An evaluation of the predictive value of mid-treatment ^{18}F-FDG PET/CT scans in pediatric lymphomas and undefined criteria of abnormality in quantitative analysis

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Abstract

Our purpose was to evaluate quantitative mid-treatment fluorine-18-fluorodeoxyglucose (^{18}F-FDG) PET/CT scans in predicting the quantitative result of the end of treatment ^{18}F-FDG PET/CT scan. With approval of Emory's Institutional Review Board, *data were extracted from 273 existing ^{18}F-FDG PET/CT scans* of 143 pediatric patients performed for evaluation of lymphoma. The inclusion criteria were the availability of an initial staging scan (D0) and a mid-treatment scan after 1 to 3 cycles of chemotherapy (D1) and a post-treatment scan (D2). Absolute and relative changed of D1 compared to D0 were measured and their values in predicting D3 values were determined. Analysis was performed on a lesion basis (N=78) in 18 patients with an average of 4.3 lesions per patients. *Results showed that* the predictive value depended on the value selected as significant for the predictors (D1 SUV and D1 %SUV), and on the limit between negative and positive selected for the predicted value D2 SUV. If the maximum SUV <2.0 in D2 was the limit for negative, the negative predictive value if D1<4 was 0.84%. If positive was defined as D2>3.0, the positive predictive value of D1>4 was 100%. In that way outcome was predictable with absolute certainty in as many as 71% of the lesions with a single limit for D1 and D2. *In conclusion,* in this limited retrospective study the positive predictive value of the mid-treatment scan, was high for the post-treatment result for patient and lesion response seen on D2.

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Introduction

In the management of pediatric lymphomas, second malignancies are the most serious late complications. The association was first reported in the early 1970s [1]. An excess of acute non-lymphocytic leukemia (ANLL), non-Hodgkin lymphomas (NHL), and solid tumors, in patients treated with chemotherapy and/or radiotherapy for Hodgkin's lymphoma (HL) has been reported [1, 2]. In a long-term follow-up study of HL patients of all ages, the standardized incidence ratio of solid tumors was high in patients treated at young age and decreased with increasing age [2]. Complications have decreased lately, partially by dose reductions. Therefore, optimization of cancer treatment by the selection of the least toxic effective treatment becomes an important goal.

In current clinical practice, the effect of treatment is evaluated at the end of the scheduled chemotherapy, at which time the decision is made to add radiation or more chemotherapy. It has been claimed that for the adult population a fluorine-18-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) scan after one to three cycles of chemotherapy is a predictor of outcome [3, 4]. With regard to treatment modification, no studies have demonstrated improved outcome and in the case of pediatric lymphomas, less has been published about the value of an ^{18}F-FDG PET scan early in the treatment to predict the effect on the result of the post treatemnt ^{18}F-FDG PET [5]. There is, however, increasing interest in the use of combined ^{18}F-FDG PET/CT in management of pediatric lymphoma in general and, in particular, to assess the response to therapy early [6, 7]. But can the findings published in the adult age group be extrapolated to pediatric age group? There is also a question on the (pseudo) quantitative criterion most in use: the standard uptake value or SUV. Is there a generally applicable limit to a normal or abnormal range? [8]. In addition, response to treatment has been defined for partial response as a percentage SUV decrease and for complete response as a "negative" study [9, 10]. A single SUV value limit between normal and abnormal may be too restrictive, and for predictive values an alternative analysis may be more appropriate. In a rigorous review paper [4] on the use of ^{18}F-FDG PET in lymphoma, Terasawa found that the majority of studies used visually interpretations rather than SUV

as metrics. In early prediction of the results after completion of therapy, most authors [3] also use visual interpretation. In this work we explore the relation between predictor values and predicted values in a quantitative way.

Materials and methods

During a 6 years period (2001 to 2007) at Emory University Hospital, 273 consecutive ^{18}F-FDG PET/CT scans of 143 pediatric patients (age ≤18 years) were performed on a GE Discovery ST (16 slice spiral scanner) for evaluation of lymphoma. Patients who did not have their initial staging scan at Emory were excluded from the study. Of the 143 patients, only 18 had a complete data set including an ^{18}F-FDG PET/CT scan for initial staging (D0), a mid-treatment scan after one to three cycles of chemotherapy (D1) and a post-treatment scan after completion of chemotherapy (D2) and were included. With approval of Emory's Institutional Review Board (IRB), informed consent was waived and data was extracted from the existing imaging studies on the included patients. The patients included in the study were between 7 and 18 years of age; 13 were male and 5 were female. From the 18 patient scans, 78 lesions were identified in the initial interpretation, all as abnormal in D0, which averages to 4-5 lesions per patient.

