Yield of routine staging laparoscopy in patients with gastric cancer in Alberta, Canada

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Background: Despite guidelines recommending diagnostic laparoscopy in patients with gastric cancer, implementation is low. We aimed to explore trends in the use of laparoscopy for staging of gastric cancer in Alberta, Canada, determine the rate of positive findings and identify factors predictive of positive staging laparoscopy (SL) findings in this patient population.

Methods: In August 2018, we sent a survey to all general surgeons in Alberta who were members of the Alberta Association of General Surgeons to identify those treating gastric cancer. The survey inquired about type of practice (academic or community), gastric cancer case volume, routine versus selective use of SL and, if selective use of SL, criteria used to select cases. Participants were also asked to provide data from their SL cases from July 2007 to February 2019. We double-checked surgeon records with chart review. The primary outcome was evidence of metastatic disease on SL or cytologic examination or both. We performed logistic regression analysis to identify factors predictive of positive laparoscopy findings.

Results: The survey was completed by 41 of 127 surgeons (response rate 32.3%). We reviewed 116 cases from 5 surgeons at 4 centres. Gross metastatic disease or positive findings on cytologic examination or both were identified in 37 patients (31.9%). On univariate analysis, the following were associated with an increased risk of identification of metastatic disease at laparoscopy: visualization of the primary tumour on computed tomography (CT) (odds ratio [OR] 9.8, 95% confidence interval [CI] 1.2–76.5), presence of abdominal lymphadenopathy greater than 1 cm (OR 2.4, 95% CI 1.1–5.4) and presence of ascites (OR 19.1, 95% CI 2.2–161.8). Visualization of the primary tumour on CT (OR 8.4, 95% CI 1.0–68.3) and the presence of ascites (OR 15.9, 95% CI 1.8–137.0) remained statistically significant predictors on multivariate analysis.

Conclusion: Metastatic disease was identified at SL in almost one-third of cases, which suggests that SL should still be used routinely in gastric cancer staging in Canadian centres. Our study identified several preoperative imaging findings associated with evidence of metastatic disease on laparoscopy; however, further studies are needed to establish robust predictors of positive findings before advocating for a selective SL approach.

Contexte : Bien que les directives recommandent une laparoscopie diagnostique chez les patients atteints d'un cancer de l'estomac, cette intervention est peu utilisée. Nous avons voulu explorer les tendances du recours à la laparoscopie pour la stadification du cancer de l'estomac en Alberta, au Canada, établir le taux de résultats positifs et cibler les facteurs prédictifs de résultats positifs de la laparoscopie de stadification dans cette population de patients.

Méthodes : En août 2018, nous avons envoyé un sondage à tous les chirurgiens généraux de l'Alberta membres de l'Alberta Association of General Surgeons pour savoir lesquels traitaient le cancer de l'estomac. L'enquête portait sur le type de pratique (universitaire ou communautaire), le volume de cas de cancer de l'estomac, le recours systématique ou sélectif de la laparoscopie de stadification et, en cas de recours sélectif, les critères de sélection. Les participants ont également été invités à fournir des données sur les cas où la laparoscopie de stadification avait été utilisée de juillet 2007 à février 2019. Nous avons revérifié les dossiers des médecins. Le principal indicateur était la présence d'une maladie métastatique lors de la laparoscopie de stadification ou de l'examen cytologique (ou les deux). Nous avons procédé à une analyse de régression logistique pour cerner les facteurs prédictifs de résultats positifs à la laparoscopie.

Résultats : Sur 127 chirurgiens 41 ont répondu au sondage (taux de réponse de 32,3 %). Nous avons examiné 116 cas traités par 5 chirurgiens dans 4 centres. Une maladie métastatique brute ou des résultats positifs à l'examen cytologique ou les deux ont été identifiés chez 37 patients (31,9 %). Une analyse univariée a révélé que les éléments suivants étaient associés à un risque accru d'identification de maladie métastatique lors de la laparoscopie : visualisation de la tumeur primaire à la tomodensitométrie (TDM) (rapport des cotes [RC] 9,8, intervalle de confiance [IC] de 95 % 1,2–76,5), présence d'une lymphadénopathie abdominale supérieure à 1 cm (RC 2,4, IC de 95 % 1,1–5,4) et présence d'ascite (RC 19,1, IC de 95 % 2,2–161,8). La visualisation de la tumeur primaire à la TDM (RC 8,4, RC de 95 % 1,0–68,3) et la présence d'ascite (RC 15,9, RC de 95 % 1,8–137,0) sont demeurées des facteurs prédictifs statistiquement significatifs dans l'analyse multivariée.

