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Predictive Value of Lung Biopsy in Ventricular Septal Defect: Long-Term Follow-Up

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Although the Heath-Edwards classification has been used for more than 25 years to evaluate pulmonary vascular changes, its potential to predict the long-term course after successful ventricular septal defect closure has not been proved. Operative lung biopsy slides obtained at the time of closure from 57 infants and children who had been among the first survivors (between 1954 and 1960) of such surgery were graded in blinded fashion according to the Heath-Edwards classification system, and the resultant biopsy grade of each was compared with the eventual long-term outcome of each child.

In 53 (93%) of the 57 cases, the Heath-Edwards system correlated well with long-term clinical or hemodynamic status of the patient. Grade IV changes were predictive of a usually fatal outcome, while grade I and II changes were generally benign. Death from pulmonary vascular disease occurred, however, in four children whose operative lung biopsy had been classified as either grade I or II, indicating that the focal nature of the higher Heath-Edwards grades, or human error, must be considered when this classification system is employed.

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The Heath-Edwards classification (1) has been used for more than 25 years to evaluate pulmonary vascular changes; however, its potential to predict the long-term course after successful ventricular septal defect closure has not been proved. Indeed, investigators (2) have recently suggested that this classification scheme alone is inadequate to predict the outcome of surgical intervention for ventricular septal defect. Other investigators (3,4) have used different classification systems to correlate the pulmonary artery morphologic features identified by operative lung biopsy with the eventual postoperative course in children having a variety of congenital cardiac anomalies. Reports of long-term follow-up of patients evaluated by any system of classification are limited.

Wagenvoort et al. (5) recently described the natural history of pulmonary vascular changes in a heterogeneous group of patients with a shunt at the ventricular level, who had first undergone palliative pulmonary artery banding and subsequent operative repair of their anomalies. Both cyanotic and acyanotic cardiac anomalies were present within this series, but the long-term outcome of the patients after complete repair was not described.

To define the limits of predictability of the Heath-Edwards system for grading pulmonary vascular changes, we report the long-term (25 years) follow-up of 57 infants and children who underwent ventricular septal defect closure between 1954 and 1960 and in whom a lung biopsy specimen had been obtained at or near the time of ventricular septal defect closure. These slides of lung tissue had been evaluated for pulmonary vascular changes according to a scheme used at that time (1957) at the University of Minnesota (6), the Heath-Edwards classification not yet being in existence. For our study, the preserved slides from these biopsies were reviewed and graded according to the Heath-Edwards classification. For each patient, the results were compared with the long-term postoperative course and, when available, postoperative cardiac catheterization data. The current results were, however, not compared with those of the original study reported in 1957, since individual biopsy scores from that study made nearly 30 years ago were not available to us.

Methods

Study patients. Between 1954 and 1960, approximately 1,000 patients underwent open heart surgery for cardiac

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disease at the University of Minnesota Hospitals, using either a cross-circulation technique or a pump oxygenator. During this time, 341 patients underwent closure of a ventricular septal defect, and 270 of these patients survived to hospital discharge (7). Open lung biopsy tissue was obtained in some of these 270 patients undergoing closure of a ventricular septal defect when clinical evidence of pulmonary artery hypertension was present. From this reservoir of material, 57 patients constituted the study group of this report by virtue of having both biopsy slides for restudy and long-term follow-up data, the former criterion being the limiting factor.

Biopsy study. The biopsy specimens had been fixed in formalin; one set of slides was stained with hematoxylin-eosin, and another set (for elastic tissue) was counterstained with the Van Gieson stain. Shortly after operation, these specimens had been evaluated for pulmonary vascular changes according to the previously mentioned scheme used at the University of Minnesota and reported by Adams et al. in 1957.

Twenty-five years after these biopsy slides were obtained, they were reevaluated by one of us (J.E.E.) and were reclassified according to the Heath-Edwards system (1). This reclassification was done without knowledge of the patient's age at operation or subsequent clinical status. If death occurred during the follow-up period, autopsy slides of pulmonary tissue were sought. When available, such slides were also reviewed without knowledge of either the operative biopsy class or the patient's previous clinical status.