The pediatric ^{18}F-FDG dose is a modified adult dose based on patient body weight by using Pediatric Dose Chart from Vanderbilt University Medical Center's Department of Radiology. The X-ray tube voltage (kV) and low Auto mA are also based on weight, but increased to the adult kV/Auto mA level if the patient weight more than 55kg. None of the pediatric patients needed sedation. Following intravenous (i.v.) injection of the ^{18}F-FDG, after an initial uptake phase of approximately 60-90min, a CT scan was started. The scan was performed with oral contrast, without i.v. contrast, and without breath holding and was acquired for attenuation correction and localization purposes. Subsequently, PET images from the skull base to mid-thigh were obtained with few exceptions due to bulky cervical lesions, where the field was extended upwards. The PET image was reconstructed with and without attenuation correction. Images from CT and PET were viewed as transaxial, coronal, and sagital slices, as such and in overlay. The PET volume was also displayed as a maximum intensity projection (MIP) image. The interpretation was performed on a SegamiVUE™ workstation.

In pediatric patients, ^{18}F-FDG uptake in brown fat, thymic hyperplasia, spleen and bone marrow after chemotherapy is often seen. Anatomic correlation with CT helps to identify these findings correctly, and these findings are excluded from the analysis.

Both absolute maximum standard uptake value (SUV_{max}) values of each included lesion and their percentage changes from the initial staging scan are recorded. The relevant metrics are:

$D0_{SUV}$: The absolute value of the lesion's SUV in the staing scan.

$D1_{SUV}$: The absolute SUV value in the mid treatment scan

$D1_{\%SUV}$: The SUV value in the mid and end-treatment scan expressed as a percentage of the D0 SUV of the matched lesion. Because of lower apparent decreases in %SUV when D0 SUV was low and the background effect [6], the D1 %SUV was computed as the ratio:

$$D1_{\%SUV} = \frac{(D0_{SUV-1}) - (D1_{SUV-1})}{D0_{SUV-1}} \times 100$$

$D2_{SUV}$: The absolute value of the corresponding lesion in D2 or in the same region of interest. $D2_{\%SUV}$ was also computed.

The analysis was conducted on a lesion basis. Lesions identified on the image from initial staging scan (D0) were looked up in the mid-treatment scan (D1) and post-treatment scan (D2) images. If no lesion was found in the location of the lesion in D0, the SUV in the identical location was taken as that of the lesion.

We investigated the predictor value in D1 with at an absolute SUV limit of 2, 3, 4, 5 and the predicted value in absolute SUV for the same values in D2. In addition, we looked at the predictor and predicted values as D1% and D2% at 70%, 60%, 50% and 40%, with an additional predictor value of 30%.

Results

D1 and D2 scans were separated from the D0 scan by a median number of 68 days and 142 days respectively. By histology, the distribution was 3 patients with NHL, 14 with HL and 1 unclassified. In most of the patients the disease was restricted to above the diaphragm; five of 18 patients presented disease both above and below the diaphragm (Fig. 1). Of the total 78 index lesions called positive on D0, 23 were cervical lesions, 27 mediastinal lesions, seven axillary lesions, three lung lesions, six hilar lesions, 11 intra- abdomen lesions, and one inguinal lesion.

A good response to treatment according to the original interpretation occurred in 16 patients (Fig. 1 and 2); two patients failed to respond (Fig. 3). In one of these patients, the D1 was more positive (with a higher $D1_{SUV}$) than the D0, but the positivity decreased in D2 with a modified treatment. Table 1 shows the average and range for the SUV values in D0, D1, and D2.

Table 2 offers a synopsis of the results: As an example, if we take the $D2_{SUV}$ value to be abnormal at 3, then a D1value >3 has a positive predictive value (PPV) of 0.69 and a negative predictive value of 0.87. With the same limit for $D2_{SUV}$=3, the PPV of $D1_{\%SUV}$<50% is 0.83 and the NPV=0.93, if $D1_{\%SUV}$>50%.