Conclusion : Une maladie métastatique a été identifiée à la laparoscopie de stadification dans près d'un tiers des cas, ce qui suggère que la laparoscopie de stadification devrait continuer d'être utilisée de façon systématique dans la stadification du cancer de l'estomac dans les centres canadiens. Notre étude a montré plusieurs résultats d'imagerie préopératoire associés à des signes de maladie métastatique à la laparoscopie; cependant, d'autres études sont nécessaires pour établir des prédicteurs solides de résultats positifs avant de préconiser une approche sélective de la laparoscopie de stadification.

Gastric cancer remains the fifth most common cancer diagnosed worldwide and the third most common cause of cancer-related death.[1] In Canada, the incidence of gastric adenocarcinoma is estimated to be 8.6/100 000.[2] Advances in treatment modalities can partially account for the trend toward improved survival rates in recent years;[3] however, mortality remains high relative to other cancers.[1]

One of the most important predictors of mortality remains the stage at diagnosis. More than one-third of patients with gastric cancer in the United States are diagnosed with advanced stage disease.[3] Surgical resection in the presence of metastatic disease offers no survival benefit over chemotherapy alone.[4] Metastatic disease found at the time of laparotomy leads to additional morbidity of nontherapeutic laparotomy.[5] In their landmark article, Burke and colleagues,[6] from Memorial Sloan Kettering Cancer Center, reported a rate of M1 disease at staging laparoscopy (SL) of 37% in patients with newly diagnosed gastric cancer deemed potentially resectable for curative intent after computed tomography (CT).

The National Comprehensive Cancer Network guidelines recommend SL for cT1bN0 or higher tumours.[7] Similarly, the European Society for Medical Oncology and the European Society of Surgical Oncology recommend SL for all stage IB–III gastric cancers considered potentially resectable.[8,9] The Society of American Gastrointestinal and Endoscopic Surgeons recommends SL for T3 or T4 gastric cancer with no evidence of lymph node or distant metastases on preoperative imaging.[10] Provincial guidelines in Alberta, Canada, state that SL may be considered before surgical resection when no metastases are seen on baseline imaging.[11] Despite these recommendations and the documented benefits of SL, rates of SL use have been reported to be as low as 8.8%[12] and 7.9%[5] in Canadian and US series, respectively. A more recent US study showed improvement, but rates remained very low, at 13%.[13]

We aimed to explore trends in SL use in Alberta for the staging of gastric cancer, determine the rate of positive findings and identify factors predicting positive SL findings in this patient population.

Methods

We sent a survey electronically in August 2018 to all general surgeons in Alberta who were members of the Alberta Association of General Surgeons. To encourage participation, we sent multiple reminders via email. In addition, a member of the research team (D.S.) communicated directly with known gastric cancer surgeons in the province. The Health Research Ethics Board of Alberta Cancer Committee approved this study (HREBA.CC-17-0561).

Survey questions elicited information about type of practice (academic or community), gastric cancer case volume, routine versus selective use of SL and, if selective use of SL, criteria used to select cases. The full survey is available in Appendix 1 (available at www.canjsurg.ca/lookup/doi/10.1503/cjs.020120/tab-related-content).

Surgeons were also asked to provide data from their SL cases from July 2007 to February 2019. We double-checked surgeon records with chart review in an attempt to limit recall bias. Data collected included patient age, gender, ethnicity, duration of symptoms before diagnosis, weight loss at diagnosis, tumour location, tumour grade, histologic tumour subtype, staging CT findings (thoracic metastases, lymphadenopathy > 1 cm, visualization of gastric mass, ascites, peritoneal nodularity, omental nodules), timing of laparoscopy, laparoscopy outcome, whether cancer resection was subsequently completed and the final pathologic staging. Metastatic disease at laparoscopy was defined as positive findings on cytologic examination of peritoneal washings, or visible lesions confirmed to be cancer on microscopy.

