The sequence of vessel interruption during lobectomy for non–small cell lung cancer: Is it indeed important?

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Objective: During pulmonary resections for non–small cell lung cancer, the pulmonary vein is traditionally interrupted first to prevent seeding of malignant cells and consequently decrease metastatic implantation. This hypothesis was never confirmed scientifically. The aim of the present study was to determine whether the sequence of vessel interruption during lobectomy (lobar vein or lobar artery first) affects disease recurrence.

Methods: A historical prospective study was performed of 279 consecutive patients with complete follow-up, who survived lobectomy for non–small cell lung cancer during 1992 to 1998, in a single center. Pre-, intra-, and postoperative variables were collected from the medical records; recurrence and vital status were obtained from follow-up files, central population registry, and personal confirmation, updated to December 2000. Comparison of recurrence rates by sequence of ligation and other independent variables was assessed by univariate and multivariate logistic regression analyses.

Results: A total of 133 patients (48%) had vein interruption before the artery (V-first) and 146 (52%) had artery interruption first (A-first). The distribution of demographic, clinical, and other characteristics was similar between the 2 groups, except for the operated side and performing surgeons. The morbidity, blood requirement, and length of stay were equal for both groups. The total recurrence rate (A-first, 53%; V-first, 51%) was similar. Multivariate analysis (controlling for the effect of the performing surgeon) revealed elevated risk for recurrence among patients with high disease stage (odds ratio = 2.54), male gender (odds ratio = 1.59), intraoperative lung manipulation (odds ratio = 2.72), and blood transfusion (odds ratio = 1.49). Sequence of vessel interruption was not found as a risk factor for recurrence (odds ratio = 1.29; 95% 0.73 to 2.29, $P = .4$).

Conclusions: Our results did not show that sequence of vessel interruption during lobectomy plays a role in tumor recurrence. A prospective study with randomization in selection of method as well as surgeons for each patient is needed to confirm these results.

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Received for publication July 17, 2002; revisions requested Sept 3, 2002; revisions received Oct 11, 2002; accepted for publication Oct 22, 2002.

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J Thorac Cardiovasc Surg 2003;125:1313-20

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0022-5223/2003 \$30.00 + 0

doi:10.1016/S0022-5223(03)00022-9

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lthough many new treatment modalities have been proposed recently to improve survival of patients with non–small cell lung cancer (NSCLC), surgery and complete removal of the primary tumor and its involved lymph nodes remains the most effective treatment for these patients.¹ The basic technique for lobectomy, the most common type of resection, did not change since the 1940s when individual hilar dissection evolved.^{2,3} During the years there were

changing fashions regarding the sequence of vessel interruption (lobar veins first and arteries to be followed or vice versa). Today's standpoint is much more liberal and the recommendation is that the order of vessel dissection and division will be according to the surgeon's preference.⁴ Theoretically, manipulation of the lung during operation can produce spillage of tumor cells into the circulation and seeding of micrometastasis to distant organs. Therefore, interruption of the lobar vein before ligation of the artery may be justified. Lobar artery interruption first, on the other hand, may have an advantage in preventing unnecessary blood loss as the blood supply to the lobe is immediately closed. Several studies support vein interruption before artery. One experimental study on animals⁵ showed that surgical manipulation of tumors evokes enhancement of metastases. In another study,⁶ higher levels of tumor marker were found in the peripheral blood of patients with NSCLC who underwent lobectomy in an artery-to-vein sequence compared with those with a vein-to-artery sequence. The claim that interruption of the artery before the vein may lessen the blood loss during surgery was rejected by Miller and colleagues⁷ in an animal study. Practical implications on prognosis, determined by the sequence of the procedure, remain unsolved.

Interestingly, the issue whether surgical manipulation affects prognosis has gained growing attention recently since the introduction of the video-assisted (VATS) lobectomy. One of the arguments against VATS lobectomy for lung cancer is that the forceful retraction of the lung, which is necessary to achieve clear video visualization during this procedure, may increase the risk of tumor cell dissemination and therefore affect the patient's prognosis.⁸

The aim of the present report was to examine the possible effect of sequence of vessel interruption (lobar vein first versus lobar artery first) on prognosis in patients undergoing lobectomy for NSCLC.