Clinical data. Clinical data, including the date of birth, cardiac catheterization and operation, were recorded for each of the 57 patients. If death occurred after hospital discharge, the date and cause of death were noted. Operative diagnosis and associated cardiac lesions if present were recorded, preoperative and postoperative catherization data were collected and, when possible, the size of the left to right shunt was calculated for each patient. Because neither oxygen consumption nor systemic arterial pressure was measured routinely at our institution during the 1950s, it was not possible to calculate either the absolute values or the ratios of pulmonary and systemic vascular resistances. Instead, mean pulmonary artery pressures were measured at both preoperative and postoperative catheterizations, and this information was combined with percent of left to right shunt to approximate the pulmonary artery resistance. In cases where only systolic and diastolic pulmonary artery pressures were recorded, mean pulmonary pressure was calculated by accepted methods (8).

Results

Clinical features. Among the 57 patients in this study, the age at the time of operation ranged from 6 months to 21 years. Only nine children in this series were younger than 2 years at the time of operation.

Table 1. Distribution of Operative Ages and Heath-Edwards Class of Operative Lung Biopsies Within Study Group of 57 Patients Undergoing Ventricular Septal Defect Closure

Heath-Edwards Class	No. of Biopsies	Age at Biopsy (yr)	
		Average	Range
0	1	4.2	—
I	37	5.8	0.6 to 21.0
II	10	7.4	1.7 to 15.2
III	5	7.5	4.8 to 10.9
IV	4	7.9	4.7 to 10.0
Total	57	6.3	0.6 to 21.0

Isolated ventricular septal defect was present in 49 patients. The remaining eight had an associated anomaly: atrial septal defect or patent foramen ovale in three, patent ductus arteriosus in four (including one patient with coarctation of the aorta as well) and mitral stenosis in one. Of the 57 patients, 22 (39%) died after hospital discharge 2 months to 23 years postoperatively. The remaining 35 patients have been followed up for a period of 21.6 to 27.4 years.

Within the study group, the biopsy grades ranged from normal (grade 0) to Heath-Edwards grade IV. Biopsy findings in most patients were classified as either grade I (37 cases 65%) or II (10 cases 18%) (Table 1). Among the 10 remaining patients, 5 (9%) showed grade III changes, 4 (7%) showed grade IV changes and 1 (2%) had normal pulmonary arteries.

Although preoperative catheterization data were available in each patient, postoperative cardiac catheterization data were available in only 27 patients. The postoperative catheterization was performed an average of 4.9 years (range 0.5 to 23) after operation. In 17 patients, there was no residual left to right shunt, in the remaining 10 patients, the shunt was usually small (17 to 46%), and in 8 of the 10 the shunt was 30% or less (Table 2).

Grade 0 (normal) lung biopsy follow-up. The one patient whose operative lung biopsy findings were classified as normal, or grade 0 by the Heath-Edwards system, underwent successful ventricular septal defect closure at 4.2 years of age (Table 1). He remains alive 26.4 years after repair, without evidence for either a residual left to right shunt or pulmonary vascular disease (Tables 2 and 3).

Grade I lung biopsy follow-up. The 37 patients whose operative lung biopsy findings were classified as grade I underwent ventricular septal defect closure at an average of 5.8 years (range 0.6 to 21.0) and were followed up for an average of 20.8 years (Tables 1 and 2). Eleven (30%) of these 37 patients died after hospital discharge an average of 9.3 years (range 0.3 to 22) postoperatively (Table 2). Death in these 11 patients was attributed to the following

Table 2. Late Mortality, Length of Time to Death and Years of Long-Term Follow-Up for the 57 Patients Since Hospital Discharge After Ventricular Septal Defect Closure

Heath-Edwards Class	No. of Patients	Average Follow-Up (yr)	No. of Deaths (% of each class)	Time to Death (yr)	
				Average	Range
0	1	26.4	0	—	—
I	37	20.8	11 (30)	9.3	4 mo to 22 yr
II	10	19.1	4 (40)	10.0	3 mo to 22 yr
III	5	15.2	3 (60)	8.2	3 mo to 23 yr
IV	4	4.0	4 (100)	4.0	2 mo to 11 yr

causes: sudden death (three cases); pulmonary vascular disease, subacute bacterial endocarditis or accident (two cases each); reoperation for residual ventricular septal defect (one case) and unknown cause (one case).

