Differentiation of Lymphoma Presenting as Retroperitoneal Mass and Retroperitoneal Fibrosis: Evaluation with Multidetector-row Computed Tomography

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Abstract

Background: Retroperitoneal fibrosis (RPF) and lymphoma presenting as retroperitoneal mass may closely resemble each other and misdiagnosis may occur. This study investigated the differential imaging features of RPF and lymphoma which presented as a retroperitoneal soft tissue using multidetector-row computed tomography (MDCT).

Methods: The 42 consecutive patients were included in this retrospective review, including 19 RPF patients (45.2%; including 13 males and 6 females; mean age: 56.7 ± 6.2 years) and 23 patients with lymphoma (54.8%; including 14 males and 9 females; mean age: 57.4 ± 12.3 years). An array of qualitative computed tomography (CT) features of lesions in 42 consecutive patients with newly diagnosed untreated RPF and lymphoma were retrospectively analyzed. The quantitative size of the lesion at the para-aortic region and attenuation in the precontrast, arterial, and portal phases were calculated in regions of interest and compared between the patients with newly diagnosed untreated RPF and with lymphoma. Receiver operating characteristic curve analysis was used to assess the potential diagnostic value of each quantitative parameter. Inter-reader concordance was also calculated.

Results: Mean ages between patients with RPF and lymphoma were not significantly different (56.7 ± 6.2 years vs. 57.4 ± 12.3 years, P = 0.595). Compared to those in patients with lymphoma, homogeneous enhancement (65.2% vs. 94.7%, P = 0.027) and pelvic extension (52.2% vs. 89.5%, P = 0.017) were significantly more common while the involvement of additional nodes (78.3% vs. 5.3%, P < 0.001), suprarenal extension (60.9% vs. 15.8%, P = 0.004), and aortic displacement (43.5% vs. 5.3%, P = 0.006) were significantly less common in patients with RPF. Lesion size at the para-aorta was significantly greater in patients with lymphoma, compared with RPF patients (3.9 ± 1.2 cm vs. 1.8 ± 0.6 cm; P < 0.001). The attenuation values in three phases were not significantly different between patients with RPF and lymphoma. Inter-reader concordance for subjective features ranged from very good to excellent (range: 85.7–100.0%).

Conclusions: This study showed that MDCT can help differentiate between untreated RPF and lymphoma on the basis of qualitative CT features and lesion sizes. Differentiating RPF from lymphoma on the basis of attenuation values in the precontrast, arterial, and portal phases was difficult to accomplish.

Key words: Lymphoma; Multidetector-row Computed Tomography; Retroperitoneal Fibrosis; Retroperitoneum

Introduction

Retroperitoneal fibrosis (RPF) is a kind of rare disease marked by the retroperitoneal tissue with marked fibrosis and chronic inflammation usually surrounding the abdominal aorta and the iliac arteries.1,2 RPF treatment is mainly based on corticosteroids with or without other immunomodulation medications.3 If promptly diagnosed and treated, most patients with RPF have a favorable prognosis.3 Lymphoma is a group of cancers originating from the lymphatic system; its most common malignancy is in the retroperitoneum.4,5 Compared with lymphoma in other locations, retroperitoneal...
lymphoma features a greater tendency to form confluent soft-tissue masses.[9] In such instances, RPF and lymphoma may closely resemble each other and misdiagnosis may occur.[7-10] Because the treatment strategies and progress of RPF and lymphoma differ, differentiating between these diseases is crucial.

To this end, medical imaging plays a key role in differential diagnosis. Magnetic resonance (MR) imaging requires longer examination times and presents a relatively low spatial resolution. In addition, patients with a cardiac pacemaker or a metal foreign body in their body or those affected by claustrophobia are not suitable for MR examination. The objective of this study was to investigate differences between RPF and lymphoma by multidetector-row computed tomography (MDCT), which was helpful for timely and effective therapy.

