1, 3IB1	28 (18–36)	8SCC, 1AC, 1CC	7	0	17 (1–83)	No	No	0		0
Slama [28]	2016	44	32	21 conization/11 simple trachelectomy	7IA2, 23IB1	31 (19–36)	26SCC, 4AC, 2AS	NS	0	23 (3–53)	9	No	6	1 recon, 1 none, 1 RH, 2 CRT, 1 DBK and CT	1
Tomao [18]	2017	54	54	Conization	13IA2, 41IB1	32 (23–40)	33SCC, 19AC, 2AS	NS	0	55 (7–144)	1	11	7	CT, CRT, recon	0
Demirkiran [29]	2018	14	13	Simple trachelectomy	3IA1, 4IA2, 7IB1	32 (27–37)	12SCC, 2AC	7	0	27 (6–56)	No	No	0	–	0
Li [16]	2020	40	39	Conization	5IA1, 21IA2,14IB1	32 (21–41)	35SCC, 3AC, 2AS	15	0	35 (8–74)	No	5	1	RT	0
Plante [17]	2020	50	50	42 simple trachelectomy/8 conization	11IA1, 13IA2, 26IB1	29 (21–44)	26SCC, 20AC, 1AC, 2 CC, 1 undifferentiated	15	4	76 (1–140)	No	2	1	Hysterectomy	1
Nica [30]	2021	44	38	Conization + SLN	18 IA1, 3IA2, 21 IB1	31 (19–61)	27SCC, 16AC, 1AS	18	3	44	No	2 CRT	0	No	0
Fanfani [31]	2021	42	42	Conization + PLD and/or SN	IB1	32 (19–44)	27SCC, 13AC, 2AS	15	0	54 (1–185)	No	No	3	Hysterectomy	0
Martinelli [34]	2021	44	31	Conization + PLD and/or SN	13IA1, 11 IA2,25 IB1	33 (22–40)	22 SCC, 17AC	15	4	51 (1–184)	No	2 CRT, 2 CRT + Cx	2	Hysterectomy	0

LVSI, lymphovascular space invasion; LLETZ, large loop excision of the transformation zone; LN, lymph node; PLD, pelvic node dissection; SN, sentinel node; SCC, squamous cell carcinoma; AC, adenocarcinoma; AS, adenosquamous carcinoma; CC, clear cell; CRT, chemoradiotherapy; Cx, surgery; TAH, total abdominal hysterectomy; VH, vaginal hysterectomy; RH, radical hysterectomy; CT, chemotherapy; DBK, debulking surgery; RT, radiotherapy; NE, not specified.

Table 6
Obstetric outcomes.

Author	Attempted to concive	Pregnancies	Births		Miscarriages			Therapeutic abortion or extrauterinepregnancy	Ongoing	N/S
			Preterm	Term	1 T	2 T	3 T			
Rob [19]	NS	29	3	9	2	3	–	3	3	–
Maneo [20]	5	21	3	11	3	1	–	2	1	–
Fagotti [15]	NS	2	–	2	–	–	–	–	–	–
Baalbergen [21]	5	18	–	13	4	–	–	–	1	–
Raju [22]	NS	12	–	4	–	–	–	–	–	8
Palaia [23]	NS	8	–	3	–	–	–	–	–	5
Biliatis [24]	NS	7	–	7	–	–	–	–	–	–
Bouchard-Fortier [25]	NS	NS	–	–	–	–	–	–	–	–
Lindsay [26]	NS	21	4	11	1	–	–	1	4	–
Andikyan [27]	9	3	–	–	–	–	–	–	–	–
Slama [28]	25	6	1	4	1	–	–	–	–	–
Tomao [18]	11	20	–	19	1	–	–	1	–	–
Demirkiran [29]	17	7	2	4	1	–	–	–	–	–
Li [16]	NS	4	–	3	–	–	–	–	1	–
Plante [17]	30	40	3	30	5	1	–	–	1	–
Nica [30]	22	20	1	16	–	–	–	3	–	–
Fanfani [31]	22	14	6	6	1	1	–	–	–	–
Martinelli [34]	NS	13	1	9	1	1	–	1	–	–

NS, not specified; 1T, first trimester; 2T; second trimester; 3T, third trimester.

more chance of nodal involvement. Therefore, it should be considered as a prognostic factor for lymph node involvement specially in I A1 tumors.