Preoperative and postoperative hemodynamic data, the latter having been obtained an average of 4.8 years (range 0.5 to 15.8) after ventricular septal defect closure, were available in 15 (40%) of these 37 patients (Table 3, Fig. 1). Preoperatively, each had at least a modest elevation of mean pulmonary artery pressure (average 57 mm Hg; range 30 to 80), and usually the left to right shunt was large (average 62%; range 44 to 86). Postoperatively, mean pulmonary artery pressure decreased to an average of 27 mm Hg (range 12 to 70). Seven patients had no residual shunt, and in the remaining eight, the residual shunt was small. In two of the seven patients who had no detectable residual shunt, significant pulmonary hypertension (mean pulmonary artery pressure 40 and 70 mm Hg, respectively) was present postoperatively.

In the two patients who had evidence of pulmonary vascular disease at postoperative cardiac catheterization, death occurred at 14 and 15.4 years, respectively, after ventricular septal defect closure (Table 4). Neither preoperative hemodynamic status nor operative age was essentially different in these two patients from that in survivors within this class who did not develop pulmonary vascular disease (Fig. 1). Autopsy slides of pulmonary tissue in one of these two patients (Case 29) were found to have grade VI Heath-Edwards changes (Table 4).

Sudden death, which occurred in three patients whose operative lung biopsy findings had been assigned to grade I classification, was associated in one patient with a ruptured berry aneurysm. In this patient and one other from this subgroup, postoperative mean pulmonary artery pressure was 18 and 19 mm Hg, respectively. The third patient who died suddenly while playing golf had not undergone postoperative catheterization.

Grade II lung biopsy follow-up. The 10 patients whose operative lung biopsy findings were classified as grade II underwent ventricular septal defect closure at an average age of 7.4 years (range 1.7 to 15); the length of follow-up averaged 19.1 years for this group (Tables 1 and 2). Four (40%) of these 10 patients died subsequent to hospital discharge an average of 10 years (range 0.2 to 22) after operation (Table 2). Among these four patients, death was attributed to either pulmonary vascular disease (two cases) or complete heart block (two cases).

Preoperative and postoperative hemodynamic data, the latter obtained an average of 3.0 years (range 1 to 6.6) after operation, were available in six (60%) of these patients (Table 3, Fig. 2). Moderate pulmonary hypertension (average mean pulmonary artery pressure 53 mm Hg; range 28 to 75) and a large left to right shunt (average 67%; range 48 to 80) had been present preoperatively. Postoperatively, four patients had a low (< 30 mm Hg) mean pulmonary artery pressure, associated in two with a residual left to right shunt. Two other patients had evidence of pulmonary hypertension (mean pulmonary artery pressure 49 and 65 mm

Table 3. Preoperative and Postoperative Mean Pulmonary Artery Pressures and Percent Left to Right Shunt in 27 Patients Whose Hemodynamic Data Were Available

Heath-Edwards Class	n	Preoperative		Average Time to Postoperative Catheterization (yr)	Postoperative	
		$\overline{PAP}$ (range)	% L-R (range)		$\overline{PAP}$ (range)	% L-R (range)
0	1	49	52	4.1	20	0
I	15	57 (30 to 80)	62 (44 to 86)	4.8 (0.5 to 15.8)	27 (12 to 70)	14 (0 to 45)
II	6	53 (28 to 75)	67 (48 to 80)	3.0 (1 to 6.6)	28 (17 to 49)	11 (0 to 46)
III	2	58 (42 to 75)	60 (50 to 69)	12.0 (0.7 to 23.2)	35 (18 to 52)	0
IV	3	68 (57 to 85)	49 (44 to 54)	4.4 (0.9 to 10)	70 (56 to 97)	0

$\overline{PAP}$ = mean pulmonary artery pressure (in mm Hg) averaged for the class indicated; % L-R = percent left to right shunt averaged for the class indicated.