Statistical analysis

We reported descriptive statistics for the study variables. We reported mean and standard deviation for continuous variables, and frequency and proportion for categorical variables. We used binary logistic regression analysis to determine the factors associated with positive laparoscopy findings. The multivariate model followed univariate logistic regression. Factors significant at $p < 0.1$ in the univariate analysis were entered into the multivariate model. Any variable significant at $p < 0.05$ was considered in the final model. We reported odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). We used SPSS version 25.0 (IBM Corp.) for all statistical analysis. A p value < 0.05 was considered statistically significant.

Results

Of the 127 surgeons to whom surveys were sent, 41 completed the survey (response rate 32.3%). A summary of the survey results is presented in Table 1. Complete survey results are available in Appendix 1. The majority of respondents (25 of 36 [69%]) practised in an academic setting. Of the 21 respondents who operated on gastric cancer as part of their practice, 11 (52%) did SL routinely, either at a separate scheduled operation (9 respondents) or at the same time as planned resection (2 respondents). The remaining 10 respondents (48%) reported using SL selectively. When SL was used selectively, the presence of lymphadenopathy greater than 1 cm, ascites or nodules on CT and tumour size were the most commonly cited factors used to determine whether to proceed with SL (Table 1). Thirteen (62%) of the 21 respondents who operated on gastric cancer reported collecting washings for cytologic examination routinely. In cases in which no metastatic disease was seen on CT scan, about half of respondents (19 of 39 [49%]) estimated that SL would show evidence of metastatic disease in 20%–30% of cases.

Five surgeons from 4 centres provided data from their SL cases. During the 12-year study period, 117 SL cases were identified. We excluded 1 case in which SL was attempted but not completed owing to dense intra-abdominal adhesions, leaving 116 cases for analysis. A selective SL strategy was used in 14 cases (12.1%), and in the remaining 102 cases (87.9%), SL was performed according to a routine practice.

Patient demographic, tumour and preoperative imaging characteristics are presented in Table 2. The mean patient age was 63 years. The majority of patients (76 [65.5%]) were male. Patient ethnicity was primarily white (77 [66.4%]); ethnicity data were missing for 12 patients (10.3%).

Symptoms had been present for 12 weeks or less before diagnosis in 45 patients (38.8%); 7 patients (6.0%) had experienced symptoms for more than 52 weeks before diagnosis. Thirty-two patients (27.6%) underwent positron emission tomography (PET) scanning. The gastroesophageal junction was the most common tumour site (34 patients [29.3%]). Poorly differentiated (high-grade) adenocarcinoma was the most common tumour grade (78 patients [67.2%]). A signet cell component was identified in 55 cases (47.4%).

Gross metastatic disease ($n = 22$) or positive findings on cytologic examination ($n = 3$), or both ($n = 12$), were identified at SL in 37 patients (31.9%). Staging laparoscopy showed evidence of metastatic disease in 34 of 102 cases (33.3%) done by surgeons using a routine SL strategy and 3 of 14 cases (21%) done by surgeons who selectively applied SL. The majority of SL procedures (106 [91.4%]) were performed as a separate scheduled procedure before chemotherapy or surgery. After SL, 40 patients (34.5%) did not go on to further surgical management, directly as a result of identification of metastatic disease on SL in 37 of 40 cases (92.5%) (Table 3). The remaining cases included 1 patient who had a fluorodeoxyglucose-avid supraclavicular node on PET scan, and 1 patient who declined surgery; the reason was unknown in 1 case.

Table 1. Summary of gastric surgeon survey responses

Item	No. (%) of respondents $n = 41$
Use of staging laparoscopy	
Routinely, separate operation from resection	9 (23)
Routinely, same operation as resection	2 (5)
Selectively, separate operation from resection	3 (8)
Selectively, same operation as resection	3 (8)
Selectively, separate or same operation depending on clinical/logistic factors	4 (10)
Does not operate on gastric cancer	18 (46)
No response	2 (5)
Criteria used for selective laparoscopy use* ($n = 37$)	
Absence of previous abdominal surgery	3 (8)
Tumour histologic findings	4 (11)
Tumour grade	4 (11)
Primary tumour location	4 (11)
Endoscopic ultrasonography findings	4 (11)
Tumour size	6 (16)
Lymphadenopathy > 1 cm on CT scan	11 (30)
Ascites on CT scan	9 (24)
Nodules on CT scan	7 (19)
Patient age	3 (8)
Availability or lack of availability of operating room	2 (5)
Not applicable	23 (62)
Collects washings for cytologic examination at time of staging laparoscopy	
Routinely	13 (33)
Sometimes	1 (3)
Rarely	4 (10)
Never	3 (8)
Does not operate on gastric cancer	18 (46)
No response	2 (5)

CT = computed tomography.
*Respondents could choose more than 1 response.