**Methods**

**Subjects**

The Institutional Review Board at Beijing Hospital approved this retrospective study, and the requirement to obtain informed consent for the review of images and records was waived. Medical records of consecutive patients diagnosed with RPF or lymphoma between February 2010 and July 2016 were retrieved from the database at Department of Radiology, Beijing Hospital. Patients with perivascular lesions of size < 5 mm on quantitative examination were excluded to avoid partial volume effects on attenuation values. Patients who were on treatment at the time of imaging examination were also excluded to eliminate the effect of treatment on imaging features. Additional exclusion criteria for the patients with RPF were: History of other neoplasms, infection, trauma, radiotherapy, surgery, and intake of related drugs. Finally, only patients who showed confluent retroperitoneal soft tissue were included. Confluent retroperitoneal soft tissue was defined as plaque-like retroperitoneal soft-tissue mass in the para-aortic region, but which excluded isolated mass or enlarged multiple lymph nodes that showed no tendency for coalescence. Finally, 42 consecutive patients were included in this retrospective review, including 19 patients (45.2%) with newly diagnosed, untreated idiopathic RPF (13 males and 6 females; mean age: 56.7 ± 6.2 years) and 23 patients (54.8%) with lymphoma who manifested confluent retroperitoneal soft tissue (14 males and 9 females; mean age: 57.4 ± 12.3 years).

**Computed tomography protocols**

Nonenhanced and contrast-enhanced abdominal computed tomography (CT) scans were performed by the Discovery CT750 HD scanner (GE Healthcare Life Sciences, USA). All patients were scanned with the following parameters: 120 kV; 100 mAs; rotation time of 0.6 s; collimation thickness of 0.625 mm, tube current of 600 mA, helical pitch of 0.984, thickness of 5 mm and gap of 5 mm. The patients were asked to empty their bowels and drink 500 ml water 30 min before the scan. Each patient underwent nonenhanced and two-phase contrast-enhanced CT examinations of the entire abdomen, from the top of the diaphragm to the inferior margin of the pubic symphysis. After initial nonenhanced CT scanning, all patients received 80–85 ml of contrast agent (iohexol, 300 mg iodine/ml; Beijing Beilu Pharmaceutical Co., Ltd., Beijing, China), which was injected using an automatic power injector (Stellant D Dual Syringe, Medrad, Indianola, PA, USA) at a rate of 1.8–2.2 ml/s, through a catheter that had been placed in the antecubital vein. For the arterial phase, a delay time of 13–17 s was used after the descending aorta attenuation reached 100 Hounsfield unit (HU) using the bolus tracking technique. Portal phase scanning was performed 60–75 s after contrast administration.

**Image analysis**

All CT images were reviewed on a picture archiving and communication system. Two experienced radiologists blinded to the final diagnosis recorded the presence of each of the following qualitative findings independently: (a) regular lesion margin, (b) suprarenal location, (c) pelvic extension, (d) aortic displacement, (e) additional nodes, (f) vascular thrombus, (g) medial ureteral bowing, (h) unilateral location, (j) splenomegaly, and (k) para-aortic space existence. In addition, enhancement patterns were evaluated and divided into homogeneous enhancement, heterogeneous enhancement, and homogeneous mixed with heterogeneous enhancement. The shape of the lesion margin was defined as regular when a regular and smooth margin without lobulated or other irregular margins was found. Suprarenal-level location was considered present if the lesion reached up to the level of kidney pole, and pelvic extension was considered present if the confluent tissue extended inferior to the aortic bifurcation. Aortic displacement was considered present if the anterior displacement of the abdominal aorta was observed from the spine due to confluent soft tissue posterior to the abdominal aorta. Additional nodes were considered present if short-axis diameter of additional retroperitoneal or mesenteric lymph nodes exceed 1 cm, aside from the confluent soft tissue, was found. Vascular thrombus was considered present if thrombus involving a major abdominal arterial or venous structure was determined. Lesions localized to one side of the aorta were considered to be of a unilateral location. Splenomegaly was defined as a splenic length greater than 9.8 cm.[11] Para-aortic space existence was defined as abdominal fat tissue that could be defect between the aorta and lesion but excluding fat density derived from atherosclerosis. Lesions with some portions showing homogeneous enhancement and other portions showing heterogeneous enhancement were considered to show homogeneous mixed with heterogeneous enhancement.

The quantitative examination of size and attenuation value was performed in all patients. The maximal thickness of the confluent retroperitoneal soft tissue was measured and defined as the size. The MDCT protocol was composed of a precontrast, arterial, and portal phases. To assess lesion attenuation, we selected the largest possible extent on a single slice and carefully placed region of interest cursors.
to contain as much of the most enhancing portions of the lesion as possible and avoid outer margin reduce partial volume averaging. Calcified, cystic, or necrotic areas were rarely identified, however, when present, these areas were not included for the analysis. At least two measurements were obtained for each mass at each imaging phase, and their mean attenuation values were recorded.