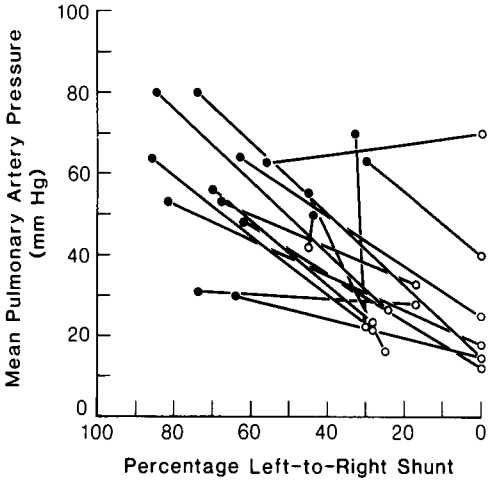

Figure 1. Preoperative (●) and postoperative (○) hemodynamic data obtained from 15 patients whose operative lung biopsy findings had been assigned grade I Heath-Edwards changes. Eight patients had a residual left to right shunt (≤30% in seven), while seven patients (one postoperative data point refers to two patients) had no residual shunt. Pulmonary hypertension (mean pulmonary artery pressure 40 and 70 mm Hg, respectively) without a residual shunt was present in two patients postoperatively, both of whom subsequently died of pulmonary vascular disease.

Hg, respectively) in the absence of a detectable left to right shunt.

Death occurred 6.7 and 17.5 years after operation, respectively, in the two patients who had evidence of pulmonary hypertension at postoperative catheterization and in whom no residual left to right shunt had been detected (Table 4). Slides of pulmonary tissue obtained at autopsy were available for review in one of these two patients, and were found to have grade V Heath-Edwards changes (Table 4).

Sudden death occurred in two patients, both of whom developed complete heart block at the time of ventricular septal defect closure and were being treated with isoproterenol, cardiac pacemakers not being in existence at that time. Postoperative mean pulmonary artery pressure was available in one of these two patients and was low (24 mm Hg).

Grade III lung biopsy follow-up. The five patients whose operative lung biopsy findings were classified as grade III underwent ventricular septal defect closure at an average age of 7.5 years (range 4.8 to 10.9); the length of follow-up averaged 15.2 years (Tables 1 and 2). Three of these five patients died subsequent to hospital discharge an average of 8.2 years (0.2 to 23) after operation (Table 2). Among these three patients, death was attributed to pulmonary vascular disease, subacute bacterial endocarditis or reoperation for residual ventricular septal defect, respectively.

Preoperative and postoperative hemodynamic data, the latter obtained an average of 12 years (range 0.7 to 23.2) after operation, were available in two (40%) of these five patients (Table 2, Fig. 3). Preoperatively, in both patients, the left to right shunt was large (50 and 69%, respectively), and mean pulmonary artery pressure was elevated (75 and 42 mm Hg, respectively). Postoperatively, although there was no left to right shunt in either patient, significant pulmonary hypertension remained in one patient, but not in the other.

Death occurred 23.2 years after surgery in the patient whose postoperative catheterization had demonstrated pulmonary hypertension in the absence of a detectable shunt (Table 4). Slides of pulmonary tissue obtained at autopsy from this patient continued to show grade III Heath-Edwards changes.

Grade IV lung biopsy follow-up. The four patients whose operative lung biopsy findings were classified as grade IV underwent ventricular septal defect closure at an average age of 7.9 years (range 4.7 to 10.0); the length of follow-up averaged 4.0 years (Tables 1 and 2). All four patients died subsequent to hospital discharge an average of 4.0 (range 0.2 to 10) years after operation (Table 2). Among

Table 4. Identifying Data, Preoperative and Postoperative Hemodynamic Data and Postmortem Classification of Pulmonary Tissue in Eight Patients Who Died of Pulmonary Vascular Disease After Ventricular Septal Defect Closure

Heath-Edwards Class	Case	Preoperative $\overline{PAP}$	% L-R	Age at Operation (yr)	Postoperative $\overline{PAP}$	% L-R	Time to Death (yr)	PM H/E
I	29	63	30	6.7	40	0	14	VI
	40	63	56	7.7	70	0	15.4	NA
II	43	60	68	5.2	49	0	6.7	NA
	44	*	NA	6.8	65	0	17.5	V
III	49	42	50	4.8	52	0	23.2	III
IV	54	57	48	8.9	58	0	2.1	NA
	56	85	44	8.1	97	0	2.3	IV
	57	62	54	4.7	56	0	11.4	NA
Average		62	50	6.6	61	0	11.6	NA

*90/0 mm Hg = right ventricular pressure; NA = not available; PM H/E = postmortem Heath-Edwards class; other abbreviations as in Table 3.