Materials and Methods

From January 1992 to December 1998, 307 patients underwent lobectomy for NSCLC in the Chaim Sheba Medical center. Of these, 10 patients were excluded from this analysis due to mixed order of vessels interruption during the lobectomy, 12 patients were excluded due to perioperative death (defined as death within 30 days after surgery or at any time if the patient was never discharged from the hospital), and 6 other patients were excluded because they were lost to follow-up. These last 6 patients are all alive according to the Israeli central population registry but their disease status is unknown. Thus, 279 patients (90.9% of the target population) were included in this study. Of them, 133 (48%) underwent interruption of pulmonary vein before artery (designated "V-first") and 146 (52%) underwent interruption of pulmonary artery first (designated "A-first"). The decision of which method to use in each operation was based on the discretion of the operating surgeon.

Demographic, preoperative, intraoperative, postoperative, and histologic data was collected by a retrospective review of the medical records. Disease status (ie, free from disease or recurrence) was updated from outpatient clinic records and telephone survey for all uncertain conditions. Vital status was updated via the Israeli's Central Population Registry.

Preoperative evaluation included smoking and medical history, previous malignancies, previous operations on the chest, laboratory tests, pulmonary function tests, and imaging evaluation. Operative data included presence of pleural adhesions, obtainment of frozen section before resection, types of lobectomy, sequence of vessel interruption, and additional resections performed during this procedure. Cases in which significant lung retraction was necessary before proceeding with lobar resection (en bloc chest wall resection before hilar dissection and management of severe adhesions) were also recorded and designated as "lung manipulation." Completeness of resection was defined as free peripheral and hilar margins and negative lymph node in the higher station sampled. Histologic data and pathologic staging according to the international lung cancer staging system⁹ were also recorded. For 38 patients who received preoperative treatment (mainly neoadjuvant chemotherapy) the preoperative clinicohistological stage of disease was used. Postoperative complications were categorized as medical (eg, fever, pneumonia) and technical complications (eg, air leak). Use of blood transfusion and length of hospital stay were also recorded.

All patients were followed until death, recurrence, or study termination on December 2000, whichever came first. Mean follow up was 22.6 months (range 0.16-106 months). The end point of the present study was defined as recurrence. This dependent variable was categorized in two groups: "recurrence" (considered as death from the disease or staying alive with a diagnosed disease) and "nonrecurrent" (all patients who were alive without disease or died from other illness).

Statistical Analysis

All statistical analysis was done with SAS software (SAS, Inc, Cary, NC). Statistical significance for difference between the two treatments groups (V-first and A-first) for each continuous variable was evaluated by means of a 1-way analysis of variance. Comparison of categorical variables between the 2 groups was performed by the χ -square test or the Fisher exact test according to the cell size examined. A correlation matrix was used to examine possible association between completeness of resection and stage of disease, between performing surgeon and stage. A logistic multivariate analysis was performed to determine whether the method of surgery (sequence of vessel interruption) had an impact on recurrence of the disease, controlling for the known and significant factors for recurrence. We first estimated the risk of recurrence for sequence of interruption, introduced the stage of disease, then included performing surgeon, and investigated the interaction between sequence of interruption and performing surgeon. Finally, we entered the remaining factors that were found to be associated with recurrence in the univariate analysis: gender, lung manipulation, and blood transfusion. This step-by-step process enabled us to determine whether the effect of sequence of interruption was changed by the above-mentioned covariates.