Table 2 (part 1 of 2). Demographic, tumour and preoperative imaging characteristics of patients with gastric cancer who underwent staging laparoscopy

Characteristic	No. (%) of patients* *n* = 116
Demographic	
Age, mean ± SD, yr	63 ± 13.1
Gender	
Male	76 (65.5)
Female	37 (31.9)
Missing	3 (2.6)
Ethnicity	
White	77 (66.4)
First Nations/Aboriginal	6 (5.2)
South American/Central American/Caribbean	5 (4.3)
Middle East	1 (0.9)
Asian	15 (12.9)
Missing	12 (10.3)
Symptom duration, wk	
≤ 12	45 (38.8)
13–24	23 (19.8)
25–52	25 (21.6)
> 52	7 (6.0)
Missing	16 (13.8)
Weight loss, pounds	
≤ 10 (4.5 kg)	35 (30.2)
11–25 (5.0–11.3 kg)	20 (17.2)
26–50 (11.8–22.7 kg)	24 (20.7)
> 50 (22.7 kg)	2 (1.7)
Missing	35 (30.2)
Preoperative imaging findings	
Primary tumour visible	
Yes	93 (80.2)
No	18 (15.5)
Equivocal	3 (2.6)
Missing	2 (1.7)
Intrathoracic metastases	
Yes	1 (0.9)
No	98 (84.5)
Equivocal	15 (12.9)
Missing	2 (1.7)
Abdominal lymphadenopathy > 1 cm	8 (6.9)
Ascites	8 (6.9)
Peritoneal nodules	
Yes	1 (0.9)
No	112 (96.6)
Missing	3 (2.6)
Omental nodules	3 (2.6)
Tumour characteristics	
Location	
Gastroesophageal junction	34 (29.3)
Upper stomach not involving gastroesophageal junction	24 (20.7)
Body of stomach	27 (23.3)
Antrum/pylorus	29 (25.0)
Entire stomach	1 (0.9)
Other	1 (0.9)

Table 2 (part 2 of 2). Demographic, tumour and preoperative imaging characteristics of patients with gastric cancer who underwent staging laparoscopy

Characteristic	No. (%) of patients* *n* = 116
Biopsy pathologic findings	
Adenocarcinoma not otherwise specified	47 (40.5)
Adenocarcinoma intestinal type	11 (9.5)
Adenocarcinoma diffuse type no signet cells	3 (2.6)
Adenocarcinoma with signet cells	55 (47.4)
Grade	
Well-differentiated, low grade	2 (1.7)
Moderately differentiated, mid-grade	6 (5.2)
Poorly differentiated, high grade	78 (67.2)
Missing	30 (25.9)

SD = standard deviation.
*Except where noted otherwise.

Table 3. Clinical course according to staging laparoscopy and cytologic examination result

Clinical course; laparoscopy result/cytologic examination result	No. (%) of patients
Curative resection (*n* = 73)	
Negative/negative	50 (43.1)
Negative/suspicious or atypical	5 (4.3)
Negative/not done or missing	18 (15.5)
No further surgical procedure (*n* = 40)	
Positive/positive	12 (10.3)
Positive/negative	4 (3.4)
Positive/suspicious or atypical	8 (6.9)
Positive/not done or missing	8 (6.9)
Negative/positive	3 (2.6)
Negative/negative*	3 (2.6)
Negative/suspicious or atypical	2 (1.7)
Palliative resection (*n* = 2)	
Negative/negative	1 (0.9)
Negative/suspicious or atypical	1 (0.9)
Missing resection data (*n* = 1)	
Negative/negative	1 (0.9)

*One patient declined surgery, and 1 patient had a fluorodeoxyglucose-avid supraclavicular node on subsequent positron emission tomography scanning; in the remaining case, the reason was unknown.