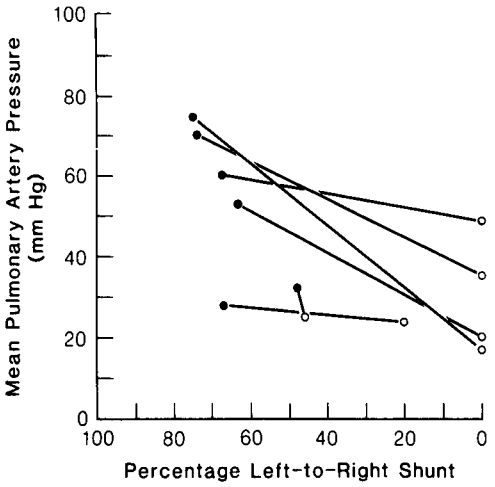

Figure 2. Preoperative (●) and postoperative (○) hemodynamic data obtained from six patients whose operative lung biopsy findings had been assigned grade II Heath-Edwards changes. Two patients had a residual left to right shunt (20 and 46%, respectively), while four patients had no residual shunt. Pulmonary hypertension (mean pulmonary artery pressure 49 and 35 mm Hg, respectively) was present in two patients postoperatively in the absence of a detectable shunt, the former patient subsequently dying of pulmonary vascular disease, the latter remaining alive and asymptomatic. (A second patient with grade II operative lung biopsy findings, who subsequently died of pulmonary vascular disease [see Table 4], had insufficient preoperative hemodynamic data to be included in this graph.)

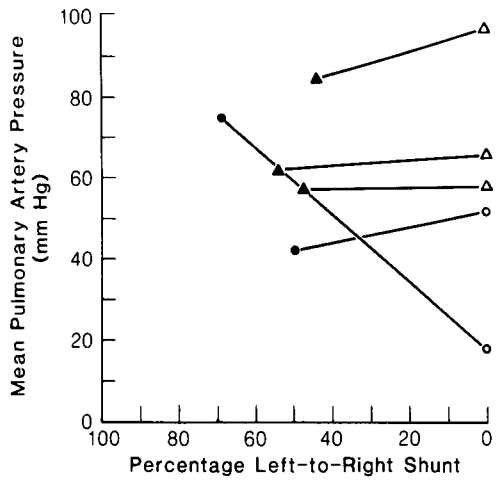

Figure 3. Preoperative (●,▲) and postoperative (○,△) hemodynamic data obtained from five patients whose operative lung biopsy findings had been assigned, respectively, grade III (●) or grade IV (▲) Heath-Edwards changes. No patient had a residual left to right shunt, but pulmonary hypertension remained (mean pulmonary artery pressure 52, 56, 58 and 97 mm Hg, respectively) in four of these patients postoperatively, each of whom subsequently died from pulmonary vascular disease. Pulmonary hypertension resolved (mean pulmonary artery pressure 18 mm Hg) in one of the two patients whose operative lung biopsy had been assigned a grade III class.

these four patients death was attributed to pulmonary vascular disease (three cases) or was sudden and unexpected (one case).

Pre- and postoperative hemodynamic data, the latter obtained 4.4 (range 0.9 to 10) years after operation, were available in three of these four patients (Table 3, Fig. 3). Among these three patients, the preoperative left to right shunt was moderate (average 49%; range 44 to 54%), and pulmonary hypertension was present (average preoperative mean pulmonary artery pressure 68 mm Hg; range 57 to 85). Although the left to right shunt was abolished surgically, significant pulmonary artery hypertension remained in each patient (average postoperative mean pulmonary artery pressure 70 mm Hg; range 56 to 97).

Death occurred 2.1 to 11 years after operation in the three patients who had evidence of pulmonary hypertension at postoperative catheterization and in whom no detectable shunt was present. One of these three deaths occurred during reoperation for tricuspid regurgitation, presumably caused by the first operation or pulmonary hypertension, or both. Pulmonary tissue obtained at autopsy was available in one of these three patients, and showed evidence for grade IV Heath-Edwards changes (Table 4).