If at the end of the scheduled therapy success if defined as a percentage decrease of D2%SUV >60%, a value of >60% for D1%SUV has a PPV of 0.88, and a value <60% has a NPV of 0.90.

Discussion

The diagnostic accuracy of ^{18}F-FDG PET to assess the presence of residual disease after therapy is superior to that of CT [11-16] and ^{18}F-FDG PET is a valid tool for follow-up of patients with HL and NHL in general [17] and has become a standard procedure for post treatment response evaluation for most lymphoma subtypes [18].

Most mid-treatment prognostic value reports were based on lymphoma studies in adults. A well designed clinical trial

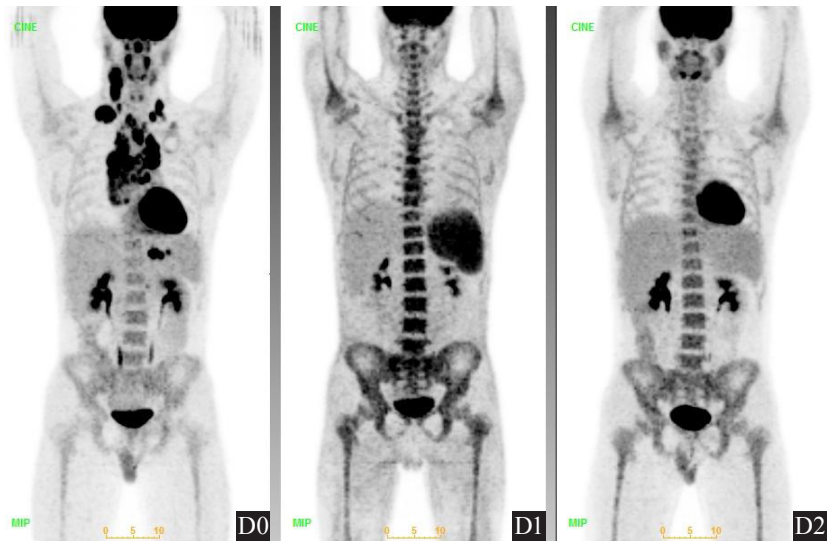

Figure 1. Anterior view of maximum intensity projection (MIP) ^{18}F-FDG PET images of initial staging scan (D0), mid-treatment scan (D1) and post-treatment scan (D2) of a 15 years old white male. One lesion from each of the following: right cervical, right supraclavicular, right mediastinum, left mediastinum and gastrosplenic region, were included for analysis. The bone marrow and spleen are excluded from the analysis.

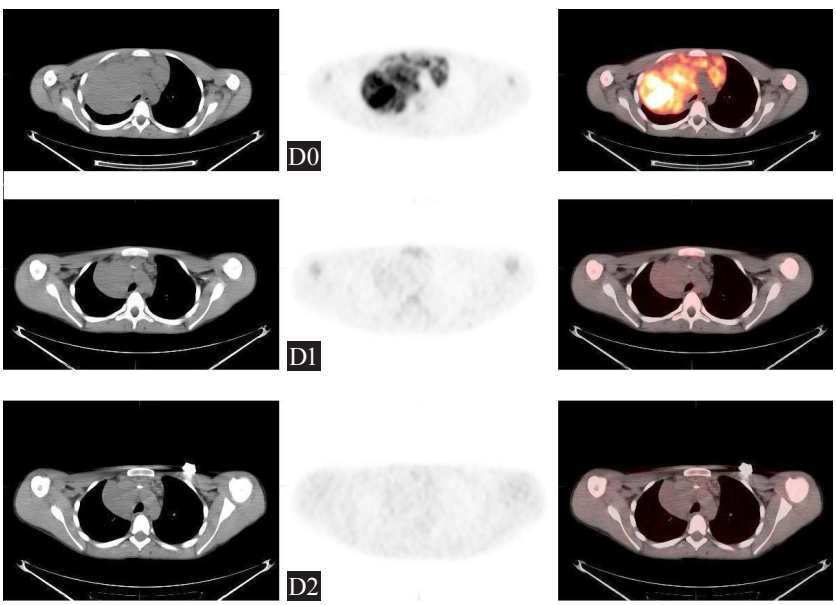

Figure 2. Example of good response to treatment. D0 demonstrated disease involving mediastinum. D1 and D2 demonstrated residual mass on CT scan, but not metabolic active on the ^{18}F-FDG PET images.