TABLE 1. Demographics and tumor-related variables

Variable	Total		V-first		A-first		P value
	No	%	No	%	No	%	
Total	279	100	133	100	146	100	
Age (mean $\pm$ SD)	65.1 $\pm$ 10		64.5 $\pm$ 10		65.7 $\pm$ 10		NS
Gender							
Male	175	62.7	86	64.7	89	61	NS
Female	104	37.3	47	35.3	57	39	
Positive history of smoking	217	77.7	109	82	108	74.5	NS
Previous malignancies*							
Yes	38	13.7	17	12.9	21	14.4	NS
No	240	88.3	115	87.1	125	85.6	
Histology							
Squamous cell	83	29.7	44	33.1	39	26.7	NS
Adenocarcinoma†	151	54.1	63	47.4	88	60.3	
Large cell	19	6.8	9	6.8	10	6.8	
Bronchoalveolar	13	4.7	9	6.8	4	2.7	
Others	13	4.7	8	6	5	3.5	
Grade							
Well diff.	58	20.9	29	21.8	29	19.9	NS
Well to mod diff.	23	8.3	12	9	11	7.5	
Mod diff.	62	22.4	33	24.8	29	19.9	
Mod to poor	13	4.7	1	0.8	12	8.2	
Poorly diff.	75	27.1	41	30.8	34	23.3	
Unknown	48	17.2	17	12.8	31	21.2	
Stage							
I	152	54.5	77	57.9	75	51.4	NS
II	50	17.9	21	15.8	29	19.9	
III	68	24.4	29	21.8	39	26.7	
IV	9	3.2	6	4.5	3	2.1	

*Missing data for one patient from the "V-first."

†Adenocarcinoma vs. all other histological types, $P = .04$.

Results

Demographic- and Tumor-Related Variables

The mean age of the study population was 65.1 (± 10) years. Male/female ratio was 1.7 (63% men and 37% women). There were no significant differences between the V-first group and the A-first group in respect to all demographic variables such as age, sex, and smoking history (Table 1).

No statistically significant differences were found between the groups regarding the percent of patients having 50% or more than the predicted forced expiratory volume in 1 second as well as in forced vital capacity (not shown).

Table 1 also includes tumor-related variables such as tumor type, grade, and stage. Adenocarcinoma was the most common histologic diagnosis in both groups, accounting for 54.1% of all tumors (60.3% among the A-first group and 47.4% among the V-first group, $P = .04$). Squamous cell carcinoma was the second most common tumor (29.7%). Mixed type and unspecified NSCLC were combined in the same category and designated as "others." A large proportion of the patients were diagnosed at stage I (54.5%), again with similarity in the 2 groups. No significant differences in the distribution of the 2 study groups by grade or by previous malignancy were observed.

Operative Approach Characteristics

As was stated before, all patients underwent lobectomy, but 66 patients (23.7%) had additional resections in the same session such as sleeve, pericardium, wedge of lung, pleura, or diaphragm (Table 2). Ten (15%) of them had 2 additional resections. There was no significant difference between the 2 study groups regarding the additional resections but wedge resection was significantly more prevalent in the A-first group (10.3%) compared with the patients in the V-first group (3.8%). Right-sided resection and hence tumor location was significantly more prevalent in the V-first group (Table 2). Complete resection was performed on 81% with no difference between the 2 study groups. There was no significant difference between the 2 study groups in obtaining frozen section before proceeding with lobar resection. Performance of lung manipulation was more common in the A-first group (10.3% versus 4.5%) ($P = .07$).

Strong correlation was found between the surgeon and the sequence of interruption that was used ($P < .001$). Most of the "V first" (48.9%) were performed by surgeon B, while most of the "A first" (56.9%) were performed by surgeon A. The group of "other" surgeons that were desig-

TABLE 2. Operative approach characteristics

Variables	No.	%	V-first		A-first		P value
			No.	%	No.	%	
Total	279	100	133	100	146	100	
Type of resection							
Lobectomy alone	213	76.3	104	78.2	109	74.7	NS
Combined resection							
Sleeve	16	5.7	11	8.3	5	3.4	NS
Pericard	2	0.7	1	0.8	1	0.7	NS
Wedge	20	7.2	5	3.8	15	10.3	.03
CW, pleura, diaphragm	38	13.6	18	13.5	20	13.7	NS
Side							
Left	113	40.6	45	34.1	68	46.6	.03
Right	165	59.3	87	65.9	78	53.4	
Complete resection							
Yes	226	81	107	80.5	119	81.5	NS
No	53	19	26	19.5	27	18.5	
Frozen section							
Yes	61	21.9	28	21.1	33	22.6	NS
No	218	78.1	105	78.9	113	77.4	
Lung manipulation							
Yes	21	7.5	6	4.5	15	10.3	NS
No	258	92.5	127	95.5	131	89.7	
Surgeon							
A	105	37.6	23	17	82	56.9	<.001
B	83	29.7	66	48.9	17	11.8	
C*	91	32.6	46	34.1	45	31.3	
Blood transfusion	75	27	37	27.8	38	26.6	NS
During surgery	35	12.6	20	15	15	10.4	
Following surgery	30	10.8	14	10.5	16	11.1	
Both	10	3.6	3	2.3	7	4.9	

*C-a group of: all other surgeons.

nated as C used both methods of interruption in similar rates.

