

Data from small cell neuroendocrine carcinoma of cervix: FIGO 2018 staging is more accurate than FIGO 2009

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Abstract

Background: To evaluate whether the addition of stage IIIC to the revised 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system of cervical cancer is reasonable based on small cell neuroendocrine carcinomas of cervix (SCNEC) data.

Methods: We retrospectively reviewed 64 SCNEC patients with FIGO 2009 stage IB–IIA from January 2014 to December 2018 at the author's hospital.

Results: Univariate analysis showed that FIGO 2018 was related to more prognostic factors than FIGO 2009. Multivariate analysis showed the FIGO stage and the degree of lymph node metastasis (LNM) were significantly related to the prognosis of SCNEC patients. The 5-year overall survival rate (OS) was 78.5% and 22.2% in stage I and II, respectively (FIGO 2009). In FIGO 2018, the 5-year OS was 74.1%, 60.2%, and 0% in stage I/II, IIIC1, and IIIC2, respectively. After IIIC stage was subgrouped by T factor (T1, limited to cervix and vagina; T2, parametrial involvement; T3, pelvic and abdominal cavity involvement), the 5-year OS of IIICT1, IIICT2, and IIICT3 was 83.3%, 30.0%, and 0%, respectively, ($P=0.010$); while by N factor (N1a and N1b, metastasis to pelvic with the rate ≤ 0.20 and >0.20 ; N1c, metastasis to the para-aortic), the 5-year OS of IIICN1a, IIICN1b, and IIICN1c was 80.0%, 26.7%, and 0%, respectively ($P=0.016$).

Conclusion: Compared with FIGO 2009, FIGO 2018 can evaluate the prognosis of SCNEC patients more accurately after subdivision of stage IIIC by combining tumor local invasion factors or the degree and location of LNM.

Introduction

Cervical cancer is a common gynecological malignancy and the fourth most common cancer in women [1]. Approximately 95% of cervical cancers are squamous cell carcinoma (SCC) and adenocarcinoma (AC), which have relatively good outcomes [1]. Small cell neuroendocrine cancer (SCNEC) is one of the remaining rare tumors with an extremely poor prognosis. Compared with common cervical cancer pathological types, SCNEC has a higher rate of lymph node metastasis (LNM). While approximately 40% of SCNEC patients are lymph node (LN)-positive, the rate is only 10%–15% for SCC and AC patients [3-5]. However, it is uncertain whether LNM affects the prognosis of patients. Most reports show that the prognostic factors include LNM in univariate analysis, but only staging is related to prognosis in multivariate analysis [3-5].

In 2018, the International Federation of Gynecology and Obstetrics (FIGO) revised the staging system for cervical cancer [8, 9]. Compared with FIGO 2009, one of the main changes of FIGO 2018 is the division of stage IB stage from two subgroups into three subgroups (≤ 4 , >4 cm vs ≤ 2 , 2–4, >4 cm) according to tumor diameter to screen out patients with tumors ≤ 2 cm who can consider preserving fertility. Another major change is to add stage IIIC according to LNM to predict patient prognosis. However, data from SCC and AC show that stage IIIC is not particularly accurate in predicting prognosis, and needs to be combined with tumor local invasion factors [10, 11].

Therefore, we chose to analyze the data of SCNEC to address the following two questions: 1. Is there any true relationship between LNM and prognosis of SCNEC? Because SCNEC has the highest LNM rate in cervical cancer, if there is no relationship, then the basic framework set by FIGO 2018 stage IIC based on LNM may have problems; 2. Assuming that LNM is related to prognosis, then compared with FIGO 2009, does FIGO 2018 have a better ability to predict prognosis and is there anything that needs to be improved?

Methods

Patients

A total of 5544 laparoscopic surgically treated patients with early-stage cervical cancer (stages IB–IIA, FIGO 2009) were reviewed after providing informed consent, between January 2014 and December 2018 at the Obstetrics and Gynecology Hospital of Fudan University, which is the largest woman's hospital in China. Among them, 64 patients were diagnosed with SCNEC by pathology based on morphological criteria and immunohistochemical staining for neuron-specific enolase, synaptophysin, chromogranin, and CD56. The morphological criteria revealed by hematoxylin-eosin staining included the presence of small cells with hyperchromatic nuclei and scant cytoplasm, absent or inconspicuous nucleoli, and numerous mitotic figures and extensive necrosis, and all tumors had to be positive for at least one neuroendocrine marker [6]. Tumors mixed with SCC or AC components were also included. All SCNEC patients underwent type III hysterectomy and pelvic lymphadenectomy, with or without para-aortic lymphadenectomy as primary treatment. The end point of follow-up was December 2019.