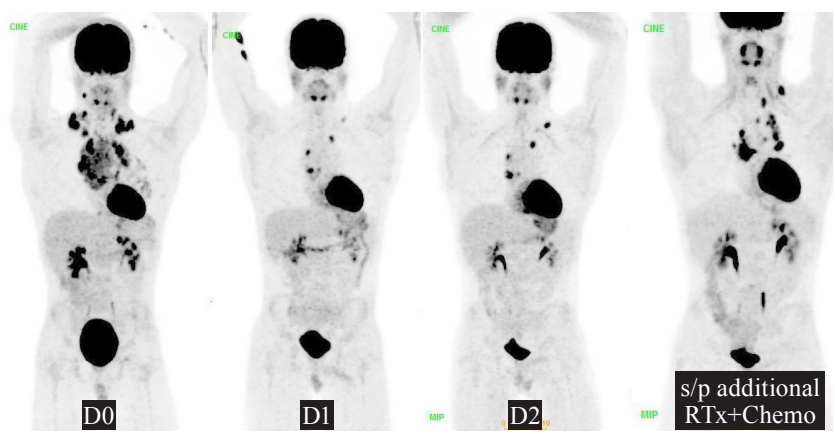

Figure 3. Example of failure to response. Anterior views of MIP ^{18}F-FDG PET imaging of D1 demonstrated small focal areas of residual disease while the majority of disease on D0 was resolved. However, the disease progressed on D2 and a follow up scan demonstrated that the disease did not respond to additional radiation therapy and chemotherapy.

from Italy evaluated 21 HL adult patients and suggested that the ^{18}F-FDG PET/CT performed after only two cycles of chemotherapy is sufficient to provide the same prognostic information as the ^{18}F-FDG PET after four and six chemotherapy cycles [19].

Another trial of 85 HL patients between 15 and 73 years of age concluded that after two or three cycles of chemotherapy ^{18}F-FDG PET is an accurate and independent predictor of progression-free survival and overall survival in HL. Specifically, a positive interim ^{18}F-FDG PET is highly predictive of relapse in advanced-stage disease [20].

For pediatric patients, a recent prospective multi-center trial concluded that pediatric HL patients with a negative mid-treatment ^{18}F-FDG PET had an excellent prognosis while

Table 2. *In this table the symbols D1, D1%, D2, D2% refer to the predictor metrics and the predicted metrics in absolute and % values. The derivations are classic Bayes theorem derivations. PPV and NPV refer to positive and negative predicted value, respectively. P(D+) is the prevalence of a positive outcome in D2 in our data*