Postoperative complications were present in 32% of the study population with no significant differences, technical or other, between the groups. The mean hospital stay was 9.51 days (± 4.98) for the A-first group and 8.88 days (± 4.93) for the V-first group. This also was without significant difference between the groups.

Follow-up and Recurrence

Total disease recurrence rate was 52.3%, 78 patients (53%) of the A-first group and 68 patients (51%) of the V-first group ($P = .7$).

Risk factors for recurrence of disease (Table 3) were: male sex ($P = .01$), high stage of disease ($P < .0001$), incomplete resection ($P < .0001$), blood transfusion ($P = .006$), and lung manipulation ($P = .006$).

Significant association was found between stage of disease and performance of complete resection; although 93% of patients in stages I to II underwent complete resection, this was achieved in only about 50% of patients in higher stages ($P < .0001$). Therefore, these 2 parameters could not be included in the same model.

Table 4 presents 4 separate models of analysis, where the variable under investigation was retained in the models, and the other variables that emerged as significant in the univariate analysis were entered gradually. Stage of disease showed about threefold increased risk for recurrence, which remained similar after introducing the influence of the performing surgeon (models 2 and 3). Because the distribution of sequence of interruption was significantly different between surgeons, and to rule out possible confounding and/or modifying effect, we investigated the main effect of surgeon and its interaction with sequence of interruption. The P value for the overall effect of surgeon was .09 and the interaction was not significant ($P = .2$; not shown).

The fourth model showed elevated risk for recurrence among patients with high stage of disease (odds ratio [OR] = 2.54, 95% confidence intervals [CI] 1.39-4.65), male gender (OR = 1.59, 95% CI 0.95-2.67), patients who underwent lung manipulation (OR = 2.72, 95% CI 0.84-8.81), and patients who received blood transfusion (OR = 1.49, 95% CI 0.82-2.73). None of the models demonstrates evidence that sequence of interruption affected disease recurrence (from OR = 1.04, $P = .9$, to OR = 1.29, $P = .4$ in models 1 and 4, respectively).

TABLE 3. Univariate analysis for disease recurrence

Parameters	Categories	Total	Disease recurrence (N = 146)		P value
			No.	%	
Gender	female	104	44	42.3	.01
	male	175	102	58.3	
Age (years)	<70	177	90	50.8	NS
	≥70	102	56	54.9	
Pathology	squamous	83	47	56.6	NS
	ACOBAC	151	79	52.3	
	others	45	20	44.4	
Stage	I	152	62	40.8	<.0001
	II	50	28	56.0	
	III	68	49	72.1	
	IV	9	7	77.8	
Method	V-first	133	70	52.6	NS
	A-first	146	76	52.1	
Complete resection	no	53	41	77.4	<.0001
	yes	226	105	46.5	
Side*	left	113	60	53.1	NS
	right	165	86	52.1	
Blood transfusion	no	202	95	47.0	.006
	yes	77	51	66.2	
Previous malignancies*	no	240	127	52.9	NS
	yes	38	19	50.0	
Frozen section	no	218	119	54.6	NS
	yes	61	27	44.3	
Lung manipulation	no	258	129	50.0	.006
	yes	21	17	81.0	

ACOBAC, Adenocarcinoma other than bronchoalveolar type.

*One subject with missing information.

TABLE 4. Multivariate logistic models results for factors influencing recurrence of disease

Variables	Categories	I			II			III			IV		
		OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Sequence interruption	A vs. V	1.04	0.65-1.66	.9	1.02	0.63-1.66	.9	1.32	0.75-2.32	.3	1.29	0.73-2.29	.4
Stage	III-IV vs. I-II				3.32	1.87-5.89	.001	3.06	1.71-5.47	.001	2.54	1.39-4.65	.003
Surgeon	Overall effect									.09			.13
Lung manipulation	Yes vs. No										2.72	0.84-8.81	.1
Blood transfusion	Yes vs. No										1.49	0.82-2.73	.2
Gender	M vs. F										1.59	0.95-2.67	.08

The same analyses were performed while replacing stage of disease by completeness of resection due to the association observed between these two variables. Sequence of interruption remained uninfluential in accordance with the findings reported in Table 4.