FIGO stage

FIGO 2009 staging is based on physical examination, while FIGO 2018 is based on pathological findings. For FIGO 2009, stage IB is defined as tumors limited to the cervix. According to the maximum tumor diameter, it is divided into IB1 and IB2 (≤ 4 and >4 cm). Stage IIA is defined as tumors involving no more than the upper third of the vagina without parametrial involvement. If there is parametrial involvement, it is classified as stage IIB. For FIGO 2018, stage IB is also limited to the cervix, but according to the maximum diameter of the tumor, it is divided into IB1, IB2, and IB3 (≤ 2 , 2–4, and >4 cm). Stages IIA and IIB are the same as FIGO 2009. However, as long as there is pelvic LNM, it is classified as IIC1, and para-aortic LNM is classified as IIC2, regardless of the local invasion of the tumor [8].

Clinical and pathological variables

Analyzed clinical and pathological variables included patient age, symptoms, human papillomavirus (HPV type, pathological diagnosis (pre- and post-surgery), FIGO stage (2009/2018), tumor size, LNM, and total number of LNs, depth of stromal invasion, lymph vascular space invasion (LVSI), parametrial extension, lower segment involvement, surgical margin, vaginal involvement, and treatment modalities. The primary end point was any cancer-related death. All end points were calculated from the date of

radical hysterectomy to death or were censored at last follow-up. The date of death was obtained from our hospital follow-up department.

Statistical analysis

Relationships between stage and clinicopathological features were analyzed by Pearson χ^2 test. The Kaplan–Meier method was used to construct survival curves, and the log-rank test was used to examine the statistical difference between curves. The Cox proportional hazards model was used to estimate the independent factors prognostic for overall survival (OS). All analyses were performed using SPSS 22 software (SPSS, Chicago, IL, USA).

Results

Compared with FIGO 2009, FIGO 2018 is related to more prognostic factors

The total number of early surgically treated cervical cancer patients was 5544, of which 64 (1.15%) were SCNEC. The mean age of SCNEC patients was 44.48 ± 10.63 years (median, 43.50 years; range, 22–76 years). The total 5-year OS was 67.9%. The main symptom was abnormal vaginal bleeding (71.9%), and other complaints included abnormal physical examination (14.1%) and abnormal vaginal discharge (10.9%). Approximately half of the patients who underwent an HPV test were HPV18-positive (56.7%); only 3.3% were HPV16-positive, and 33.3% were not classified. The remaining 6.7% patients were HPV-negative. These results indicated that more than 90% of SCNEC patients were HPV-positive, and most were HPV18-positive. However, before surgery, the rate of pathological diagnosis for SCNEC was only 48.3% because some SCNEC cases were mixed type.

Other clinicopathological parameters are detailed in **Supplementary Table 1**, and were compared between the two staging systems. Because FIGO 2009 is a clinical staging system, it is not accurate in determining vaginal involvement, parametrial infiltration, and tumor size. Therefore, it was observed that a small number of stage I patients had pathological indications of vaginal involvement, and a small number of stage IIA patients had parametrial infiltration, while some tumor sizes did not match the stage standard. However, the FIGO 2009 staging system is also related to LNM ($P=0.023$), parametrial infiltration ($P<0.001$) and lower uterine involvement ($P=0.014$), which may be related to prognosis [12, 13] suggesting that the FIGO 2009 staging system also has a role in predicting prognosis. Compared with the old system, FIGO 2018 staging based on pathological staging is more accurate regarding pathological parameters such as vaginal involvement, parametrial involvement, tumor size, and LNM, and is related to more prognostic factors (two medium risk factors in Sedlis standard: tumor invasion depth and LVSI). Therefore, it can be theoretically inferred that the FIGO 2018 staging system is more accurate for prognosis.