Statistical analysis
SPSS software (version 13.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The Fisher’s exact test was used to assess whether the diagnosis of RPF or lymphoma was associated with qualitative CT features. Owing to terms of patient age, size, and attenuation value did not coincide with normal distribution according to normal distribution test, the Mann-Whitney test was used to compare RPF and lymphoma in terms of patient age, size, and attenuation value. Receiver operating characteristic (ROC) curve analysis was used to assess the potential diagnostic value of each quantitative parameter. Binary logistic regression analysis was used to identify features showing significant differences at the univariate analysis that represented significant independent predictors of a diagnosis of RPF or lymphoma; thresholds levels associated with optimal sensitivity and specificity were identified, and variables were expressed as frequencies and percentages. All reported P values are two-sided and considered statistically significant when <0.05.

Results
Clinical data of untreated retroperitoneal fibrosis and lymphoma
The mean ages between patients with RPF and lymphoma were not significantly different (Z = −0.532, P = 0.595). The diagnosis of RPF was established by histology and at least 1 year of follow-up which showed stability or a decrease in size after treatment with corticosteroids. The most common presenting symptoms were back pain or abdominal pain (n = 15), fatigue (n = 7), fever (n = 6), high erythrocyte sedimentation rate (n = 3), and proteinuria (n = 2). Among 23 patients with lymphoma, the specific diagnoses were non-Hodgkin lymphoma (n = 18, 78.3%) and Hodgkin’s disease (HD; n = 5, 21.7%). The diagnosis of lymphoma was histologically established in all cases, and the majority of the patients exhibited multiple symptoms, mainly including abdominal pain (n = 19), fatigue (n = 15), abdominal swelling (n = 9), fever (n = 8), high erythrocyte sedimentation rate (n = 4), and anemia (n = 4).

Comparison of qualitative examination between untreated retroperitoneal fibrosis and lymphoma
The qualitative CT features of the patients with RPF and lymphoma are summarized in Table 1. Compared the patients with lymphoma, the CT features, including homogeneous enhancement (65.2% vs. 94.7%, P = 0.027), pelvic extension (52.2% vs. 89.5%, P = 0.017), medial ureteral bowing (4.3% vs. 78.9%, P < 0.001), were significantly more common [Figure 1]; but aortic displacement (43.5% vs. 5.3%, P = 0.006), splenomegaly (30.4% vs. 0.0%, P = 0.011), or para-aortic space existence (26.1% vs. 0.0%, P = 0.024) was rarely or not involved in patients with RPF. Compared the patients with RPF, the CT features, including additional lymph nodes (5.3% vs. 78.3%, P < 0.001) and supraprenal level extension (15.8% vs. 60.9%, P = 0.004) were significantly more common in patients with lymphoma [Figure 2]. However, heterogeneous enhancement (0.0% vs. 4.3%, P = 1.000) and homogeneous

Table 1: Comparison of qualitative CT features between patients with RPF and lymphoma

| CT features                  | Patients with RPF | Patients with lymphoma | P     |
|-----------------------------|-------------------|------------------------|-------|
| Regular lesion margin       | 84.2 (16/19)      | 60.9 (14/23)           | 0.169 |
| Supraprenal level extension | 15.8 (3/19)       | 60.9 (14/23)           | 0.004 |
| Pelvic extension            | 89.5 (17/19)      | 52.2 (12/23)           | 0.017 |
| Aortic displacement         | 5.3 (1/19)        | 43.5 (10/23)           | 0.006 |
| Additional lymph nodes      | 5.3 (1/19)        | 78.3 (18/23)           | <0.001|
| Vascular thrombus           | 5.3 (1/19)        | 4.3 (1/23)             | 1.000 |
| Medial ureteral bowing      | 78.9 (15/19)      | 4.3 (1/23)             | <0.001|
| Unilateral location         | 5.3 (1/19)        | 17.4 (4/23)            | 0.356 |
| Splenomegaly                | 0.0 (0/19)        | 30.4 (7/23)            | 0.011 |
| Para-aortic space existence | 0.0 (0/19)        | 26.1 (6/23)            | 0.024 |
| Enhancement pattern         |                   |                        |       |
| Homogeneous                 | 94.7 (18/19)      | 65.2 (15/23)           | 0.027 |
| Heterogeneous               | 0.0 (0/19)        | 4.3 (1/23)             | 1.000 |
| Homogeneous mixed with      | 5.3 (1/19)        | 26.1 (6/23)            | 0.105 |
| heterogeneous               |                   |                        |       |