On univariate analysis, the following preoperative CT findings were associated with an increased risk of metastatic disease at SL: visible primary tumour (OR 9.8, 95% CI 1.2–76.5), presence of abdominal lymphadenopathy greater than 1 cm (OR 2.4, 95% CI 1.1–5.4) and presence of ascites (OR 19.1, 95% CI 2.2–161.8). Although not statistically significant, weight loss greater than 30 pounds (13.6 kg) also suggested increased risk of evidence of metastatic disease on SL (OR 3.52, 95% CI 0.95–12.32). The presence of ascites (OR 15.86, 95% CI 1.84–137.02) and a visible primary tumour on staging CT (OR 8.44, 95% CI 1.04–68.26) remained statistically significant on multivariate analysis (Table 4).

Table 4. Predictors of finding metastatic disease or positive result of cytologic examination or both at the time of staging laparoscopy on univariate and multivariate analysis

Predictor	OR (95% CI)
Univariate analysis	
Age	0.99 (0.96–1.02)
Gender	1.59 (0.69–3.67)
Symptom duration > 24 wk	0.77 (0.33–1.76)
Weight loss > 30 lbs (13.6 kg)	2.98 (0.92–9.61)
Tumour location other than GEJ	0.75 (0.33–1.77)
High-grade tumour	1.68 (0.32–8.89)
Signet cell subtype	1.98 (0.87–4.52)
Tumour visible on staging CT	9.75 (1.24–76.50)
Abdominal lymphadenopathy > 1 cm	2.38 (1.06–5.35)
Ascites	19.1 (2.24–161.80)
Omental nodules	4.65 (0.41–53.00)
Multivariate analysis	
Weight loss > 30 lbs (13.6 kg)	3.52 (0.95–12.32)
Tumour visible on staging CT	8.44 (1.04–68.26)
Ascites	15.86 (1.84–137.02)

CI = confidence interval; CT = computed tomography; GEJ = gastroesophageal junction; OR = odds ratio.

Discussion

In the current study, 33% of SL procedures done by surgeons using a routine SL strategy showed evidence of metastatic disease. For surgeons who selectively applied SL, the positivity rate was 21%. One would expect the selective strategy group to have a higher proportion of positive findings than the routine SL strategy group. However, there was a higher proportion of signet cell and poorly differentiated cancers in the routine SL strategy group than in the selective SL strategy group. This, along with the small number of SL cases done with the selective approach, may account for this finding.

Despite advances in preoperative imaging, SL has been shown to be superior to CT in detecting peritoneal metastases[14–16] and can alter the treatment plan in at least 30% of cases.[13,17,18] In a US study of more than 11 000 patients who underwent SL, 30% of patients did not go on to further therapeutic intervention.[5] Patients who had SL alone had a significantly lower in-hospital death rate (5.3% v. 13.1%) and shorter length of hospital stay (2 d v. 10 d) than patients who had futile laparotomy. In a more recent study, SL changed management plans in 35% of 733 patients who underwent SL for gastric cancer.[13] The current study gave a similar result, with SL directly altering treatment in 31.9% of cases.

The routine use of SL, particularly at a separate operation from planned resection, requires additional resources. This was a major contributor to the variability in practice noted among surgeons in the current study. The resource demand must be balanced with the potential to avoid the morbidity associated with nontherapeutic laparotomy. With the ideal selection criteria, the selective use of SL would identify patients more likely to have evidence of metastatic disease on SL, thus avoiding procedures that would give negative findings as well as nontherapeutic laparotomy. Our respondents reported performing SL selectively when the following criteria were met: T3 or greater, any N, larger tumours (visible on CT) or visible nodes on CT, or CT findings suggestive of peritoneal disease (but not definitive).

Multiple investigators have aimed to identify factors predictive of positive SL findings in Eastern populations; there are fewer studies in Western populations. Huang and colleagues[19] determined that tumour size of 8 cm or greater, Borrmann type III (ulcerating growth) or IV (diffusely infiltrating growth) disease, and preoperative staging T4a or T4b were predictors of peritoneal disease. When SL was done selectively for patients with Borrmann type III or IV disease, tumour size greater than 8 cm, bulky lymphadenopathy, para-aortic nodes or clinically suspected peritoneal disease, the diagnostic accuracy of these criteria was 92%.[20] When SL was done for more simplified criteria that included tumour size greater than 5 cm or bulky regional nodes, SL gave positive results in 45% of cases.[21] In a US study, Hispanic ethnicity, bulky lymphadenopathy, signet ring cells and poor differentiation were found to be predictive of radiographically occult disease.[22] The current study identified visible tumour on staging CT, abdominal lymphadenopathy greater than 1 cm and ascites as predictive factors of evidence of metastatic disease on SL. Lymphadenopathy and ascites have been shown to predict positive SL findings;[22] however, previous studies looked at actual tumour size rather than visible tumour on CT.[19,21] This may be a result of CT protocol. In the current study region, a gastric distension protocol is not used routinely for staging CT; therefore, smaller tumours are often not visualized well, whereas larger tumours tend to still be more clearly identified.