FIGO stage (2009/2018) and the degree of lymph node metastasis were significantly related to patient prognosis

There was no difference in the 5-year OS between IB1 and IB2 (78.2% vs 80%, $P=0.723$), as well as between IIA1 and IIA2 (20.0% vs 25.0%, $P=0.463$) of FIGO 2009. The same was true in stage I and stage II groups of FIGO 2018 (**Table 1**). We conducted univariate analysis by not subdividing substage; the results are shown in **Table 2** together with other parameters. Five variables with P -values of less than 0.01 (involvement of the lower uterine segment, LNM, parametrial involvement, and FIGO stage (2009 and 2018)) and another four clinically important variables (depth of tumor invasion, LVSI, tumor size, and surgical margin) were included in the multivariate Cox regression analysis. The results showed that only FIGO 2009 stage ($P<0.001$) had statistical significance, and the other variables with $P<0.10$ were LNM ($P=0.058$) and FIGO 2018 ($P=0.062$). This result was consistent with most other studies, where stage (FIGO 2009) was the most important prognostic factor .

It has been reported that the ratio of LNM is more helpful than the presence of LNM in determining prognosis [16]. Therefore, we calculated the rate of LNM; the mean was 0.201 ± 0.156 . According to the receiver operating characteristic curve (ROC), we confirmed that rate of LNM was more effective than the presence LNM to predict survival (AUC 0.631 vs 0.604), and calculated the optimal threshold value of 0.20 (Fig 1A). According to this threshold value, patients were divided into different degrees of LNM: non LNM group (ratio = 0), low LNM group (ratio ≤ 0.20), and high LNM group (ratio >0.20). After the status of LNM was replaced by the degree of LNM, multivariate Cox regression analysis showed that FIGO 2009 stage (HR 1.85, 95%CI 1.34–2.56, $P<0.001$), FIGO 2018 stage (HR 1.63, 95%CI 0.92–2.87, $P=0.015$) and the degree of LNM (HR 2.52, 95%CI 1.36–4.67, $P=0.003$) were independent prognostic factors.

The optimized staging system (FIGO 2018) can predict the prognosis of patients more accurately

Furthermore, we compared the prognosis of the two staging systems. The 5-year OS of patients at stage I and II (FIGO 2009) was 78.5% and 22.2%, respectively (Fig 1B). There was also no difference in 5-year OS between FIGO 2018 stage I and II ($P=0.761$), and the 5-year OS for FIGO 2018 stage I/II, IIIC1, and IIIC2 was 74.1%, 60.2%, and 0%, respectively ($P=0.003$; Fig 1C). However, in FIGO 2018 staging, as long as there is LNM, it will be classified as stage IIIC, which ignores an important prognostic factor, tumor local invasion [16]. Therefore, we further divided stage IIIC into IIICT1, IIICT2, and IIICT3 according to pathological findings (T1, limited to the cervix and vagina, and no parametrial infiltration; T2, parametrial involvement; and T3, pelvic and abdominal cavity involvement). The 5-year OS of IIICT1, IIICT2, and IIICT3 was 83.3%, 30.0%, and 0%, respectively ($P=0.010$; Fig 1D). Another interesting finding was that when IIIC was divided into IIICN1a, IIICN1b, and IIICN1c according to the degree and location of LNM (N1a, limited to the pelvic cavity with a metastasis rate ≤ 0.20 ; N1b, limited to the pelvic cavity with a metastasis rate >0.20 ; N1c, metastasis to the para-aortic LNs), the 5-year OS was 80.0%, 26.7%, and 0%, respectively ($P=0.016$; Fig1E).

Taken together, the prognosis of stage II (FIGO 2009) was underestimated, and stage IIIC (FIGO 2018) was ambiguous. Therefore, the combination of the FIGO 2018 staging system and tumor local invasion factors can more individualize and accurately evaluate the prognosis of SCNEC patients. It is also a reasonable method to combine the FIGO 2018 staging system with the factors of LNM for SCNEC.