All data are shown as % (n/N). RPF: Retroperitoneal fibrosis; CT: Computed tomography.
mixed with heterogeneous enhancement (5.3% vs. 26.1%, \( P = 0.105 \)) were not significantly different between patients with RPF and lymphoma. No significant differences in terms of regular lesion margin (84.2% vs. 60.9%, \( P = 0.169 \)) and unilateral location (5.3% vs. 17.4%, \( P = 0.356 \)) were also observed between these two groups. On univariate analysis, pelvic extension (odds ratio [OR] = 7.8, \( P = 0.016 \)) and medial ureteral bowing (OR = 82.5, \( P < 0.001 \)) were identified as significant predictors for a diagnosis of RPF. Suprarenal extension (OR = 8.3, \( P = 0.005 \)) and involvement of additional lymph nodes (OR = 13.8, \( P = 0.018 \)) were identified as significant predictors for a diagnosis of lymphoma. However, on multivariate logistic regression analysis, none of the variables was found to be an independent predictor for a diagnosis of RPF.

Comparison of quantitative examination between untreated retroperitoneal fibrosis and lymphoma

The quantitative measures of patients with RPF and lymphoma are summarized in Table 2. The size of lesions at the para-aorta in patients with lymphoma was larger than that in the RPF patients (3.9 ± 1.2 cm vs. 1.8 ± 0.6 cm, \( P < 0.001 \)). The attenuation values in the precontrast (45.4 ± 8.4 HU vs. 44.8 ± 3.4 HU, \( P = 0.639 \)), arterial (61.4 ± 20.5 HU vs. 65.0 ± 9.7 HU, \( P = 0.336 \)), and portal phases (68.5 ± 19.3 HU vs. 73.7 ± 9.1 HU, \( P = 0.800 \)) did not significantly differ between patients with RPF and lymphoma. The ROC curves were used to compare the diagnostic performance of lesion sizes at the para-aorta and attenuation values in the precontrast, arterial, and portal phases for assessment of RPF [Figure 3].

The corresponding area under the ROC curves, sensitivities, specificities, and threshold values are shown in Table 3. ROC analysis showed that lesion size at the para-aorta with high sensitivity (100.0%) and specificity (84.2%) was identified as a predictor for RPF. The inter-reader concordance of the two readers for qualitative features ranged from very good (85.7%) to excellent (100%; Table 4).

**DISCUSSION**

RPF encompasses a range of diseases characterized by proliferation of abnormal fiber inflammatory tissue usually surrounding the abdominal aorta, inferior vena cava, and iliac vessels.\[^{12,13}\] Lymphoma can migrate to the lymph nodes, causing lymph node enlargement, and lesions may become confluent as the disease progresses.\[^{14}\] Enlarged lymph nodes resulting from these two diseases can be misdiagnosed because of atypical, diverse, or similar symptoms in clinics\[^{7-10}\]. This issue is a critical consideration because the diseases are managed by relatively effective but very distinct treatments. Although biopsy is often considered as the gold standard for final diagnosis, it is usually performed after CT examination and is invasive. With the development of MDCT technologies, routine evaluation of retroperitoneal tissue has become possible. Compared with traditional CT, MDCT provides a higher spatial and temporal resolution as well as a shorter examination time. Volumetric CT acquisition allows the generation of high-resolution multiplanar reformation images. We, therefore, adopted MDCT as a means of distinguishing RPF from lymphomas in this study.