	Absolute-absolute						Relative-absolute						Relative-relative				
	Sensitivity P(S+|D+)						Sensitivity P(S+|D+)						Sensitivity P(S+|D+)				
D1→ D2↓	1.00	2.00	3.00	4.00	5.00		D1%→ D2↓	"70%"	"60%"	"50%"	"40"	"30%"	D1%→ D2%↓	"70%"	"60%"	"50%"	"40"	"30%"
D2=2	1.00	0.77	0.40	0.30	0.27		D2=2	0.30	0.27	0.20	0.20	0.17	D2%=70	1.00	0.88	0.63	0.38	0.50
D2=3	1.00	0.92	0.69	0.62	0.54		D2=3	0.62	0.54	0.38	0.38	0.31	D2%=60	1.00	0.88	0.63	0.63	0.50
D2=4	1.00	1.00	1.00	0.89	0.78		D2=4	0.89	0.78	0.56	0.56	0.44	D2%=50	1.00	0.83	0.50	0.50	0.33
D2=5	1.00	1.00	1.00	0.88	0.75		D2=5	0.88	0.75	0.50	0.50	0.38	D2%=40	1.00	0.80	0.40	0.40	0.20
	Specificity (P(S-|D-)						Specificity (P(S-|D-)						Specificity (P(S-|D-)				
D1→ D2↓	1.00	2.00	3.00	4.00	5.00		D1→ D2↓	"70%"	"60%"	"50%"	"40"	"30%"	D1%→ D2%↓	"70%"	"60%"	"50%"	"40"	"30%"
D2=2	0.10	0.81	0.98	1.00	1.00		D2=2	1.00	1.00	1.00	1.00	1.00	D2%=70	0.99	0.99	0.99	0.99	0.99
D2=3	0.08	0.69	0.94	0.98	0.98		D2=3	0.98	0.98	0.98	0.98	0.98	D2%=60	0.99	0.99	0.99	0.99	0.99
D2=4	0.07	0.67	0.94	0.99	0.99		D2=4	0.99	0.99	0.99	0.99	0.99	D2%=50	0.96	0.96	0.96	0.96	0.96
D2=5	0.07	0.66	0.93	0.97	0.97		D2=5	0.97	0.97	0.97	0.97	0.97	D2%=40	0.95	0.95	0.95	0.95	0.95
	Prevalence (P(D+)						Prevalence (P(D+)						Prevalence (P(D+)				
D1→ D2↓	1.00	2.00	3.00	4.00	5.00		D1→ D2↓	"70%"	"60%"	"50%"	"40"	"30%"	D1%→ D2%↓	"70%"	"60%"	"50%"	"40"	"30%"
D2=2	0.38	0.38	0.38	0.38	0.38		D2=2	0.38	0.38	0.38	0.38	0.38	D2%=70	0.10	0.10	0.10	0.10	0.10
D2=3	0.17	0.17	0.17	0.17	0.17		D2=3	0.17	0.17	0.17	0.17	0.17	D2%=60	0.10	0.10	0.10	0.10	0.10
D2=4	0.12	0.12	0.12	0.12	0.12		D2=4	0.12	0.12	0.12	0.12	0.12	D2%=50	0.08	0.08	0.08	0.08	0.08
D2=5	0.10	0.10	0.10	0.10	0.10		D2=5	0.10	0.10	0.10	0.10	0.10	D2%=40	0.06	0.06	0.06	0.06	0.06
	PPV P(D+|S+)						PPV P(D+|S+)						PPV P(D+|S+)				
D1→ D2↓	1.00	2.00	3.00	4.00	5.00		D1→ D2↓	"70%"	"60%"	"50%"	"40"	"30%"	D1%→ D2%↓	"70%"	"60%"	"50%"	"40"	"30%"
D2=2	0.41	0.72	0.92	1.00	1.00		D2=2	1.00	1.00	1.00	1.00	1.00	D2%=70	0.89	0.88	0.83	0.75	0.80
D2=3	0.18	0.38	0.69	0.89	0.88		D2=3	0.89	0.88	0.83	0.83	0.80	D2%=60	0.89	0.88	0.83	0.83	0.80
D2=4	0.12	0.28	0.69	0.89	0.88		D2=4	0.89	0.88	0.83	0.83	0.80	D2%=50	0.67	0.62	0.50	0.50	0.40
D2=5	0.11	0.25	0.62	0.78	0.75		D2=5	0.78	0.75	0.67	0.67	0.60	D2%=40	0.56	0.50	0.33	0.33	0.20
	NPV (P(D-|S-)						NPV (P(D-|S-)						NPV (P(D-|S-)				
D1→ D2↓	1.00	2.00	3.00	4.00	5.00		D1→ D2↓	"70%"	"60%"	"50%"	"40"	"30%"	D1%→ D2%↓	"70%"	"60%"	"50%"	"40"	"30%"
D2=2	0.14	0.63	0.80	0.84	0.86		D2=2	0.84	0.86	0.89	0.89	0.91	D2%=70	0.90	0.91	0.93	0.96	0.95
D2=3	0.28	0.79	0.87	0.89	0.90		D2=3	0.89	0.90	0.93	0.93	0.94	D2%=60	0.90	0.91	0.93	0.93	0.95
D2=4	0.36	0.84	0.88	0.89	0.91		D2=4	0.89	0.91	0.93	0.93	0.94	D2%=50	0.92	0.93	0.96	0.96	0.97
D2=5	0.38	0.85	0.89	0.91	0.92		D2=5	0.91	0.92	0.94	0.94	0.96	D2%=40	0.93	0.95	0.97	0.97	0.99

Table 1. *Mean SUV values of 78 lesions in 18 patients. The effect of treatment was seen in the decrease of the mean value in D1 and D2, but the failures in the maximum value in D1*

Lesion SUV values in 18 patients			
	D0	D1	D2
Mean	11.5	2.9	2.4
Minimum	3.8	0.6	0.6
Maximum	22.1	23.0	9.2

mid-treatment PET-positive patients have an increased risk for relapse [21]. The study was not based on a threshold SUV as a criterion of positivity nor was it based on a formal comparison with D0 data. The sensitivity to predict a positive D2 was only 43%. This may be seen as one reason to question the value of interim ^{18}F-FDG PET/CT scans [22].