Discussion

Our study showed that SCNEC accounted for 1.15% of cervical cancer cases with a 5-year OS of approximately 67.9%, similar to another report [17]. Before 2018, most studies reported that staging (FIGO 2009) was the most important prognostic factor for surgically treated SCNEC [17]. For example, Wang et al. analyzed 116 cases of surgically SCNEC. Multivariate analysis showed that only stage (FIGO 2009) was an independent prognostic factor, while in univariate analysis, LNM was also related to prognosis [7], consistent with our initial results in the current study. Several studies have suggested several other prognostic indicators, including age, ethnic background, tumor size, and depth of invasion [4, 18, 19]. However, only stage (2009) and LN status are the most consistent prognostic factors in retrospective studies [15, 20]. Coupled with the decision of FIGO to introduce LNM into staging in 2018, we speculated that LNM was a definite prognostic factor. Therefore, we attempted to change the analysis strategy to prove this.

Many literatures reported that quantitative analysis of LNM can better predict patient prognosis than qualitative analysis (LNM rate vs LNM or not) [16, 21, 22]. First, we compared the efficiency of the LNM rate and the presence of LNM with prognosis by ROC curve. The results showed that the former was better (AUC 0.631 vs 0.604). Then we divided the patients into different degrees of LNM according to the rate of LNM. Multivariate regression analysis showed that staging (FIGO 2009/2018) and the degree of LNM were significant prognostic factors. This result addresses the first question in the Introduction and confirms that the basis of stage IIIC is correct. But it also raises another question as to whether we need to optimize stage IIIC with the rate of LNM. In fact, the rate of LNM cannot fully represent the role of LNM in tumor prognosis. Therefore, we divided stage IIIC into three groups according to the LNM rate and location and found that the prognosis information was more detailed (IIICN1a, IIICN1b, and IIICN1c: 80.0%, 26.7%, and 0%, respectively; $P=0.016$). Thus, for SCNEC, a special type of cervical cancer, stage IIIC could be divided into three groups: IIICN1a, IIICN1b, and IIICN1c.

For our second question, our data showed that FIGO 2018 was significantly better than the old version. FIGO 2009 underestimated the prognosis of most stage II patients, which might bring a negative psychological burden to the patients and is not conducive to treatment. Compared with the old staging system, the new one was associated with more prognostic factors and more detailed prognosis evaluation. However, it has also been highlighted that in AC and SCC, stage IIIC only refers to the LN factor and ignores the local invasion factor, and thus its role in predicting prognosis is not so accurate [11]. For this reason, stage IIIC was further divided into IIICT1, IIICT2, and IIICT3 with 5-year OS rates of 83.3%, 30.0%, and 0%, respectively. Thus, this strategy is also applicable to SCNEC, and is expected to be extended to all pathological types of cervical cancer.

What is special about our study is that SCNEC, in which LNM easily occurs, was selected to validate the effectiveness of FIGO 2018, especially for stage IIIC. However, our study also had some limitations. First, the number of cases was small because of the rarity of this disease. Second, our data did not include patients of advanced stage, who are not suitable for surgery.

Conclusion

FIGO (2009/2018) stage and LNM rate are important prognostic factors of SCNEC. Compared with the FIGO 2009 staging system, the new system is associated with more prognostic factors and more detailed prognosis evaluation. Furthermore, it is more individualized and accurate in evaluating prognosis when it is combined with the degree and location of LNM, as well as the local tumor invasion factors.

Abbreviations

SCNEC: Small cell neuroendocrine carcinomas of cervix; LNM: lymph node metastasis; LN: lymph node; HPV: Human papillomavirus; SCC: squamous cell carcinoma; AC: adenocarcinoma; LVSI: lymph vascular space invasion; OS: overall survival; ROC: receiver operating characteristic curve

Declarations

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Author contributions

KQ Hua: study conception and design. YQ Zhang: data collection and analysis, manuscript writing. JX Ding: data collection and manuscript editing. The manuscript has been read and approved by all the authors. The requirements for authorship have been met. Each author believes that the manuscript represents honest work.

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Availability of data and materials

The dataset supporting the conclusions of this article is included within the article and its additional files.

Competing interests

The authors declare that they have no conflict of interests.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University.

Consent for publication

Not applicable.