There are three validated techniques for sentinel lymph node detection, radiocolloid, blue dye and indocyanine green (ICG). ICG has not only shown the highest sensitivity (96%) for sentinel lymph node detection, but also outperforms blue dye in bilateral detection rate [37]. The sensitivity for lymph node detection using blue dye and radiocolloid together or radiocolloid alone is between 92% and 97.8%, but the sensitivity is reduced to 81% when using blue alone [46,39]. The ideal would be to use ICG, but due to the cost of the equipment it is not available in all centers and specially in developing countries. Sentinel node ultrastaging can detect low-volume metastases of less than 2 mm, including micrometastases (MM) and isolated tumor cells (ITC). Micrometastases are associated with lower survival rate. Such a technique can identify lymph node metastases in 11% of patients with low-volume disease in SNL that would not be detected by standard pathologic processing [40]. We await the results of three ongoing prospective studies (GOG 278, SHAPE, and ConCerv) that will probably establish the safety of less radical surgery (simple trachelectomy or cervical cone plus lymphatic evaluation) for this group of patients.

Preliminary results from the ConCerv trial [41], a prospective multicenter cohort trial presented by Schmeler at the International Gynecologic Cancer Society meeting in Rio de Janeiro, reported two (4.3%) of 44 patients who underwent cervical conization with lymph node assessment had recurrences at a median follow-up of 25 months. Marie Plante [17] observed recurrence in one case (2%) in the largest case series to date of less radical fertility preservation surgeries for low-risk cervical cancer.

Fertility and obstetric outcomes of these patients treated with less radical surgeries is the other important discussion point when comparing it to radical trachelectomy. Neglecting parametrial removal in view of the low risk of its involvement could explain the lower rate of miscarriages and premature deliveries observed for up front cervical conization. Pareja et al. [8] report a fertility preservation rate of 85% and a pregnancy rate of 16.2% after radical abdominal trachelectomy. Pregnancy loss rate for this group was 24%. Ribeiro [42] reports 24% pregnancy rate in patients after vaginal radical trachelectomy (VRT). A systematic review by Bentivenga et al. [9] reports a miscarriage rate in vaginal, laparotomic and minimally invasive trachelectomy of 20%, 21% and 22%, respectively, and a prematurity rate between 39% and 50% according to the approach used in radical trachelectomy.

Our fertility preservation rate was 96.8% and the overall pregnancy rate was 29%. We had 7 (77%) term pregnancies, one first-trimester miscarriage (11.1%) and one patient with an ongoing pregnant. In the literature review we observed 245 pregnancies with 27 miscarriages, giving us a first- and second-trimester miscarriage rate of approximately 11%, which is similar to that of the general population [43] and a preterm birth rate of 13.7%.

In a recent review, Noll et al. [44] reported an overall fertility preservation rate of 99.1%, with a pregnancy rate of 30.5%, a loss rate of 17.2% and a live birth rate of 74.1% in patients treated with cervical conization or simple trachelectomy. These findings are very similar to ours contrasting with those previously described by Pareja et al. [8] and Bentivegna et al. [9] for radical trachelectomy.

Finally, in ours series only one complication was observed: a case of lymphocele with spontaneous resolution. This is neglectable compared with the publication of Pareja et al. [8] where a complication rate of 35% was reported, being the most frequent cervical stenosis (9.5%).

Our study shows that cervical conization with lymph node assessment by SLN mapping/lymphadenectomy is an oncologically safe procedure in patients with low-risk cervical cancer.

There are some limitations to be taken into account when interpreting these results, such as the limited number of patients in our series, and the fact that not all patients underwent sentinel lymph node with ultastaging, so that some patients with low-volume metastases may have been missed. The strengths of our study are that our patients, like the 545 in the included review, have both oncologic and obstetric follow-up, and that almost 70% of our patients have follow-up of more than 2 years, like the patients in our review.

In summary, our study demonstrates that, in well-selected patients with low-risk cervical cancer, less radical fertility-preserving surgery, such as up-front cone or simple trachelectomy with bilateral pelvic lymphadenectomy/SLN, has similar oncologic outcome with better obstetric outcome and fewer complications than radical trachelectomy.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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