When used for early prediction of response ^{18}F-FDG PET images, some have evaluated the response visually and classified them as complete response, partial response, or progression of disease [23]. However, the paradox is that RECIST, PERCIST [9] and EORTC [10] use a percentage change for progressive disease, stable disease, and partial response but a complete response is defined as "no lesion".

There are two problems which we tried to tackle here. The first is that while the metric of an early response can rationally be expressed as a percentage decrease, the metric of a complete response should be an absolute metric and the evaluation should according to RECIST include a correction for background [6]. The term background is unfortunate, but refers in this case to the normal activity in the region where the lesion was.

The second problem is the problem of limits both for the definition of disease and symptom. Many authors remain attached to a binary expression of Bayes' theorem. In that case, as an example, the sensitivity is expressed as the conditional probability P(S+|D+). But if the system is not binary and the metrix are continuous variables, the expression should be $P(S+_{\text{if } x>n}|D+_{\text{if } y>m})$, where n and m are selected thresholds for the continuous variables x, and y.

In addition, the limits of the predictor to obtain an optimal PPV and NPV do not necessarily have to be the same: If $D1_{\%SUV}$ <30%, then all $D2_{SUV}$>2 will be predicted in 100% of the cases, however, only 91% of the $D2_{SUV}$<2 will have been detected. However, If $D1_{\%SUV}$>30%, then 96% of the cases will have a $D2_{SUV}$<5, and only 60% $D2_{SUV}$>5.

Over the past two decades, attempts have been made to determine global metabolic activity by PET in a variety of

disorders including those related to the central nervous system and cancer. The initial application with this approach was reported by Alavi et al. (1993) in patients with Alzheimer's disease and age-matched controls [24]. This methodology proved to be very sensitive for separating patients from normal volunteers who were enrolled in the study. In recent years, attempts have been made to apply this technique in patients with cancer either at primary or metastatic sites. This approach requires measuring the volume of the lesions and the partial volume corrected quantitative data, from PET images of the lesions [25]. Following such measurements, global metabolic activity can be calculated by multiplying the volume of the lesion by the corrected metabolic activity per unit of volume of the tissue in each site. Thereafter, by adding the values generated from various lesions throughout the body, global disease activity can be assessed in patients with a variety of malignant diseases. Berkowitz et al. (2008) were the first to introduce this concept to the literature which appears to be very effective for following patients after therapeutic interventions [25]. This method is very sensitive and reproducible in following patients with cancer and other disorders. In recent years, the group at the University of Pennsylvania has employed an automatic thresholding software that allows measuring the volume of the lesions from PET images alone without the need for utilizing structural imaging results. This leads to correcting for partial volume effect of metabolic activity of disease sites and calculating global disease activity in a relatively simple and straightforward manner [26, 27].

Conclusion

It appears that the results from the adult studies are indeed applicable in pediatric cases. Even though with a small patient population, this study strongly suggests that the predictive value of the mid treatment scan for the end of treatment scan is high, both on a patient basis and a lesion basis. However, there is not a single limit separating good and bad outcomes however they are defined. We did not answer the question on the significance of a poor response in mid-treatment for the long-term prognosis. The study was retrospective and the number of patients is limited. Yet at some level a poor mid-treatment response may warrant the consideration of a changed treatment strategy.

This limited study suggests that in pediatric cases as in adult studies, a good mid-treatment response could eliminate the need for post-treatment scan and a poor mid-treatment response could warrant the consideration of a changed treatment strategy. More importantly, the analysis suggests that SUV limits are different for negative and positive predicted values.

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The authors declare that they have no conflicts of interest.

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Cornelis Dusart: The surgeon of the village 1695, in bronze.