Sudden death occurred in one patient in whom complete heart block was known to have been present since the time of operation. Neither postoperative hemodynamic data nor slides of pulmonary tissue from autopsy in this patient were available to us.

Comments

Although the Heath-Edwards grading system dates from 1958, its predictive value had not been validated in a long-term study of survivors after the surgical closure of a ventricular septal defect. At our institution, lung biopsy was commonly performed during the early period of surgical closure of ventricular septal defects, and we were afforded the unique opportunity to determine the potential for the Heath-Edwards classification in predicting long-term outcome in children who underwent successful ventricular septal defect closure. Our 25 year clinical follow-up in conjunction with a blinded review of the lung biopsy slides define the limits of the predictability of the Heath-Edwards classification scheme. To date, such long-term predictability remains lacking in other systems currently employed.

Mortality as a function of Heath-Edwards grade. Among our findings is that death from any cause or from pulmonary vascular disease occurred more frequently among patients with a higher Heath-Edwards class. Although 11 (30%) of 37 patients who had grade I changes in the operative lung biopsy specimen died during the follow-up period, all patients with grade IV changes died during this time. Similarly, for patients in whom both postoperative hemodynamics and clinical data were available, death from

pulmonary vascular disease increased from 13% (2 of 15 cases) for those with grade I biopsy findings to 75% (3 of 4 cases) for those with grade IV operative biopsy findings. As a consequence of this increased mortality rate, the length of follow-up decreased as Heath-Edwards class increased (Table 2).

Sudden death, which may occur from a variety of causes postoperatively, including pulmonary vascular disease, occurred in six patients during the follow-up period. Mean pulmonary artery pressures had been measured postoperatively in three of these patients, including one with known complete heart block, and was not higher than 24 mm Hg in our patients. Three patients in this category were known to have had complete heart block (one having also undergone postoperative catheterization) since the time of operation, suggesting that, at least in five of the six patients within this group, pulmonary vascular disease was not likely to be responsible for postoperative death.

Postoperative hemodynamic data, available in 27 (47%) of the 57 patients, supported the concept that the higher Heath-Edwards classes were associated with a higher postoperative pulmonary artery pressure in the absence of a residual detectable shunt (Table 3, Fig. 1 to 3).

Exceptions to the Heath-Edwards classification. Although the Heath-Edwards system appeared predictive of long-term (25 years) outcome in more than 53 (90%) of our cases, there were notable exceptions. Among four of our patients whose biopsy specimen showed grade I or II changes, the postoperative clinical course was characterized by persistent pulmonary hypertension after documented closure of the ventricular septal defect and death from obstructive pulmonary vascular disease. In two of these, autopsy performed 14 and 17.5 years, respectively, after operation, showed high grades of pulmonary vascular disease. The disparity between the biopsy grade and the postoperative course in these instances may have been related to one or a combination of factors, including small size of biopsy specimen, the focal nature of lesions of at least grade II severity (9), human error or a contribution from the passage of time. The presence of associated anomalies (coarctation of aorta, mitral stenosis), although small in number within our series, did not appear to influence the assignment of the appropriate Heath-Edwards grade. In those instances of disparity between biopsy grade and clinical outcome, when we reread slides, again blindly, it was not uncommon for the grade to increase by one or more scores. In this report, we have given the first score assigned.

Perhaps newer schemes that utilize abnormalities of the normally occurring developmental changes within the lung (3,4) might have been able to predict the postoperative course more accurately than the Heath-Edwards classification. The 1 year predictability of such a classification appears good (4). Additionally, few of our patients were younger than 2 years of age at the time of operation, while today, operative repair is generally performed at or before this age if pulmonary hypertension is found. Utilization of the Heath-Edwards system may be less necessary under these circumstances (4).

Conclusions. We have found that 1) the Heath-Edwards classification scheme accurately predicts the long-term contribution of pulmonary vascular disease to prognosis in children undergoing ventricular septal defect closure. 2) Grade IV biopsy findings presage a usually fatal outcome from pulmonary vascular disease. 3) Grade 0, I or II biopsy findings generally presage a good outcome, but the grading can, on occasion, be wrong because of the focal nature of higher grade pulmonary lesions or human error. 4) The lung biopsy grade assigned should correspond with the highest grade lesion identified.

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