The results of this study showed that RPF occurred at mean age of 56.7 ± 6.2 years with a male-to-female ratio of 2.2:1.0, similar to findings in previous study.\[^{15}\] However, this study showed no significant difference in terms of mean age between patients with RPF and lymphoma. Lymphomas are classified into HD and non-Hodgkin’s lymphoma, and the former occurs predominantly in younger patients.\[^{16}\] A previous study showed that the mean age of patients with
lymphoma is generally greater than that of patients with RPF.\[15\] We speculated that the difference between our findings and those of the previous reports was related to our inclusion of HD patients into the lymphoma group in our study. Compared with patients with lymphoma, ureters were common involved in the RPF patients, accounting for 80–100% of all cases. The study also showed that medial ureteral bowing was more frequent in patients with RPF than patients with lymphoma. The absence of fibrotic effects, such as medial deviation of the ureter, can help differentiate a cloak of dilated lymphatics from RPF. Additional lymph nodes were more common in the patients with lymphoma than the RPF patients in our study; these lymph nodes often localized in the lesser omentum, the anterior pararenal space, and the para-aortic and mesenteric regions. Lymphoma typically begins as discrete lymph nodes that subsequently form confluent masses with disease progression. Thus, the presence of additional lymph nodes, as observed in the patients with lymphoma in our study, was an anticipated finding. Additional lymph nodes were also detected in one case in the RPF patient, but this finding was adjacent to the RPF lesion and involved no other regions. In terms of mass location, RPF, unlike lymphoma, is usually located distal to the kidney hilum and anteriorly or laterally to the aorta, which is usually not displaced forward. Lymphoma can dislocate the aorta or reach up to the mediastinum. RPF can also dislocate the aorta and involve thoracic aorta, but this occurrence is rare.\[16,17\] The study found one RPF patient with aortic displacement, but the degree of displacement determined was less than that often observed in lymphoma, and the thickest part of the lesion was located in the preaorta. In RPF, the inflammatory infiltrate consists of a variety of lymphocytes, plasma cells, and macrophages, and these inflammatory cells tend to accumulate around blood vessels.\[18\] These lesions involve not only the periaortic retroperitoneum but also the aortic wall.

In typical cases with periaortic RPF distribution, the fibroinflammatory reaction involved the aortic adventitia, and other aortic layers showed atherosclerotic changes.\[19\] Our study showed that RPF lesions were often located close to the aorta, but that some retroperitoneal fat might exist between lymphoma lesions and the aorta. Splenomegaly was defined as a splenic length greater than 9.8 cm. In this study, splenomegaly was found in 30.4% of all patients with lymphoma. A spleen may be of normal size and still contain lymphomas while it may be enlarged as a result of variations in blood volume, use of hematopoietic growth factors, or other unrelated causes.\[14\] No agreement as to whether single, multiple, or volumetric measurements should be used to measure spleen size has been achieved. Thus, a single measurement that correlates well with volume was often preferred to a volumetric measurement.\[11\]

In lymphoma, the main contrast enhancement pattern was a uniform homogeneous enhancement. Peripheral rim or heterogeneous enhancement of lesions may be observed in some cases because of intranodular necrosis.\[20\] Homogeneous mixed with heterogeneous enhancement was found in 26.1% of all patients with lymphoma in our study, which was similar to the results of a previous study.\[21\] As a

### Table 2: Comparison of quantitative measures of lesions between patients with RPF and lymphoma

| Parameters                                      | Patient with RPF (n = 19) | Patients with lymphoma (n = 23) | Z     | P       |
|------------------------------------------------|---------------------------|--------------------------------|-------|---------|
| Precontrast attenuation value (HU)              | 45.4 ± 8.4 (30–56)        | 44.8 ± 3.4 (39–52)             | −0.469| 0.639   |
| Arterial phases attenuation value (HU)          | 61.4 ± 20.5 (31–111)      | 65.0 ± 9.7 (42–86)             | −0.961| 0.336   |
| Portal phases attenuation value (HU)            | 68.5 ± 19.3 (29–95)       | 73.7 ± 9.1 (59–95)             | −0.253| 0.800   |
| Lesion size at the para-aorta (cm)              | 1.8 ± 0.6 (0.9–3.2)       | 3.9 ± 1.2 (2.3–7.2)            | −5.161| <0.001  |

Data are shown as mean ± SD (range). RPF: Retroperitoneal fibrosis; SD: Standard deviation.