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Tables

Table 1. Analysis of 5-year OS of SCNEC patients in different subgroups

| | N | OS | P |
|-----------------|----|-----------------|-------|
| | | 5-year rate (%) | |
| FIGO stage 2009 | | | |
| I | | | 0.723 |
| IB1 | 40 | 78.2 | |
| IB2 | 8 | 80.0 | |
| II | | | 0.463 |
| IIA1 | 5 | 20.0 | |
| IIA2 | 4 | 25.0 | |
| FIGO stage 2018 | | | |
| I | | | 0.707 |
| IB1 | 19 | 68.4 | |
| IB2 | 17 | 73.5 | |
| IB3 | 2 | * | |
| II | | | 0.564 |
| IIA1 | 3 | 66.7 | |
| IIA2 | 2 | * | |
| III | | | 0.040 |
| IIIC1 | 12 | 60.4 | |
| IIIC2 | 2 | 0.0 | |

*The number of cases was too small and the patients were all alive. The current follow-up time was too short to calculate the OS.

Table 2. Univariate analysis of prognostic factors in patients with SCNEC

| | N | DFS | P | OS | P |
|-----------------------|----|-----------------|--------|-----------------|--------|
| | | 5-year rate (%) | | 5-year rate (%) | |
| Age | | | 0.464 | | 0.210 |
| ≤30 | 2 | * | | * | |
| 30-39 | 18 | 74.6 | | 77.0 | |
| 40-49 | 18 | 72.2 | | 77.8 | |
| 50-59 | 13 | 37.5 | | 53.8 | |
| ≥60 | 5 | 75 | | 50.0 | |
| HPV | | | 0.588 | | 0.598 |
| Negative | 2 | * | | * | |
| 16 | 1 | * | | * | |
| 18 | 14 | 70.7 | | 69.2 | |
| Unclassified | 9 | 75.0 | | 75.0 | |
| Histological homology | | | 0.524 | | 0.763 |
| Pure | 35 | 62.5 | | 66.5 | |
| Mixed | 22 | 72.5 | | 70 | |
| Surgical margins | | | 0.286 | | 0.161 |
| Positive | 4 | 37.5 | | 37.5 | |
| Negative | 53 | 67.5 | | 70.6 | |
| LNM | | | 0.140 | | 0.049 |
| No | 43 | 69.1 | | 74.1 | |
| Yes | 14 | 55.1 | | 50.2 | |
| Parametrial | | | ≤0.001 | | ≤0.001 |
| Positive | 4 | 0.0 | | 0.0 | |
| Negative | 53 | 71.0 | | 74.4 | |
| LVSI | | | 0.466 | | 0.566 |
| Yes | 36 | 63.9 | | 65.8 | |
| No | 21 | 66.8 | | 71.5 | |
| Depth invasion | | | 0.606 | | 0.283 |
| ≤1/3 | 24 | 61.2 | | 69.2 | |
| 1/3-2/3 | 2 | 50.0 | | 50.0 | |
| ≥2/3 | 30 | 68.7 | | 67.4 | |

| | | | | | |
|-----------------------|----|------|--------|------|--------|
| Tumor size(cm) | | | 0.656 | | 0.840 |
| ≤2 | 27 | 55.7 | | 61.4 | |
| 2≤4 | 21 | 72.7 | | 73.5 | |
| ≥4 | 9 | 77.8 | | 76.2 | |
| Lower segment | | | 0.100 | | 0.099 |
| Positive | 7 | 42.9 | | 35.7 | |
| Negative | 50 | 69.1 | | 73.5 | |
| Adjuvant therapy | | | 0.571 | | 0.466 |
| Chemotherapy only | 8 | 71.4 | | 85.7 | |
| Chemoradiotherapy | 43 | 65.5 | | 65.2 | |
| none | 3 | * | | * | |
| Involvement of vagina | | | 0.754 | | 0.678 |
| Yes | 8 | 58.3 | | 57.1 | |
| No | 47 | 69.1 | | 69.2 | |
| FIGO stage 2014 | | | ≤0.001 | | ≤0.001 |
| I | 48 | 74.0 | | 78.5 | |
| II | 9 | 22.2 | | 22.2 | |
| FIGO stage 2018 | | | 0.239 | | 0.082 |
| I | 38 | 67.8 | | 73.9 | |
| II | 5 | 80.0 | | 75.0 | |
| III | 14 | 55.1 | | 50.2 | |

DFS, disease-free survival; OS, overall survival

*The number of cases was too small and the patients were all alive. The current follow-up time was too short to calculate the DFS or OS.