Optimal, standardized criteria for selective use of SL have not yet been established. In one study, SL showed peritoneal disease in 23.1% of patients with tumours less than 8 cm and non-Borrmann type III or IV disease who did not have lymphadenopathy.[23] Li and colleagues[24] investigated additional subtle CT findings that could help predict occult peritoneal metastases. That study was performed in China, where gastric cancer is often diagnosed at an earlier stage than in Western countries. The low rate of positive laparoscopy findings reported is much lower than the rate observed in the current study and reported for other Western populations.[5] Decisions based on these subtle CT findings would need to be validated in Western cohorts before implementation in selective SL use.

Future study on the role for more selective use of SL could involve expanding the survey to include gastric cancer surgeons across Canada. A prospective National Gastroesophageal Cancer Database is currently being developed.

This will be a REDCap-based database housed at the University of Alberta, with participation expected from multiple other sites across the country. As these data accumulate, this topic can be revisited with a larger sample, including all gastric cancer cases. Comparator groups could then be established to enable assessment of more meaningful outcomes, working toward incorporation of reliable criteria for SL into optimal gastric cancer staging guidelines.

Limitations

We recruited patients through participating surgeons and, as such, included only patients who had undergone SL; thus, we are unable to comment on rates of SL use in our region. This methodology further limited our study in that not all SL procedures performed during the study period will have been captured. Furthermore, without knowing the total number of gastric cancer cases during the study period, and specifically without knowing the overall rate of futile laparotomy among patients who did not undergo SL, the interpretation of our data is limited. Similarly, there was a small number of cases in which SL was performed selectively. Although the SL findings changed management in a large number of cases, the methodology did not allow for direct comparison of routine versus selective SL strategies, and, therefore, we cannot make conclusions as to whether one strategy is superior to the other.

Gastric adenocarcinoma is a rare cancer. As a result, this study is further restricted by having a small sample, which limits the strength of the conclusions, particularly with respect to identifying factors predictive of evidence of metastatic disease. The fact that we included only patients with gastric cancer treated in Alberta limits our conclusions to this population, which may not necessarily be representative of the rest of Canada or the US. The retrospective nature of this study also resulted in missing data, which further limits the findings.

Smyth and colleagues[25] found that PET scanning plus CT detected occult metastases in about 10% of patients with locally advanced gastric cancer. In the current study, 27.6% of patients had a PET scan. In at least 1 patient, distant metastatic disease was identified, which led to a change in management. The interpretation of this finding is limited by the retrospective nature of the study: PET findings were not available for the majority of patients, as this was not a focus of the study. Brenkman and colleagues[26] are currently recruiting patients for a prospective observational cohort study that will evaluate the impact and cost-effectiveness of PET and SL in addition to initial staging in patients with locally advanced gastric cancer. The primary outcome is the proportion of patients in whom adding PET and SL changes the treatment strategy. The results will provide further information on the potential role of PET scanning in gastric cancer staging as an adjunct to SL.

Conclusion

Staging laparoscopy identified metastatic disease, leading to a change in management, in 31.9% of cases of gastric cancer in Alberta treated from July 2007 to February 2019. The vast majority of SL procedures were performed at a separate operation before any other surgery or chemotherapy. Visible tumour on staging CT, abdominal lymphadenopathy greater than 1 cm and ascites correlated with positive SL findings. Staging laparoscopy remains a critical component of gastric cancer staging. Further study is needed to clearly define its optimal use.

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Contributors: S. Turner and D. Schiller designed the study. J. Nostedt, C. Sample, S. Turner, L. Mack and D. Schiller acquired the data, which J. Nostedt, C. Sample, S. Ghosh, L. Mack, M. McCall and D. Schiller analyzed. J. Nostedt wrote the manuscript, which all authors critically revised. All authors gave final approval of the article to be published.

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