### Table 3: Diagnostic performance of attenuation values in precontrast, arterial phases and portal phases and lesion size at the para-aorta for assessment of RPF by ROC analysis

| Parameters                                      | AUC                      | Sensitivity (%) | Specificity (%) | Threshold value |
|------------------------------------------------|--------------------------|----------------|-----------------|-----------------|
| Precontrast attenuation value                   | 0.458                    | 100.0          | 21.1            | 38.5 HU         |
| Arterial phases attenuation value               | 0.587                    | 87.0           | 42.1            | 56.5 HU         |
| Portal phases attenuation value                 | 0.523                    | 100.0          | 26.3            | 58 HU           |
| Lesion size at the paraaorta                    | 0.967                    | 100.0          | 84.2            | 2.25 cm         |

AUC: Area under the ROC curve; RPF: Retroperitoneal fibrosis; ROC: Receiver operating characteristic.

### Table 4: Inter-reader concordance between two readers for qualitative CT features

| CT features                          | Concordance* |
|--------------------------------------|--------------|
| Lesion margin                        | 92.9 (39/42) |
| Suprarenal level extension           | 100.0 (42/42) |
| Pelvic extension                     | 88.1 (37/42) |
| Aortic displacement                  | 100.0 (42/42) |
| Additional lymph nodes               | 95.2 (40/42) |
| Vascular thrombus                    | 100.0 (42/42) |
| Medial ureteral bowing               | 85.7 (36/42) |
| Unilateral                           | 90.5 (38/42) |
| Splenomegaly                         | 97.6 (41/42) |
| Para-aortic space existence          | 95.2 (40/42) |
| Enhancement pattern                  | 88.2 (37/42) |

All data are shown as % (n/N); data in parentheses are raw data used to calculate concordance. *Defined as percentage of cases for which both radiologists provided the same reading. CT: Computed tomography.
heterogeneous enhancement of lymphoma after treatment has been reported, knowledge of whether a patient has undergone therapy is necessary before examination to obviate improper diagnosis.\textsuperscript{[21]}

Enhancement pattern of the RPF lesion depended on the stage of the disease, and different stages of enhancement could be helpful in evaluating therapeutic response.\textsuperscript{[3]}

Lesions in malignant tumors and active RPF showed similar enhancement patterns, while lesions in chronic RPF demonstrated weak enhancement. As we included very few cases of RPF in our study, we did not stratify the patients by acute and chronic RPF. Our study showed that the attenuation values in the precontrast, arterial, and portal phases did not significantly differ between patients with RPF and lymphoma. Thus, the attenuation values in contrast CT did not appear to play an important role in differentiating RPF from lymphoma. In addition, as intravenous administration of contrast agents might be harmful in high-risk cases because of nephrotoxicity, their use for differential diagnosis is inadvisable. However, the technique may be considered for differentiation between lymphoma and other malignant tumors, such as metastatic tumors.\textsuperscript{[22]}

Further studies to compare attenuation values between lymphoma and acute and chronic RPF are necessary in the future.

Confluent retroperitoneal soft tissue may also be found in metastatic tumor and other benign diseases.\textsuperscript{[23–25]}

Retroperitoneal tuberculosis might easily be confused with lymphomas. The lesions of retroperitoneal tuberculosis are relatively concentrated, and CT might show rim enhancement of enlarged lymph nodes. In the cases of lymph node metastasis, a primary tumor often can be found. The enlarged lymph nodes are usually near to the primary lesion and show rim or heterogeneous enhancement because of lymph node necrosis with frequent occurrence of ascites.

The present study had several limitations. First, we did not stratify patients by active and chronic RPF or by HD and non-Hodgkin’s lymphoma because of the small sample size. We also did not distinguish primary and secondary lymphoma due to the difficulty of diagnosis and small sample size. Therefore, future studies must be performed with larger numbers of patients. Second, we excluded patients with perivascular lesions which were \textless{}5 mm in size on quantitative examination to avoid partial volume effects on the attenuation values. Finally, since only patients with RPF and lymphoma who presented as confluent retroperitoneal soft tissue were included in the present study, further research is required to evaluate RPF and lymphoma in other locations in the future.

In conclusion, this study showed that MDCT can help differentiate between untreated RPF and lymphoma on the basis of qualitative CT features and lesion sizes. Differentiating RPF from lymphoma on the basis of attenuation values in the precontrast, arterial, and portal phases was difficult to accomplish.

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### Conflicts of interest
There are no conflicts of interest.

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