Discussion

Although the assumption that certain manipulations on the lung during resection for malignancy causing shedding of tumor cells into the blood stream may eventually cause metastasis and adversely affect the prognosis makes sense, it has never been proven by clinical evidence. Moreover, the

sequence of vessel interruption during lobectomy for NSCLC as an independent prognostic variable was never examined in an epidemiologic study.

Our main aim in this study was to evaluate the impact that the sequence of hilar vessel interruption during lobectomy for NSCLC has on prognosis. Our results did not confirm that the sequence of interruption (artery first versus vein first) is a risk factor for disease recurrence (OR = 1.29, 95% CI 0.73-2.29). The report by Kurusu and associates⁶ is the only previous study in the literature that evaluated the sequence of vessel ligation during lobectomy for NSCLC as an independent variable for outcome, and indeed found that

it is a predictor for tumor cell spread in the circulation. They examined the presence of a peripheral epithelial marker (carcinoembryonic antigen messenger ribonucleic acid) in the circulation before, during, and after lobectomy in 30 patients with NSCLC. Each patient was randomly assigned to have either lobar vein interruption or lobar artery interruption first. Nine of the 14 patients with preoperative negative test results became positive during the operation. Such conversion was more common with arterial interruption first than with vein interruption first (6/7 versus 3/7 patients). They concluded that ligation of the pulmonary vein before ligating the artery may lessen intraoperative hematogenous dissemination. In another similar study by this group,⁸ using the same peripheral marker, VATS lobectomy was compared with open lobectomy. The authors found that VATS lobectomy was associated with a higher risk of seeding of tumor cells into the circulation during operation. This phenomenon was suggested to be related to a more frequent and forceful retraction and manipulation of the diseased lobe to attain better fields of vision during VATS lobectomy. However, no survival or recurrence rate data were available for the patients in both studies. The presence of circulating tumor cells is an indirect parameter for metastatic spread and does not necessarily predict the subsequent appearance of clinical metastatic disease. The clinical significance of the findings in these 2 studies remains unclear.

Although the main goal of the present study was to determine the significance of the sequence of vessel interruption, we evaluated multiple factors. In most multivariate analyses for operated patients, stage of disease and performance status were found to be the most important prognostic factors for survival.^{1,10-12} In our study, stage of disease emerged as the strongest risk factor for disease recurrence (OR = 2.54, 95% CI 1.39-4.65). Because performance status was not specified in all charts it was not included as a variable in our model. Incomplete resection highly correlated with stage in our analysis and was found to be strong prognostic risk factor for recurrence. The prognosis and management of an incompletely resected NSCLC is somewhat disputed in the current surgical literature, resulting mainly from differences in terminology. Traditionally, macroscopic or microscopic residual disease at the resection margin has been designated as incomplete resection, but many investigators include also the presence of tumor in the highest mediastinal node sampled.¹³ Lacasse and colleagues¹⁴ studied incomplete resection in NSCLC using the broader definition in a logistic regression model for disease recurrence or death, and did not find it to be a prognosticator.

Other risk factors that showed borderline significant evidence in this study for disease recurrence were: male gender ($P = .08$) and lung manipulation ($P = .1$). The per-

forming surgeon had some influence although with borderline significance ($P = .13$). Our finding of a lower risk for recurrence among women is in accordance with the literature, where female sex was associated with significantly longer survival¹⁵ and event-free survival.¹⁶

Blood transfusion also showed excess risk for recurrence (OR = 1.49, 95% CI 0.82-2.73). This issue was discussed in previous reports and a dispute exists about the impact of perioperative blood transfusion on patient prognosis.¹⁷⁻¹⁹ Our finding with regard to the nil effect of a previous malignancy on the outcome is in accordance with other studies.²⁰⁻²²

The inclusion of frozen section and lung manipulation in our analysis mandates explanation. We believe that while waiting for the frozen section result, the surgeon might have continued with hilar dissection and fissure division. In this case the sequence of interruption would not considerably affect tumor dissemination as it could have occurred before the vessels were addressed. This variable was similarly distributed between the 2 study groups and also did not affect recurrence rate. Inclusion of lung manipulation in the analysis had a similar rationale, as manipulations and forceful retraction of the lung prior to vessel interruption could cause more tumor cell dissemination than the lobectomy itself. Our results confirmed that lung manipulation is a risk factor for recurrence.