Figures

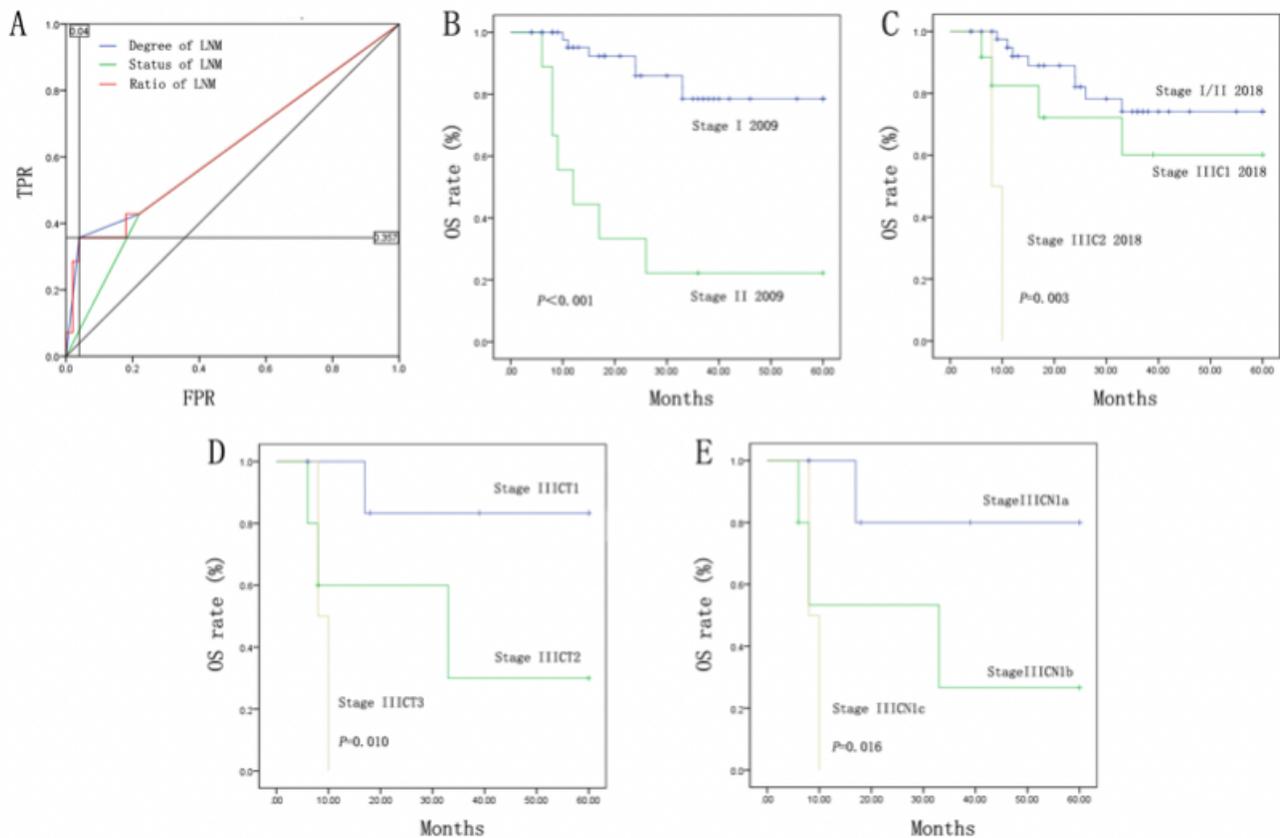


Figure 1

A. ROC curve of LNM status, ratio, and degree. The area under the curve (AUC) of LNM status, ratio, and degree was 0.604, 0.631, and 0.635, respectively. When the Youden index was the largest, the true positive rate (TPR) = 0.357, the false positive rate (FPR) = 0.040, and ratio = 0.204. B and C. Five-year OS of SCNEC patients for FIGO stage 2009 and 2018. D and E. FIGO 2018 stage IIICT combined with local invasion factors and LNM degree and location.

Supplementary Files

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