Three operative variables analyzed in the current study (ie, lung manipulation, interruption of the pulmonary artery first, and frozen section examination) share a common feature (ie, the increased risk of disseminating tumor cells into the circulation). The first 2 were proven by clinical or laboratory studies as discussed earlier^{5,6} to increase the presence of malignant cells in peripheral blood. Whether this phenomenon also increases the hazard for metastatic spread is yet to be determined. The process of metastatic formation depends on a myriad of host, tumor, and tumor-host relationship factors. Malignant cells are constantly shed from primary tumors into the blood stream. The majority of them are consumed by circulating macrophages²³ and only a minority would complete the sequence of events required to cross the endothelium. Most of the later are destroyed by tissue defense mechanisms. Only 1:10,000 circulating malignant cells eventually creates a metastasis.²³ Increased shedding of tumor cells into the circulation was demonstrated in breast cancer during surgery,²⁴ fine needle aspiration biopsy,²⁵ resection of hepatic metastases of colorectal carcinoma,²⁶ and brachytherapy for prostatic cancer.²⁷ Hayashi and colleagues²⁸ showed that no-touch isolation techniques may lower shedding of malignant cells into the portal vein during colorectal resection. Unfortunately, none of these studies sought prognostic correlations. Thus, similar to NSCLC, the clinical importance of tumor cell dissemination during various manipulation is still a

puzzle. Resembling but not identical to vascular dissemination is the phenomenon of a positive pleural lavage cytology in patients undergoing resection for NSCLC and presenting without pleural spread. Some investigators^{29,30} have shown that this is associated with a poor prognosis. In our retrospective study we have shown that lung manipulation is associated with a worse outcome, although interruption of the pulmonary artery first and frozen section are not. The impact of tumor manipulation (including sequence of interruption and use of frozen section) during surgery on recurrence could be determined by a prospective study combining clinical variables and the detection of circulating tumor cells.

The role of the operating surgeon on recurrence is one of the limitations of this study. Evidently, each surgeon is bound to his own method so that the sequence of interruption is highly associated with the surgeon performing the operation. We have tried to cope with this issue by including the effect of the operating surgeon in the multivariable analysis. The overall effect of the surgeon was with borderline significance and the interaction did not seem to alter the results. Interestingly, a review of the literature revealed that the majority of the studies that involve surgical therapy ignore the performer, the surgeon, as a possible prognostic factor for recurrence or survival. This subject was extensively discussed by Fielding and colleagues,³¹ who studied surgical treatment in colorectal cancer and found a wide range of postoperative mortality rates among 28 different surgeons. Our findings supported their claim that surgeons vary in the ability to produce a given result, a phenomena known as “surgeon related variability.” To overcome this problem, they suggested listing the predictive variables that are “surgeon-related” and treating them in the same way that “patient-related” variables are being treated. In this way a similarity in the study groups can be achieved or, when stratification is not possible, to demonstrate when the results are reported that randomization has succeeded in equally distributing the variables. Unfortunately, these principles cannot be fully applied by and large in a retrospective study and indeed “surgeon-related” variables are hardly evident in recent studies of any type in respect to prognosis, recurrence, or survival in lung cancer. In addition, although in multicentric clinical trials the large scale of surgeons participating in the study increases the variance and the severity of this problem, it is evident that the small number of surgeons who participated in our study contributed to the presented problem. Because each surgeon was bound to his own method, only a prospective study with randomized selection of the method for each patient and defining the “surgeon-related” predictive variables can provide definite answer to this puzzling issue.

Our results do not support the hypothesis that the sequence of vessel interruption during lobectomy for NSCLC

affects disease recurrence. A prospective study with randomized selection of method for each patient is needed to confirm these results.

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